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The differential involvement of inferior parietal lobule in number comparison: a rTMS study

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Abstract

Number processing is known to involve several sites within the posterior regions of parietal cortex. Here, we investigated whether neural activity in the inferior parietal lobule (IPL) is essential for number processing, by observing the effects of interfering with its activity during the execution of a standard number comparison task. Subjects performance on the task was significantly slowed down when we delivered trains of repetitive transcranial magnetic stimuli (rTMS) to the posterior parietal scalp site overlying the left IPL, while rTMS did not affect the number comparison task if delivered to homologous, contralateral (right) IPL. In conclusion, the present findings add support to a growing body of evidence from neuropsychology and neuroimaging studies that the left inferior parietal lobule is an important component of the networks subserving the representation of quantity.
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1. Introduction

The manipulation of numbers is a fundamental ability involved in a wide range of daily activities, like estimation of quantities, managing money, telling the time or planning scientific experiments. In recent years, experimental studies have begun to address the origins of the human mind's competence for mathematics. Indeed using the methods of cognitive neuroscience, we can now ask what internal representations are used to manipulate numbers mentally, when and how they develop, and which brain areas are involved.

In humans, internal representation of numerical quantities develops very rapidly in the first year of life (Wynn, Bloom, & Chiang, 2002; Xu & Spelke, 2000); and later, this representation underlies our ability to learn symbols for numbers and to perform simple calculations. It has been indicated that this ability is specifically associated with neural circuitry relaying in the inferior parietal lobule (IPL). Brain damage to these circuits can cause highly specific impairments in the representation and manipulation of numbers (Dehaene & Cohen, 1997; Delazer & Benke, 1997; Grafman, Passafiume, Faglioni, & Boller, 1982; Henschen, 1919; Mayer

et al., 1999) while functional imaging techniques have revealed that this region is active during number processing and calculation (Chochon, Cohen, van de Moortele, & Dehaene, 1999; Dehaene, 1996; Naccache & Dehaene, 2001; Pinel et al., 1999, Pinel, Dehaene, Riviere, & Le Bihan, 2001; Pesenti, Thioux, Seron, & De Volder, 2000; Piazza, Mechelli, Butterworth, & Price, 2002; Zago et al., 2001).

Moyer and Landauer (1967) were the first to describe the existence of quantitative number representations in humans, but many researchers before them (e.g. Galton, 1880; Piaget, 1952) suggested the existence of quantitative number representation. Moyer and Landauer found, in a number comparison task, that the reaction time to state the larger of two Arabic numerals is inversely proportional to the difference between the two numbers (distance effect). In other words, small differences (e.g. 2 3) take longer to be recognized whereas large differences (e.g. 2 8) are identified more rapidly. The classical interpretation of the distance effect supposes that all one- and two-digit numbers are automatically converted into percept like analogical representations that are then in turn compared with each other. In non-numerical contexts the effect has been also found when judging non-numerical perceptual or imaginable features such as line length (Johnson, 1939), size of named objects, animals, or countries (Moyer, 1973; Paivio, 1975), and even

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abstract features such as ferocity or intelligence of animals (Banks & Flora, 1977). The distance effect has been extensively replicated and its characteristics have been determined. Even when two-digit numbers are compared, the distance effect remains constant with a significant influence of the units, and little or no discontinuity at decade boundaries (e.g. when comparing numbers against a standard 65, 61 is classified more slowly than 59, which is itself slower than 51; Dehaene, Dupoux, & Mehler, 1990). Nonetheless, Nuerk, Weger, and Willmes (2001) found significant influences of the decades. Using a two-digit Arabic number comparison task, the authors demonstrated that compatible comparisons in which separate decade and unit comparisons lead to the same decision (32_47, 3 < 4 and 2 < 7) were faster than incompatible trials (37_52, 3 < 5, but 7 > 2). They concluded that the idea of one single number line for one- and two-digit numbers alone could not account for the compatibility effect. Therefore, different bins for magnitude representations of tens and units within or in addition to the mental number line have to be assumed. Dehaene (1992) and Dehaene and Cohen (1995) proposed, on the basis of number-processing deficits observed in patients, a model of the cerebral circuits implicated in calculation and number processing: the triple code model. This model predicts that, depending on the task, three distinct systems of representation may be recruited. First, a visual system (i.e. strings of digits manipulated on a spatially extended representational medium) would be used to process Arabic numerals, in multi-digit operations and in parity judgements. This visual Arabic code is localized in the left and right occipito-temporal area belonging to the ventral visual pathway dedicated to visual recognition. Second, a verbal system (i.e. syntactically organized sequences of number words) would be involved when hearing or reading number words, when counting, and when solving simple additions and multiplications. This verbal code is localized in the perisylvian language areas of the left hemisphere. Finally, an analogical system (i.e. mental continuum oriented left-to-right, from small to large numbers compressed near the large numbers, representing numerical quantities as distributions of activation) would give rise to approximate calculation and would be used in number comparison. This magnitude code is assumed to have a copy in the inferior parietal areas of both hemispheres. However, these authors initially proposed that the parietal activations during number processing reflected solely the contribution of the quantity system and afterwards, on the basis of a detailed review of the recent literature, Dehaene, Piazza, Pinel, and Cohen (2003) proposed a speculative model in which the parietal activation in number-related tasks can be segregated into three distinct sites, each associated with a distinct process: a bilateral intraparietal system associated with a core quantity system; a region of the left angular gyrus associated with verbal processing of numbers; and a posterior superior parietal system for spatial and non-spatial attention.

