Single pulse TMS induced disruption to right and left parietal cortex on addition and multiplication.

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Abstract

Whether or not mathematical operations are dependent on verbal codes in left hemisphere areas – particularly the left intraparietal sulcus – remains an issue of intense debate. Using single pulse transcranial magnetic stimulation directed at horizontal and ventral regions of the left and right intraparietal sulcus, we examined disruption to reaction times in simple addition and multiplication. Results indicate that these two operations differ in the pattern of lateralization across time for the two areas studied. These show that computational efficiency is not specifically dependent on left hemisphere regions and, in particular, that efficiency in multiplication is dependent the ventral region of the intraparietal sulcus in the right hemisphere considered to be critical for motion representation and automatization.

Keywords: mathematics, intraparietal sulcus, verbal codes

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In mapping mathematical abilities in the brain, a still very coarse distinction is made, despite recent progress, between the respective functions of the left and of the right hemisphere. Traditionally, since acalculia mostly derives, in several varieties, from left hemisphere lesions, mathematical cognition has been linked in large measure to the left hemisphere and to linguistic functions (Jackson and Warrington, 1986). Number words have been considered to provide a verbal code that facilitates exact calculation (Dehaene et al., 1999; Spelke and Tsivkin, 2001). In this respect, activation in left hemisphere (LH) brain regions has been found in fMRI studies in operations relying on memory retrieval (Dehaene et al., 1999, 2003; Stanescu-Cosson et al., 2000; Pinel and Dehaene, 2010; Zhou et al., 2007). In particular, operations such as addition and multiplication involve activation of the left horizontal portion of the intraparietal sulcus (lHIPS) – an area seen to be critical in the representation of quantities. Although the left angular gyrus (lANG) can also be activated in operations as addition or multiplication, it has been seen to concern linguistic processing more than the specific processing of quantity, and the role of the lANG in calculation appears dependent on the lHIPS (Dehaene et al., 2003; Dehaene et al., 2004, p. 219). By this account, emphasis has been placed on the predominance of a left hemisphere network for calculation. In sum, although the processing of number magnitude has been proposed to reside bilaterally in HIPS, it has been proposed that the lANG jointly with parietal areas is of prime importance for retrieving results in arithmetic problems. (Dehaene et al., 2003, 2004).

Within this context, our first research question concerns whether *both right and left parietal regions are critical for exact numerical processing.* There are reasons to further explore the contribution of the right hemisphere and non-language-related processing during these tasks. First, not all neuroimaging studies have found more activation in left hemisphere language regions on calculation tasks (Pesenti et al., 2000; Zago et al., 2001). There are investigations that have shown right posterior parietal activations (Dehaene et al., 2009; McCrink et al., 2007; Hubbard et al., 2005;

Knops et al., 2009a) and these activations have been attributed to the need of a visuospatial medium for arithmetic. Second, there is evidence from neuropsychological data showing dissociations between linguistic and mathematical abilities in developmental and acquired language disorders (Landerl et al., 2004; Varley et al., 2005), and patient studies have documented that acalculia can occur without damage to LH language areas (Granà et al., 2006; Hartje, 1987) or that simple calculation can be preserved in persons with aphasia (Rossor et al., 1995; Warrington, 1982; Whalen et al., 2002).

Lesion studies are indeed important for discovering whether a given anatomical structure is necessary to carry over a given task. However, a structure may contribute to performing a task and yet be not strictly necessary. Results from the use of TMS techniques imply causal relationships, overcoming the limitations of correlation approaches in neuroimaging and the lack of clearly identifiable neural loci in the study of patients. The virtual lesion approach provided by TMS can therefore help to establish the importance of left and right parietal areas in calculation. Use of these techniques should facilitate investigation of the extent to which both left and right IPS are fundamental for addition and/or multiplication.