Data from split-brain patients (Cohen & Dehaene, 1996; Seymour, Reuter-Lorenz, & Gazzaniga, 1994) and behavioral visual field studies (see Ratinckx, Brysbaert, & Reynvoet, 2001 for a review) indicated that the quantity system is bilaterally represented in the brain. However, some data from single-case studies suggest a lateralization of quantity representations. For instance, Lemer, Dehaene, Spelke, and Cohen (2003) described a patient, with a focal lesion of the left parietal lobe, who showed evidence of impairments in subitizing and numerical comparison. Dehaene and Cohen (1997) described a patient, suffering from a unilateral right parietal lesion, that was impaired when the quantities were presented in verbal or Arabic digits format, while he performed much better when the input was in a non-symbolic format, though, this patient was left-handed and thus may have been cross-lateralized.

The involvement of the inferior parietal lobules in the manipulation of numerical quantities has been confirmed in several brain-imaging studies (Chochon et al., 1999; Dehaene, 1996; Göbel, Walsh, & Rushworth, 2001; Fias, Lammertyn, Reynvoet, Dupont, & Orban, 2003; Naccache & Dehaene, 2001; Pesenti et al., 2000; Pinel et al., 1999; Pinel et al., 2001). Several studies have found a bilateral involvement in the inferior parietal lobules during a comparison task, whereas Chochon et al. (1999) in a fMRI study and Dehaene (1996) using ERPs showed a predominance for the right hemisphere. Using fMRI with two-digit numbers, bilateral intraparietal activation was found to correlate directly with the numerical distance between two numbers and this effect was observed whether the numbers were presented as words or as digits (Pinel et al., 2001). A specific modulation of this area was found by Naccache and Dehaene (2001). In a fMRI study they used the priming method to investigate the coding of numerical quantity in the parietal lobe. They observed less intraparietal activation when numbers of identical versus different magnitude were repeated, irrespective of number notation (verbal versus Arabic). This indicates that this region comprises distinct neural assemblies for differential numerical quantities. Recently, Pinel, Piazza, Le Bihan, and Dehaene (2004) investigated the cerebral substrates of comparative judgements on three different dimensions: number size, physical size, and luminance. The results suggest that during comparative judgments, the relevant continuous quantities are represented in distributed and overlapping neural populations, with number and size engaging a common parietal spatial code, while size and luminance engage shared occipito-temporal perceptual representations.

Regarding the left inferior parietal lobule involvement, during a comparison task, Pinel et al. (1999) found a left sided predominance using small numbers. Pesenti et al. (2000) used a version of the number comparison task, in which subject had to decide if the third digit was larger than the largest of the pair. The authors found activation mainly in the left hemisphere (namely IPL, intraparietal sulcus and superior parietal lobule). Finally, Fias et al. (2003) tested the hypothesis that the processing of magnitude information has a common neural basis, whether that information is conveyed by symbolic and non-symbolic stimuli. In their

PET study, they isolated a site in left intraparietal sulcus that was specifically responsive when two stimuli had to be compared along a quantitative dimension, irrespective of the symbolic or non-symbolic presentation of the quantitative information (two-digit numbers, angles and lines). Hence, this region can be considered a neural correlate of an abstract representation of magnitude, independent of presentation format. In addition, they observed a second slightly more anterior site, not specific to quantitative processing but instrumental to number processing.

The present study investigated the role of the parietal cortex in number representation using repetitive transcranial magnetic stimulation (rTMS). By inducing transient regional alteration, rTMS provides the possibility to manipulate brain activity as an independent variable and therefore investigates its influence on the performance of different cognitive tasks within a controlled experimental design. Imaging studies can reveal the brain regions that are active during the execution of a number comparison task, but not which areas are essential for the performance of that task. With rTMS it is possible to interact with specific cortical areas at specific points in time so that it can be used to establish the role of a brain region in a particular task. The effects are time limited, reversible, and repeatable (Jahanshahi & Rothwell, 2000; Walsh & Rushworth, 1999).

Only one previous study used repetitive transcranial magnetic stimulation to investigate the role of parietal cortex in number representation (Göbel et al., 2001). Using a paradigm in which subjects compared numbers to a standard, these authors showed a bilateral involvement of the angular gyrus in representing number magnitude, especially for large numbers (i.e. from 31 to 99). Although there was an increase in RTs when rTMS was applied over either of the angular gyri, the effect was larger for stimulation over left angular gyrus (by contrast, there was only a trend toward an increase in RTs after stimulation over the right angular gyrus). Furthermore stimulation on the left tended to interfere more with numbers close to the reference (in this case 65), particularly for those that were larger than the reference, providing evidence for a spatial representation of these numbers akin to a mental number line within the left angular gyrus.

The aim of the study was to investigate the role of the inferior parietal lobule, and its hemispheric lateralization, in the representation of small numbers (from 1 to 9) during a standard number comparison task in which subjects were requested to select the largest of two visually presented digits, and we chose to stimulate this area on the basis of a detailed review of the recent literature, and of a meta-analysis of the available activation images proposed by Dehaene et al. (2003). In particular, we intend to temporarily interfere with the processing taking place in the IPL by means of rTMS, and if we assume that number magnitudes are represented in the right IPL we would expect that number comparison should be delayed after right-rTMS, irrespective of distance.

2. Methods

2.1. Participants

Nine healthy volunteers, aged between 25 and 32 years (mean age 28.4), participated in this study. Informed consent was obtained prior to the experiment, and the protocol was approved by the local ethics committee for research with human subjects. All were right-handed (mean score on the Edinburgh Handedness Inventory = 92.82) and had normal or corrected-to-normal vision.

2.2. Procedure

The experiment included three blocks, counterbalanced between subjects as to order of presentation (rTMS to the left, or to the right IPL or sham stimulation). Each block consisted of 36 pairs of digits, presented on a 17 inch monitor as black against a white background. Numbers were displayed using the font Times New Roman (type size 50) and subtended an observer's visual angle of approximately $0.9°$ high $\times$ $0.5°$ wide. The experiment was controlled by a PC running the Superlab Pro Software (Cedrus Corporation, San Pedro, CA, USA) version 2.0 with an RB-400 response pad. Subjects were seated in a lit room at a distance of approximately 60 cm from the computer screen. During the experiment subjects had to perform a standard number comparison task. On each trial, a fixation point first appeared for 1500 ms on the center of the screen. Then, the fixation point disappeared and a pair of Arabic digits was presented to the left and to the right of it (midpoint at $2.2°$ eccentricity) aligned along the horizontal meridian. Participants were instructed to press the left- or right-hand key according to the position (left or right) of the target stimulus (the "larger" number). They used the left hand for a left response and the right hand for a right response. The use of the left and right response/hand was fully balanced for all the conditions to avoid effects of side. Stimuli remained on the screen until subjects made a response. The inter-trial interval was 4000 ms (see Fig. 1). The number '5' was never presented. The pairs of digits were distributed in two categories of numerical distances: "close" pairs (differing by only 1, 2 or 3 units) and "far" pairs (differing by 5, 6 or 7 units). The two categories defined the following experimental pairs: numbers "close" (1 2, 2 1, 3 4, 4 3, 6 7, 7 6, 8 9, 9 8, 1 3, 3 1, 4 6, 6 4, 7 9, 9 7, 1 4, 4 1, 6 9, 9 6); numbers "far" (1 6, 6 1, 2 7, 7 2, 3 8, 8 3, 4 9, 9 4, 1 7, 7 1, 2 8, 8 2, 3 9, 9 3, 1 8, 8 1, 2 9, 9 2). Extreme values, i.e. 1 and 9, appeared equally often in close and far pairs. Before the experiment began, subjects were presented with 10 non-TMS training trials in order to provide practice with the task and the experimental setting. The experimental session lasted approximately 25 min.

2.3. Repetitive transcranial magnetic stimulation

Subjects wore a bathing cap on which the relevant coordinates of the International 10/20 EEG System were
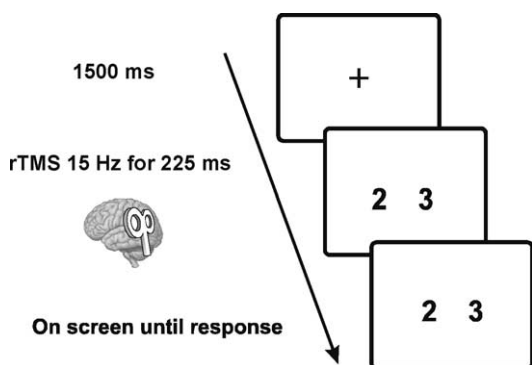
Fig. 1. Subjects fixated on a small cross at center of the screen and monitored for the appearance of target stimuli that consisted of two digits ($0.9° \times 0.5°$ each) to the left and right hemifield (midpoint at $2.2°$ eccentricity). Trains of rTMS at 15 Hz (10% below individual motor threshold) were delivered in the first 225 ms of digits appearance, to the left or right IPL, when required by the experimental design. Subjects were asked to press the left or right hand key congruent to the position (left or right) of the larger of the two digits (the target). Distribution of left or right response were counterbalanced within subjects, stimulation condition and type of stimulus.

reproduced. For generating the magnetic pulses we used a Magstim stimulator, Model Super Rapid (The Magstim Co. Ltd., Whitland, UK) with a 70-mm figure 8 coil.