Therefore the present study used single-pulse TMS to explore the role of bilateral IPS in calculation. Our focus was on two areas: **HIPS** and **VIPS**. Stimulation was directed at the *right and left HIPS* in order to compare whether interference to operations of addition and multiplication would be confined to the lHIPS in a LH network dedicated to calculation, as consistent with a verbally-mediated account (Dehaene et al., 2003, 2004), or to the HIPS bilaterally as would be consistent with an account in which verbal mediation is not specifically necessary and sufficient to calculation (Bloom and Keil, 2001; Campbell and Epp, 2004; Gelman and Butterworth, 2005).

We also examined the effects of TMS on the *ventral portion of the intraparietal sulcus* bilaterally (rVIPS and lVIPS). Recently, fMRI activation accompanying numerical processing in adults in the HIPS has been reported to extend adjacently to the rVIPS region (Cantlon et al., 2006). Moreover, applying TMS to the ventral portion of the rIPS (mean Talairach coordinates, x = 22.0, y

= 68.6, z = 39.8) impairs processing of number magnitude (Cohen Kadosh et al., 2007). Although this location differs from the posterior superior parietal lobe studied by Andres et al. (2011) in a TMS study of calculation, it is in the region studied by Salillas et al. (2009) who showed that TMS inhibition of VIPS results in impaired efficiency in both motion perception and number comparison. As Salillas et al. (2009) have suggested, VIPS may be recruited within a network sustaining number comparison to complement HIPS by facilitating use of a mental number line. In order for a person to decide whether a number is higher or lower than a reference number, the focus of attention has to "move" along the mental number line in a way similar to that in which sensory motion is computed. This process may be carried by adjacent motion sensitive areas such as VIPS forming the basis of visuospatial operations implied in arithmetic (Knops et al. 2009b; Salillas et al., 2009). Therefore, concerning our first research question, if right IPS is essential for efficiency in exact calculation, then no differences across hemispheres should be obtained. Only a main effect of site of stimulation or visual field should be found. In this regard, we predicted a joint involvement of ventral and horizontal IPS in calculation as shown through TMS induced disruption to these regions.

In contrasting addition and multiplication, our study was intended to address a second research question concerning *whether multiplication is more verbally-mediated than addition.* We examined the neural basis of computations involving simple addition and multiplication – operations that have both been considered to be especially dependent on verbally-coded facts (Lemer, Dehaene, Spelke, and Cohen, 2003). Nevertheless, simple addition is usually done with the use of procedural strategies whereas multiplication is thought to rely more in memorization (e.g., Dehaene and Cohen, 1997; Roussel et al., 2002). These strategies may lead to differences in the form of final representations (e.g., Siegler and Shipley, 1995; Siegler and Shrager, 1984). Thus as has often been reported (e.g. Cohen et. al., 2000; Dehaene and Cohen, 1997; Delazer and Benke, 1997; Lemer et al., 2003; Pesenti, Seron, and van der Linden, 1994; van Harskamp, Rudge, and Cipolotti, 2002), mental representations of multiplication facts may have greater reliance on verbal memory and hence greater left hemisphere involvement than those for addition facts.

A third research question involved examination of *the temporal pattern of left and right parietal contributions to calculation*. The study of the time course of IPS involvement in calculation can be achieved using single pulse TMS while targeting left or right parietal areas. However, to date, research has been limited to studies of repetitive TMS effects on number processing that have mainly concerned magnitude comparisons (Andres et al., 2005; Cohen Kadosh, 2007; Göbel et al., 2001; Knops et al., 2006; Sandrini et al., 2004). Recently, Andres et al. (2011) have used rTMS to address lateralization effects in the HIPS during simple arithmetic. They have reported that rTMS directed at the bilateral HIPS during simple subtraction and multiplication influences calculation, thus questioning the proposal of a left lateralized network for exact arithmetic.