Before the experiment, individual resting excitability thresholds of stimulation were determined by stimulating the left motor cortex and measuring the amplitude of muscle twitch evoked by a single TMS pulse in the contralateral first interosseus dorsalis muscle. The threshold was defined as the minimum intensity, which induced a visible contraction in the tested muscle, as agreed by two experimenters on at least three trials. The stimulation intensity used during the experiment was set at 10% above of each subject's motor threshold. Trains of rTMS at 15 Hz were delivered according to the experimental design simultaneously to stimuli presentation for 225 ms (total of four stimuli) on the defined scalp location that was, on average, 1-cm lateral to CP3 or CP4, respectively (10/20 International EEG System). The same intensity and timing of rTMS were used for sham stimulation: in this case, the coil was centered on CPZ and was perpendicular to the scalp surface. As known by previous experiments (Lisanby, Gutman, Luber, & Schroeder, 2001), by adopting this procedure, no effective magnetic stimulation reached the brain during the sham condition, while subject feeling of coil–scalp contact and discharge noise were similar to the real simulation. Frequency, intensity, and duration of rTMS were in accordance with the safety international guidelines (Wasserman, 1998).

A common problem in most TMS studies regards the location of the stimulating coil with respect to the anatomy of the targeted cortex, in the single subject. In this regard, recently-developed neuronavigation TMS systems are a tool (Bohning, Denslow, Bohning, Walker, & George, 2003) but not always the subjects' magnetic resonance images (MRIs) are available.
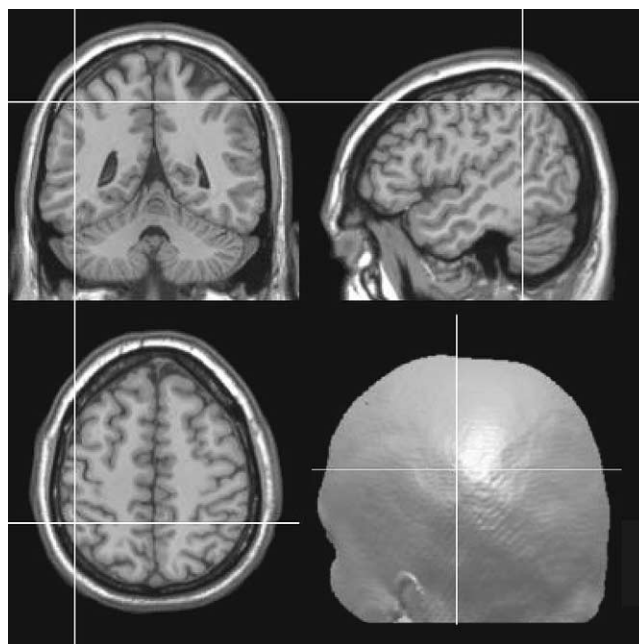

Fig. 2. Coronal, axial, sagittal and surface views of the stimulated site depicted on a standard template from MRIcro (v1.37; htt://www.mricro.com). This template is used only for display purposes here, for details on the precise coil location see the methods section. The cross hairs indicate the estimated left site stimulated by TMS that led to a significant delay of reaction times. The Talairach co-ordinates of this site, calculated with the Softaxic Navigator software, are $X = -48$, $Y = -47$, $Z = 52$, corresponding to inferior parietal lobe. On average the coil was located about 1 cm lateral to CP3 (10–20 International EEG System).

In this study left and right IPL were stimulated by placing the anterior end of the junction of the coil wings on one of two points marked on the close-fitting cap. These points on the subject's scalp were automatically identified using the SoftTaxic Evolution Navigator system that works in the absence of radiological images on the basis of digitized skull landmarks (nasion, inion and two pre-auricular points) from which 40 uniformly-distributed points can be mapped out on the scalp (3D Fastrak Polhemus digitizer) and related to cerebral anatomy. Although individual radiological head images (i.e. MRIs) were not available, Talairach coordinates of cortical sites underlying coil locations (Fig. 2) were automatically estimated for the subjects by the SoftTaxic Evolution Navigator system, on the basis of an MRI-constructed stereotaxic template (accuracy > 1 cm, Talairach space).

This method represents a good compromise among the localization accuracy, the high economical demands of neuronavigation devices, and the availability of the single subject MRI. It should be noted that we can compute with very high precision the location of the coil but this does not strictly imply that we know with such a high precision the width of brain areas that are directly or even indirectly influenced by the magnetic field, independently of the presence of single subject MRI. Therefore, we can only assume that we were stimulating the estimated cortex site underling the coil. The location of these points was on average
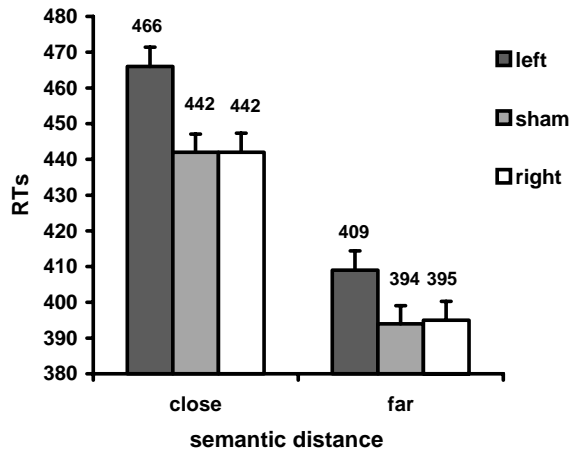
Fig. 3. Effects of TMS on mean reaction times (RTs) across sites of stimulation and semantic distance. As can be noted, rTMS significantly delayed task performance, for both the close and far conditions, only when applied to the left inferior parietal lobule but not after sham or right IPL stimulation. Verticals bars represent standard errors of the mean.

centered on Talairach co-ordinates $X = \pm 48$, $Y = -47$, $Z = 52$ (Brodmann's area 40) (Talairach & Tournoux, 1988).

3. Results

The analysis was based on reaction times from correct trials only. RTs that fell below or above 2 S.D.s from each individual's average were discarded. This procedure eliminated 2% of responses. Subjects showed high levels of accuracy in task performance and the error rate was very low (1.2%).

A preliminary analyze showed no main effect of the factor of response hand and no interaction between response hand and any other factor, indicating that nonspecific factors (i.e. motor impairment/facilitation by TMS) were not contributing to significant variations. Differences on RTs were assessed by repeated-measures analysis of variance (ANOVA). The within-subjects factors tested were semantic distance ("close" pairs versus "far" pairs) and site of stimulation (left IPL, right IPL, and sham). The main effect of semantic distance was significant [$F(1,8) = 119.528$; $P < 0.001$], indicating that overall RTs were shorter for far digit-pairs (399 ms) than for close digit-pairs (450 ms). Also, the main effect of site of stimulation [$F(2,16) = 15.259$; $P < 0.001$] was significant. Direct post hoc comparison (*t*-tests) showed that RTs after left IPL stimulation (438 ms) were significantly slower than RTs to both sham (418 ms) and right (419 ms) stimulation ($P < 0.001$) (see Fig. 3). The interaction between semantic distance and site of stimulation was not significant although the difference close versus far was larger for left rTMS (57 ms) then right rTMS (47 ms) and sham stimulation (48 ms), indicating a slowing down of RTs for the close compared to far condition, after left TMS.

4. Conclusions

This study provides a replication of the distance effect indicating that overall RTs were shorter for far digit-pairs than for close digit-pairs.

More importantly, left IPL stimulation led to slowing down of performance during a standard number comparison task compared with right IPL or sham stimulation irrespective of the distance effect. Left rTMS stimulation produced a larger distance effect than right rTMS and sham stimulation. However, even if a difference was present, rTMS does not significantly interact with the numerical distance effect. These results suggest that by stimulating IPL we temporarily slowed the processing taking place in this area.

An alternative explanation for the lack of influence by TMS on subject accuracy or an interaction with the numerical distance effect is related to the low level of task difficulty. With the inherent redundancy of the brain and its resulting high capacity to compensate for interference caused by TMS, it is perhaps only through straining the available neuronal resources with a reasonably complex task that it becomes possible to observe a strong behavioral impairment. Nevertheless TMS interfered equally with both tasks (close, far) and that was what we would have expected after stimulation of IPL.

This result could also be interpreted as evidence that a processing chain is interfered before the magnitude is accessed, so that the processing sequence from input to semantics is slowed down and as it stand we cannot discard such a possibility.

Nevertheless, these data cannot be interpreted as evidence of an effect at motor level. Despite IPL being close to the motor cortex involved in motor response preparation (Deiber, Ibanez, Saadato, & Hallett, 1996; Rushworth, Ellison, & Walsh, 2001, Rushworth, Paus, & Sipila, 2001), we did not find any effect on the factor of response hand or any interaction between response hand and side of stimulation, indicating that these results could not be explained by motor impairment or facilitation of the contralateral hand.

These findings indicate that the left inferior parietal lobule plays a crucial role in the number comparison task for small digits, while the right inferior parietal lobule does not appear to be critically involved in this process. Our failure to obtain evidence that the right parietal lobe plays an essential role in number comparison is somewhat surprising given that many functional imaging studies have found evidence for bilateral parietal activation with a right-sided predominance (Chochon et al., 1999; Pinel et al., 2001).

However, given the limitation of neuroimaging studies, it is difficult from these results to know, beyond greater precision in mapping a process, whether the active areas in both hemispheres correspond to excitatory or inhibitory process, since fMRI does not allow to disentangle these aspects and their implications on behavioral performance.

Our findings are, therefore, in accordance with results from lesion studies which show that acalculia is more

commonly associated with left than right hemisphere damage (Cipolotti, Butterworth, & Denes, 1991; Delazer & Butterworth, 1997; Grafman et al., 1982; Henschen, 1919; Mayer et al., 1999; Sandrini, Miozzo, Cotelli, & Cappa, 2003) and with brain imaging studies showing a left-sided activation in numerical comparison (Pesenti et al., 2000; Fias et al., 2003) or a left-sided predominance (Pinel et al., 1999). During comparisons of various continua, Fulbright, Manson, Skudlarski, Lacadie, and Gore (2003) observed overlapping intraparietal activation for judgments of letter, number, and size ordering, though the left supramarginal gyrus was involved in the distance effect with numbers.