The use of single pulse TMS at different stimulus onset asynchronies (SOAs) in our investigation was aimed to determine whether lateralization is constant across time or whether left and right IPS areas are necessary at different moments (i.e. visuospatial processes are used before a left lateralized verbal recovery of the answer occurs). Stimulation was delivered at one of four SOA intervals (150, 200, 250 and 300 ms.). These SOAs were chosen because they have been shown to be critical time points where arithmetic processes are detected in ERP studies. Specifically, similar arithmetic problems elicit ERP components starting as soon as 250 ms after problem presentation, and this effect lasts until 280, 350 or 400 ms (e.g., Galfano et al., 2009; Stanescu-Cosson et al., 2000). Since no study has addressed the time course in lateralization due to restrictions in the imaging techniques used, our investigation of SOA effects was exploratory.

In the two experiments reported here, lateralization was examined in two ways: through the presentation of lateralized stimuli and through the selective stimulation of a hemisphere at a time. In Experiment 1, we compared stimulation in the contralateral visual field to TMS stimulation with the interhemispheric sulcus as the control site. In Experiment 2, stimulation in the contralateral field was compared to ipsilateral stimulation as the control site. These two approaches allowed us to give consistency to the results and a more fine grained timing of processes could be observed in Experiment 2. Lateralized presentation was intended to maximize the projections of the stimuli contralaterally and the involvement of the TMS stimulation to each hemisphere. In Experiment 1, the critical comparison concerned RTs after contralateral stimulation vs. central stimulation. Therefore, maximal effects were expected since disruption was compared against a neutral condition. As in Experiment 2, the critical comparison concerned the visual field that was ipsilateral vs. contralateral to the stimulated hemisphere in tracking how and when ipsilateral stimuli presentation differs with the maximum expected disruption after contralateral presentation. Thus this experiment was expected to yield weaker effects due to inter-hemispheric transfer although the comparison between visual fields entailed a finer investigation of interhemispheric differences.

Experiment 1

Method

The procedure was approved by the Ethics Committee of the Department of Psychology of the University of Pavia.

Participants

Twelve right-handed undergraduates participated in the study (mean age: 23 yrs. range 21 to 26; 3 males and 9 females; average + 91% laterality index scores as indicated from the Oldfield Handedness Questionnaire (1971). All of them provided informed consent before the experiment.

Design and Stimuli

The participants were given two types of tasks: addition and multiplication consisting of one-digit operands and operators from 3 to 9. The items were classified as easy and difficult after observing differences in reaction times in a preliminary study involving a different group of four undergraduates who were given the calculation items using the same paradigm as in the main TMS experiments, except that the operations appeared centrally on the screen. During this item classification phase, each of the 28 addition or multiplication items was presented seven times. Each item was then classified as easy or hard on the basis of mean RTs to a button press after arriving to a solution. Easy tasks were defined using the median of RTs as those with RTs of 1042 ms or less for addition and with RTs of 1290 ms or less for multiplication employing the same experimental paradigm as that used during TMS. These criteria served to divide the items in two halves, with 50 % above and below those cut-offs. As the multiplication item classification closely replicated that of Campbell and Graham (1985; see Table 1), RTs proved to be good indices of item difficulty. The use of a varied pool of pairs was intended to maximize the novelty of each pair of operands and solutions to examine the association of the studied areas with problem size variation. Items were divided into easy and hard in order to maximize effects for hard items.

Figure 1 about here

Procedure

The task consisted of the presentation of two lateralized digits to the right visual field or the left visual field in different blocks. Participants were asked to look at a central fixation point while attending parafoveally to the problems. After mentally arriving at a solution for each addition or multiplication task, participants pressed a button with their right hand. They were told to be careful and not to press the button until they really knew the solution. Afterwards they were asked to verbalize the solution; this was a control task in order to assure participants were really calculating. The position of the larger digit in each equation was randomized across trials with the restrictions that the larger digit did not appear first more than twice and the digits could not appear in consecutive equations as commuted pairs (e.g., 3 + 6, 6 + 3). In order to project the digits to the hemisphere to which TMS was applied, the stimuli were presented lateralized with respect to a central fixation asterisk (the 4.6º visual angle of the mathematical sign at the center of the equation). The addition and multiplication equations were presented in three blocks each for each visual field in a total of 12 blocks. The order of the blocks was fully counterbalanced. Within each block, participants were given 112 trials. For each trial, RTs between the interval from the initial display of the equation and button pressing were recorded. Participants were tested in two sessions on different days. In the first session, they received three blocks for addition and three blocks for multiplication. One session included TMS stimulation of the rHIPS, rVIPS, and the control area while, in the other session, TMS was delivered to lHIPS, lVIPS, and the control area. Half the participants began with the first session, while the other half began with the second session. The order of stimulation sites within each session was randomized.

Following the procedure used by Salillas et al. (2009), single pulse TMS was applied at 110% of the phosphene threshold (mean MT=37.4±4.3), with a figure-of-eight coil and a Magstim 200 stimulator. Stimulation was delivered (see Figure 1) either to Talairach coordinates in (1a) the rHIPS or lHIPS (±43, -48, 47), to (1b) the right or left VIPS (±24,-76, 30) or to (1c) the interhemispheric sulcus (central/control site: 0, -76, 30). These points were identified using the SoftTaxic Evolution Navigator system. This system works in absence of radiological images on the basis of digitized skull landmarks (nasion, inion and two preauricular points) from which it maps 40 uniformly-distributed points in the scalp. Talairach coordinates of cortical sites underlying coil locations are then estimated for each subject MRI constructed stereotaxic template. The coil, perpendicular to the scalp surface, was positioned with the handle pointing up either with the wings parallel to the coronal plane when stimulating VIPS, or with the wings 30° from the sagittal plane when stimulating HIPS. The coil position on the stimulation sites was continuously monitored using the navigation software coupled with the Fastrak Polhemus system (1d). Stimulation was delivered at one of four stimulus onset asynchrony (SOA) intervals. These were 150, 200, 250 or 300 ms. after the operation appeared. Single pulse stimulation was delivered after the operation was presented at one of these SOAs randomly.

Results

One participant was excluded from the analysis on the basis on an abnormally high error rate (9 to 16%). The verbal response errors of the other 12 participants were rare (1.8% of answers in multiplication; 1.1% in addition). Two separate 2 (difficulty: easy vs. difficult) X 2 (hemisphere: RH vs LH) X 3 (site: HIPS, VIPS, central) ANOVAs on the proportion of errors in addition and multiplication respectively indicated that errors were associated with item difficulty. More errors were produced in difficult items both for multiplication (3% vs. 0.7%: $F(1,10)=24.5$; $p=0.001$; $\eta^2=0.71$) and for addition (1.5% vs. 0.6%: $F(1,10)=13.4$; $p= 0.004$; $\eta^2=0.57$). Errors were not associated with TMS location. Reaction times (RTs) for each operation were examined in two separate 2 (difficulty: easy vs. hard) X 2 (hemisphere: RH vs. LH) X 3 (site: HIPS, VIPS, central) x 4 SOA (150/200/250/300) ANOVAs. Subsequent RT analyses were carried out using correct responses.

For *addition*, there were no significant main or interaction effects involving hemisphere or SOA (all *F*s < 1). However, there was a significant difficulty X site interaction, $F(2,20)=4.12$; $p=0.03$; $\eta^2=0.29$ (Figure 2a). The effects of site were confined to difficult items: $F(2,20)=3.65$; $p=0.04$ $\eta^2=0.27$. TMS induced disruption in VIPS did not affect performance compared to the control, $F(1,10)=1.92$; $p=0.19$; $\eta^2=0.16$. By contrast, disruption directed at the HIPS bilaterally increased reaction times: $F(1,10)=6.891$; $p=0.02$; $\eta^2=0.41$.