Furthermore, our results are also consistent with recent neuropsychological evidence in which a patient with focal lesion of the left parietal lobe exhibited impairments in number comparison capability with Arabic digits or arrays of dots (Lemer et al., 2003).

Partially in accord to our data, there is a previous rTMS study investigating the contribution of the parietal lobes to number representation (Göbel et al., 2001). In a number comparison task with two-digit numbers, the authors found a bilateral interference effect of TMS over the angular gyrus, with a larger effect on the left hemisphere.

Regarding neuroimaging studies (fMRI and PET) the differences in the hemispheric side of activation or site within the inferior parietal lobes could be attributed to differences in absolute number sizes, type of number comparison tasks and control conditions. In addition, most of the tasks used did not focus on clearly defined numerical processes, and often involved a working memory load and/or a verbal response (either aloud or covertly). For these reasons, it is not easy to disentangle which activations were specifically linked to number processing, and which were related to more general processes. In the literature, there are many studies showing the contribution of the parietal lobe in many aspects of cognitive function, including hand reaching, grasping, attention orienting, mental rotation, spatial working memory and phonological word processing (Culham & Kanwisher, 2001; Jonides et al., 1998; Harris & Miniussi, 2003; Simon, Mangin, Cohen, Le Bihan, & Dehaene, 2002). Regarding working memory, in our study this component was kept equivalent between all the conditions in order to avoid a possible involvement of this process in the automatic and/or voluntary semantic processing of the magnitude dimension.

Though it is possible that evidence of right inferior parietal lobe activation in some fMRI studies might have been due to more general processes, this is certainly not so for the priming effect (Naccache & Dehaene, 2001). In fact, the priming effect demonstrates that the intraparietal sulcus activation reported by the authors is magnitude specific as discussed in Section 1.

Another possible explanation about this left involvement is what one might call the "finger-counting" model (Butterworth, 1999). It may be the case that smaller numbers, which are often learned early in life, depend on a distinct code that may emphasize verbal memory for route

counting or hand-based counting strategies. The model emphasizes the role of the left parietal lobe as well as the coincidence of numerical deficits and Gerstmann's syndrome. It is worth noting that parietal lobes, and particularly the intraparietal sulci, are part of the neural circuit that controls hand shapes and finger movements (Jeannerod, Arbib, Rizzolatti, & Sakata, 1995). This raises the possibility that these brain regions contribute to finger counting and finger calculation—an almost universal stage in the learning of exact calculation. This connection between fingers and arithmetic prompts the suspicion that the parietal lobes, in the course of development and learning, come to support the digital representation of numbers.

The results obtained in this study extend previous evidences obtained in patients with focal brain lesions, or neuroimaging studies suggesting a critical role for the left inferior parietal lobule in representation of quantity. However, there is a discrepancy between lesion and imaging studies regarding the lateralization of the representation for numerical quantity. In quantity-related dyscalculia and in our study, there is a contribution of left hemisphere while, neuroimaging studies show bilateral activation in quantity tasks. Regarding the right hemisphere, its role in number representation is still unclear.

The few imaging studies of basic numerical processes such as enumerating dot arrays (Piazza et al., 2002; Sathian et al., 1999) suggest that enumerating arrays of up to nine dots involves occipital lobes bilaterally and the right superior parietal lobe, which is consistent with patient studies showing right-hemisphere involvement in dot enumeration (Warrington & James, 1967; Warrington, 1982). One can speculate (see Piazza & Dehaene, in press) that our core numerical system is initially bilateral and progressively becomes biased for symbolic manipulation of numbers in the left hemisphere and for non-symbolic tasks in the right hemisphere. However, also this interesting speculation awaits confirmation.

Overall, even within the triple-code model, the left and right parietal lobe representations of quantity are not equivalent. Both are involved in manipulating quantity information, but only the left parietal region provides a direct interconnection of the quantity representation with the linguistic code (Dehaene & Cohen, 1997). This may explain the greater severity of acalculia following a left parietal lesion.

In conclusion, the present findings add to a growing body of evidence that these areas also constitute important components of the networks subserving representation of quantity. As such, they are consistent with a model in which smaller numbers may depend on a distinct code that may emphasize verbal aspects or hand-based counting left-hemisphere strategies (Butterworth, 1999).

References

Banks, W. P., & Flora, J. (1977). Semantic and perceptual processes in symbolic comparison. *Journal of Experimental Psychology: Human Perception and Performance*, *3*, 278–290.

Bohning, D. E., Denslow, S., Bohning, P. A., Walker, J. A., & George, M. S. (2003). A TMS coil positioning/holding system for MR image-guided TMS interleaved with fMRI. *Clinical Neurophysiology*, *114*, 2210–2219.

Butterworth, B. (1999). A head for figures. *Science*, *284*, 928–929.

Chochon, F., Cohen, L., van de Moortele, P. F., & Dehaene, S. (1999). Differential contributions of the left and right superior parietal lobules to number processing. *Journal of Cognitive Neuroscience*, *11*, 617–630.