Figure 2 about here

For *multiplication*, there was a significant main effect for site: $F(2,20)=3.40$; $p=0.05$; $\eta^2=0.25$, as well as a significant difficulty x site interaction effect: $F(2,20)=5.35$; $p=0.018$; $\eta^2=0.35$, and a difficulty x hemisphere x site interaction effect, $F(2,20)=5.48$; $p=0.02$; $\eta^2=0.35$ (Figure 2b). Again significant effects were confined to the difficult items, $F(2,20)=4.23$; $p=0.03$; $\eta^2=0.30$. Interference to VIPS bilaterally compared to the relevant central control sites significantly increased RTs, for rVIPS, $F(1,10)=6.62$; $p=0.03$; $\eta^2=0.40$; for lVIPS, $F(1,10)=6.75$; $p=0.03$; $\eta^2=0.40$. Although disruption directed at lHIPS compared to the relevant control site also resulted in significantly increased RTs, $F(1,10)=6.14$; $p=0.03$; $\eta2=0.38$, disruption of the rHIPS did not, $F(1,10) < 1$, $\eta2<0.01$. In both analyses, the SOA main effect was significant, addition: $F(3,30) = 4.31$; $p=0.012$; $\eta2 =0.30$; multiplication: $F(3,30)=6.42$; $p=0.006$; $\eta2 =0.39$. Addition was significantly more impaired with SOAs of 250 ms (*M* =1161.3, *SD* = 152.9) and 300 ms (*M* =1114.63, *SD*=137.4) compared to an SOA of 150 ms. (*M* =1155.6, *SD* =145.8), F (1,10) >5.10; p >0.88; η2 > 0.33. Multiplication was significantly more impaired with SOAs of 250 ms (*M*=1419.1, *SD* = 176.4) and 300 ms (*M* = 1421.1, *SD* =172.1) compared to SOAs of 150 ms. (*M*=1369.2, *SD* =174.4) and 200 ms. (*M* =1381.8, *SD* =169.8), *Fs* (1,10) >6.41; p > 0.002; η2 > 0.35. However, there were no significant interaction effects involving SOA.

Size effects in rVIPS. The effects of TMS-induced disruption on the rVIPS for multiplication were related to solution size. Regression analyses of solution size using the difference between RTs for each site stimulated and control sites as the dependent measure revealed that solution size significantly decreased calculation efficiency only in the case of TMS induced disruption to the rVIPS (*t*=3.39; *ß*=0.7; *p*<0.005) for the difficult multiplication items. There were no significant relationships for other sites of disruption or for either the easy or difficult addition items or for the easy multiplication items. For either addition or multiplication, the order of the larger and smaller numbers in the operation (e.g., 3 + 6 vs. 6 + 3; 3 X 6 vs. 6 X 3) did not significantly influence RTs.

Table 1 about here

The goal of Experiment 2 was to compare the effects of ipsilateral vs. contralateral stimulation for both VIPS and HIPS sites – a contrast aimed to provide fine grained comparisons between hemispheres. In addition, structural MRIs were used to localize the sites in order to facilitate precise localization of the sites with respect to that in Experiment 1. As the contralateral hemisphere serves to process preferentially lateralized stimuli, our hypothesis was that contralateral TMS stimulation would impair calculation efficiency compared to ipsilateral stimulation. We expected a similar pattern of results as in Experiment 1 such that (1) stimulation to the HIPS bilaterally either to the RH or LH would impair efficiency in addition and that (2) stimulation to the VIPS bilaterally either to the RH or LH would impair efficiency in multiplication. Further, we hypothesized that multiplication would be impaired by stimulation directed at the lHIPS compared to the rHIPS. Thus although Experiment 2 aimed again to characterize the lateralization pattern for exact calculation, our comparison of ipsilateral versus contralateral stimulation allowed for a more precise look at the interplay of the two hemispheres along time.

Experiment 2

Method

The procedure was approved by the Ethics Committee of the Department of General Psychology of the University of Padua.

Participants

These were 10 right-handed undergraduates (mean age: 24 yrs, range 23 to 27; 3 males and 7 females; average + 83.3% laterality index as indicated on the Oldfield Handedness Questionnaire (1971)). All provided informed consent before the experiment. None had been participants in Experiment 1.

Stimuli

The material was identical to Experiment 1, with the exception that only difficult items for both operations were used since these produced the strongest effects in Experiment 1.

Procedure

The session consisted of 16 blocks as a combination of site of stimulation (HIPS/VIPS), hemisphere (left/right), visual field for the stimulus (ipsilateral/contralateral) and operation. The order of blocks was randomized between participants and none of them was given the same order. The procedure was otherwise identical to that of Experiment 1.

As in Experiment 1, single pulse TMS was applied at 110% of the phosphene threshold (mean MT=55.3±3.6), with a figure-of-eight coil and a Magstim Rapid^2 stimulator. Stimulation was delivered either to VIPS and HIPS, either to left and right hemispheres following the same coil positions used in the previous experiment. The TMS coil was placed on the skull of each subject and continuously monitored during the whole experiment with the Brainsight stereotaxic neuronavigator (Rogue Research Inc, Montreal, Canada) coupled with a Polaris Vicra infrared camera system (NDI, Waterloo, Canada) using individual MRI images of the participants. T1-weighted MR scans were obtained from each participant using a Signa 3T system GE Healthcare, Milwaukee, WI, USA (1.3 × 1.3 × 1.3 mm, sagittal acquisition). The four sites were localized through optical inspection of anatomical MRI images considering for VIPS the ventral part of the caudal IPS and for HIPS the site between the two giri separated by the anterior part of the IPS, 1 cm posterior to the postcentral girus (see resulting average coordinates in Table 2). Stimulation was again delivered at one of four SOAs intervals: 150, 200, 250 and 300 ms. after each item had been presented.

Table 2 about here

Results

Participants' verbal response errors were infrequent (2% for addition and 3 % for multiplication) and did not follow any systematic pattern. RTs are shown in Table 2. Two separate 2 (site: VIPS/HIPS) x 2 (hemisphere: left/right) x 2 (visual field: ipsilateral/contralateral) x 4 (SOA: 150/200/250/300) ANOVAs were performed for each operation.

For *addition***,** only the site x hemisphere x visual field x SOA interaction was significant ($F(3, 27)= 6.62$; $p=0.002$; $\eta2=0.42$). There were no other significant main or interaction effects. We then proceeded to analyze each stimulation site separately to determine the extent of lateralization effects.

For HIPS, the hemisphere x visual field x SOA interaction was not significant, ($F(3,27)=1.93$; $p=0.14$; $\eta2 =0.18$) indicating, as in Experiment 1, the absence of significant effects for hemisphere. For VIPS, the hemisphere x visual field x SOA interaction effect was significant ($F(3,27)=6.38$; $p=0.005$; $\eta2 =0.41$). However, there were no simple main or interaction effects for either hemisphere or for any of the SOAs (see Figure 3 and Table 2)

Figure 3 about here

For *multiplication,* no main or interaction effects were significant, although the site x hemisphere x visual field marginal interaction approached significance ($F(1,9)=3.54$; $p=0.09$; $\eta2=0.28$). A separate analysis for each site revealed a significant hemisphere x visual field x SOA interaction ($F(3,27)=3.48$; $p=0.03$; $\eta2=0.28$) for HIPS. Similar to Experiment 1, simple effects tests showed a visual field effect restricted to lHIPS. However, this effect was only significant at the 300 ms. SOA ($F(1,9)=5.27$; $p=0.047$; $\eta2=0.37$). Again as in Experiment 1, the analysis for VIPS showed a significant visual field main effect ($F(1,9)=6.35$; $p=0.03$; $\eta2=0.41$) but also there was a significant visual field x hemisphere interaction ($F(1,9)=6.35$; $p=0.03$;$\eta2=0.41$), with the effect of visual field restricted to the rVIPS ($F(1,9)=7.92$; $p=0.02$; $\eta2=0.47$). This significant effect extended throughout 150 ms. to 250 ms. SOAs (150 ms: $t=2.51$, $p=0.03$; false discovery rate (FDR) correction $p=0.049$); 200 ms: $t=2.76$, $p=0.02$; FDR $p=0.049$; 250 ms: $t=2.44$, $p=0.037$; FDR $p=0.049$), becoming marginal at 300 ms ($t=1.99$, $p=0.07$; FDR $p=0.07$).