Cipolotti, L., Butterworth, B., & Denes, G. (1991). A specific deficit for numbers in a case of dense acalculia. *Brain*, *114*, 2619–2637.

Cohen, L., & Dehaene, L. (1996). Cerebral networks for number processing: Evidence form a case of posterior callosal lesion. *NeuroCase*, *2*, 155–174.

Culham, J. C., & Kanwisher, N. G. (2001). Neuroimaging of cognitive functions in human parietal cortex. *Current Opinion in Neurobiology*, *11*, 157–163.

Dehaene, S. (1992). Varieties of numerical abilities. *Cognition*, *44*, 1–42.

Dehaene, S. (1996). The organization of brain activity in number comparison: Event-related potentials and the additive-factors methods. *Journal of Cognitive Neuroscience*, *8*, 47–68.

Dehaene, S., & Cohen, L. (1995). Towards an anatomical and functional model of number processing. *Mathematical Cognition*, *1*, 83–120.

Dehaene, S., & Cohen, L. (1997). Cerebral Pathways for calculation: Double dissociation between rote verbal and quantitative knowledge of arithmetic. *Cortex*, *33*, 210–250.

Dehaene, S., Dupoux, E., & Mehler, J. (1990). Is numerical comparison digital—analogical and symbolic effects in 2-digit number comparison. *Journal of Experimental Psychology: Human Perception and Performance*, *16*(3), 626–641.

Dehaene, S., Piazza, M., Pinel, P., & Cohen, L. (2003). Three parietal circuits for number processing. *Cognitive Neuropsychology*, *20*(3/4/5/6), 487–506.

Deiber, M. P., Ibanez, V., Saadato, N., & Hallett, M. (1996). Cerebral structures participating in motor preparations in humans: A PET study. *Journal of Neurophysiology*, *75*, 233–247.

Delazer, M., & Benke, T. (1997). Arithmetic facts without meanings. *Cortex*, *33*(4), 697–710.

Delazer, M., & Butterworth, B. (1997). A dissociation of number meanings. *Cognitive Neuropsychology*, *14*, 616–636.

Fias, W., Lammertyn, J., Reynvoet, B., Dupont, P., & Orban, G. A. (2003). Parietal representation of symbolic and nonsymbolic magnitude. *Journal of Cognitive Neuroscience*, *15*, 47–56.

Fulbright, R., Manson, C., Skudlarsky, P., Lacadie, C., & Gore, J. (2003). Quantity determination and the distance effect with letters, numbers and shapes: A functional MR imaging study of number processing. *American Journal of Neuroradiology*, *23*, 197–200.

Galton, F. (1880). Visualised numerals. *Nature*, *21*, 252–256.

Göbel, S., Walsh, V., & Rushworth, M. F. S. (2001). The mental number line and the human angular gyrus. *Neuroimage*, *14*, 1278–1289.

Grafman, J., Passafiume, D., Faglioni, P., & Boller, F. (1982). Calculation disturbances in adults with focal hemispheric damage. *Cortex*, *12*, 37–50.

Harris, I. M., & Miniussi, C. (2003). Parietal lobe contribution to mental rotation demonstrated with rTMS. *Journal of Cognitive Neuroscience*, *15*(3), 315–323.

Henschen, S. E. (1919). Über Sprach- Musik- und Rechenmechanismen und ihre Lokalisationen im Grosshirn. *Zeitschrift für die desamte Neurologie und Psychiatrie*, *52*, 273–298.

Jahanshahi, M., & Rothwell, J. C. (2000). Transcranial magnetic stimulation studies of cognition: An emerging field. *Experimental Brain Research*, *131*, 1–9.

Jeannerod, M., Arbib, M. A., Rizzolatti, G., & Sakata, H. (1995). Grasping objects: The cortical mechanisms of visuomotor transformation. *Trends in Neuroscience*, *18*, 314–320.

Johnson, D. M. (1939). Confidence and speed in the two-category judgment. *Archives of Psychology*, *241*, 1–52.

Jonides, J., Schumacher, E. H., Smith, E., Koeppe, R. A., Awh, E., & Reuter-Lorenz, P. A. et al., (1998). The role of parietal cortex in verbal working memory. *The Journal of Neuroscience*, *18*(13), 5026–5034.

Lemer, C., Dehaene, S., Spelke, E., & Cohen, L. (2003). Approximated quantities and exact number words: Dissociable systems. *Neuropsychologia*, *41*, 1942–1958.

Lisanby, H. S., Gutman, D., Luber, B., & Schroeder, C. (2001). Sham TMS: Intracerebral measurement of the induced electrical field and the induction of motor-evoked potentials. *Biological Psychiatry*, *49*, 460–463.

Mayer, E., Martory, M. D., Pegna, A. J., Landis, T., Delavelle, J., & Annoni, J. M. (1999). A pure case of Gerstmann syndrome with a subangular lesion. *Brain*, *122*, 1107–1120.

Moyer, R. S. (1973). Comparing objects in memory—evidence suggesting an internal psychophysics. *Perception Psychophysics*, *13*, 180–184.