Table 3 about here

Size effects in rVIPS. A regression analysis between the different sites/visual field/SOAs and the size of the result in an analysis by items showed a significant relationship between rVIPS disruption and the size of the result. The difference of RTs after contralateral minus ipsilateral stimulation was predicted by the problem size ($t=2.28$; $p=0.04$; $\beta=0.5$).This relationship became larger when only those SOAs with significant effects were considered (150 ms. to 250 ms.) ($t=2.56$; $p=0.02$; $\beta=0.6$).

DISCUSSION

Both left and right IPS were implicated in efficiency of exact calculation. Overall, results from Experiments 1 and 2 converge in showing that disruption of IPS in either hemisphere compared to control sites or contrasting ipsi vs. contralateral visual presentation results in loss of efficiency in the form of increased RTs. This result occurs both in addition and multiplication.

Addition differs from multiplication. For *addition,* disruption of the HIPS in either hemisphere compared to control sites results in loss of efficiency in the form of increased RTs. rHIPS disruption is consistent with the use of the analogue magnitude representation jointly with verbal coding strategies (Göbel et al, 2001). By contrast, for *multiplication*, significantly increased RTs resulted only from disruption of the lHIPS – and not the rHIPS. However, disruption to the rVIPS was as effective as lHIPS disruption in increasing RTs on multiplication items. The absence of a widespread increase across SOAs in RTs following disruption to the lVIPS in Experiment 2 points to a weaker involvement of this site compared to the rVIPS. Solution size predicts the extent of TMS disruption to the rVIPS. This result indicates an overlap between number processing and the motion representation and automatization of cognitive function that has been shown to occur in this region (Cohen-Kadosh et al., 2007; Orban et al., 2003). As we have noted, it has been shown in a related study that TMS induced interference in VIPS affects both motion perception and numerical comparison (Salillas et al., 2009). Efficient calculation is based on the automatic retrieval of multiplication facts. This process involves scanning correct products as well as cohort candidate solutions (Campbell, 1994; Galfano et al., 2003). For example, the selection of 56 as the correct product to 7 X 8 involves scanning cohort solutions such as the table errors 49 and 54. Impairment to this automatized scanning process through TMS-induced disruption to the rVIPS points to the presence of a RH network that supports multiplication – one that is retained by persons with LH lesions (Varley et al., 2005) and that may be impaired by RH damage (Granà et al., 2006). Thus, although both addition and multiplication imply bilateral IPS, specific recruited areas for each operation differ, and rHIPS is only important for addition as proposals based on learning processes suggest (Siegler and Shipley, 1995; Siegler and Shrager, 1984).

Patterns of lateralization along time. Involvement of both hemispheres appears in fact to be sustained across time. Lateralization tends to appear when the process of result retrieval is disrupted through stimulation on lHIPS at a late onset time (300 ms), however. This lateralization in lHIPS is found for multiplication at this SOA but again, a sustained disruption of the retrieval process is found while disrupting rVIPS from 150 ms. SOAs until a later lateralization to lHIPS. The tendency for a late lateralization to the lHIPS suggests involvement of visuospatial processes early during calculation. Other studies have focused on lateralization during fact retrieval using repetitive TMS. Left lateralization has been found using this technique and focusing on left angular gyrus (lANG: Göbel et al., 2001) with a very different experimental paradigm. While a lateralization was found on lANG, stimulating IPS has led to a bilateral pattern in the recent report of Andres et al. (2011). Our investigation is the first to address patterns of lateralization in the IPS using single pulse TMS with different SOAs and provides a description of the temporal course of the bilateral involvement. In our study, we included an observation of the role of VIPS in the automatization of solution search, indicating that use of repetitive stimulation in periods up to 300 ms after stimulus may not reveal possible rapid changes in the use of right and left areas of IPS or even lANG. This temporal sensitivity is lacking both in neuroimaging studies using fMRI and of course in patient data.