Moyer, R. S., & Landauer, T. K. (1967). The time required for judgements of numerical inequality. *Nature*, *215*, 1519–1520.

Naccache, L., & Dehaene, S. (2001). The priming method: Imaging unconscious repetition priming reveals an abstract representation of number in the parietal lobes. *Cerebral Cortex*, *11*, 342–345.

Nuerk, H. C., Weger, U., & Willmes, K. (2001). Decade breaks in the mental number line? Putting the tens and units back in different bins. *Cognition*, *82*(1), B25–B33.

Paivio, A. (1975). Perceptual comparisons through the mind's eye. *Memory and Cognition*, *3*, 636–647.

Pesenti, M., Thioux, M., Seron, X., & De Volder, A. (2000). Neuroanatomical substrates of Arabic number processing, numerical comparison, and simple addition: A PET study. *Journal of Cognitive Neuroscience*, *12*, 461–479.

Piaget, J. (1952). *The child's conception of number*. New York: Norton.

Piazza, M., & Dehaene, S. (in press). From number neurons to mental arithmetic: The cognitive neuroscience of number sense. In M. Gazzaniga (Ed.), *The cognitive neuroscience* (3rd ed.). Cambridge, MA: MIT Press.

Piazza, M., Mechelli, A., Butterworth, B., & Price, C. J. (2002). Are subitizing and counting implemented as separate or functionally overlapping processes? *Neuroimage*, *15*, 435–446.

Pinel, P., Dehaene, S., Riviere, D., & Le Bihan, D. (2001). Modulation of parietal activation by semantic distance in a number comparison task. *Neuroimage*, *14*, 1013–1026.

Pinel, P., Le Clec'H, G., van de Moortele, P. F., Naccache, L., Le Bihan, D., & Dehaene, S. (1999). Event-related fMRI analysis of the cerebral circuit for number comparison. *NeuroReport*, *10*, 1473–1479.

Pinel, P., Piazza, M., Le Bihan, D., & Dehaene, S. (2004). Distributed and overlapping cerebral representations of number, size, and luminance during comparative judgments. *Neuron*, *41*, 983–993.

Ratinckx, E., Brysbaert, M., & Reynvoet, B. (2001). Bilateral field interactions and hemispheric asymmetry in number comparison. *Neuropsychologia*, *39*, 335–345.

Rushworth, M. F. S., Ellison, A., & Walsh, V. (2001a). Complementary localization and lateralization of orienting and motor attention. *Nature Neuroscience*, *4*, 656–661.

Rushworth, M. F. S., Paus, T., & Sipila, P. K. (2001b). Complementary lateralization of attention and intention in the human brain. A PET study. *Journal of Cognitive Neuroscience*, *13*, 698–710.

Sandrini, M., Miozzo, A., Cotelli, M., & Cappa, S. F. (2003). The residual calculation abilities of a patient with severe aphasia: Evidence for a selective deficit of subtraction procedure. *Cortex*, *39*, 85–96.

Sathian, K., Simon, T. J., Peterson, S., Patel, G. A., Hoffman, J. L., & Grafton, S. T. (1999). Neural evidence linking visual object

enumeration and attention. *Journal of Cognitive Neuroscience*, *11*, 36–51.

Seymour, S. E., Reuter-Lorenz, P. A., & Gazzaniga, M. (1994). The disconnection syndrome: Basic findings reaffirmed. *Brain*, *117*, 105–115.

Simon, O., Mangin, J., Cohen, L., Le Bihan, D., & Dehaene, S. (2002). Topographical layout of hand, eye, calculation, and language-related areas in the human parietal lobe. *Neuron*, *33*, 475–487.

Talairach, J., & Tournoux, P. (1988). *Coplanar sterotaxic atlas of the human brain*. Stuttgart: Thieme.

Walsh, V., & Rushworth, M. (1999). A primer of magnetic stimulation as a tool for neuropsychology. *Neuropsychologia*, *37*, 125–135.

Warrington, E. K. (1982). The fractionation of arithmetical skills: A single case study. *Quarterly Journal of Experimental Psychology*, *34A*, 31–35.

Warrington, E. K., & James, M. (1967). Tachistoscopic number estimation in patients with unilateral lesions. *Journal of Neurology, Neurosurgery, and Psychiatry*, *30*, 468–474.

Wasserman, E. M. (1998). Risk and safety of repetitive transcranial magnetic stimulation: Report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June, 5–7, 1996. *Electroencephalography and Clinical Neurophysiology*, *108*, 1–16.

Wynn, K., Bloom, P., & Chiang, W. C. (2002). Enumeration of collective entities by 5-month-old infants. *Cognition*, *83*(3), B55–B62.

Xu, F., & Spelke, E. S. (2000). Large number discrimination in 6-month-old infants. *Cognition*, *74*(1), B1–B11.

Zago, L., Pesenti, M., Mellet, E., Crivello, F., Mazoyer, B., & Tzourio-Mazoyer, N. (2001). Neural correlates of simple and complex mental calculation. *Neuroimage*, *13*, 314–327.