A methodological limitation for the present study comes from the anatomical localization used to identify the target regions that may have added a source of variability, as suggested by Rosenberg-Lee et al. (2011). However, we used a single pulse paradigm that, with respect to rTMS studies, decreased the probability that the stimulation would spread to other regions, thus limiting variability in the TMS methodology.

In sum, our investigation demonstrates for the first time using evidence from TMS that simple addition and multiplication calculations involve different RH and LH substrates. For addition, disruption to both rHIPS and lHIPS resulted in impaired efficiency. For multiplication, efficiency was unaffected by disruption to the rHIPS. However, disruption of the rVIPS resulted in a loss of efficiency and increased RTs and these effects were significantly related to problem size. Although adults – at least in Western cultures – may have achieved efficient, automatized calculation though a verbally-mediated route during childhood (Rivera et al. 2005; Tang et al., 2006), verbal mediation may no longer be sufficient for calculation in the mature cognitive system and numerical processing may also rely on visual representation of numerals and arithmetic facts.

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Table 1. Items used in the experiment for addition and multiplication (D=Difficulty; H=Hard; E=Easy). For multiplication, the disruption index average is provided based on the RT difference when rVIPS, lVIPS, rHIPS or lHIPS is disrupted by TMS minus the RT when the control-central site is disrupted. Item= number of the item. Num1 and num2 = numbers presented for addition and multiplication items. Res= correct calculation result.

ADDITION						**MULTIPLICATION**								
item	num1	num2	res	D		item	num1	num2	res	D	rVIPS	rHIPS	lVIPS	lHIPS
1	3	3	6	E		1	3	3	9	E	64,14	2,01	288,80	185,08
2	3	4	7	E		2	3	4	12	E	132,20	140,34	105,05	84,82
3	3	5	8	E		3	3	5	15	E	41,46	-94,28	233,54	108,47
4	3	6	9	E		4	3	6	18	E	289,62	182,39	116,75	219,97
5	3	7	10	E		5	3	7	21	E	-88,85	-125,91	199,99	195,52
6	3	8	11	H		6	3	8	24	E	68,91	66,69	218,00	166,60
7	3	9	12	H		7	3	9	27	E	200,13	54,25	192,85	131,93
8	4	4	8	E		8	4	4	16	E	188,31	32,24	341,42	123,11
9	4	5	9	E		9	4	5	20	E	159,09	-91,20	246,22	110,84
10	4	6	10	E		10	4	6	24	H	191,06	122,28	63,30	565,45
11	4	7	11	H		11	4	7	28	H	268,89	-47,76	262,14	108,69
12	4	8	12	H		12	4	8	32	H	130,38	169,79	230,73	193,96
13	4	9	13	H		13	4	9	36	H	261,60	-19,50	297,67	261,42
14	5	5	10	E		14	5	5	25	E	-30,42	-68,02	349,88	-9,55
15	5	6	11	E		15	5	6	30	H	103,16	11,23	174,35	59,20
16	5	7	12	H		16	5	7	35	H	58,89	1,89	250,23	18,91
17	5	8	13	H		17	5	8	40	H	-2,33	-19,33	204,79	183,72
18	5	9	14	H		18	5	9	45	H	224,09	-52,84	203,78	196,95
19	6	6	12	E		19	6	6	36	E	48,69	-1,49	194,35	-16,06
20	6	7	13	H		20	6	7	42	H	215,66	-63,23	202,73	354,30
21	6	8	14	H		21	6	8	48	H	197,57	97,55	18,21	158,58
22	6	9	15	H		22	6	9	54	H	467,25	27,57	603,31	308,74
23	7	7	14	E		23	7	7	49	E	220,79	204,89	278,82	436,92
24	7	8	15	H		24	7	8	56	H	492,32	-110,98	453,80	668,78
25	7	9	16	H		25	7	9	63	H	992,76	338,77	629,66	519,31
26	8	8	16	E		26	8	8	64	H	222,57	47,93	-114,84	74,84
27	8	9	17	H		27	8	9	72	H	628,49	256,24	303,63	529,02
28	9	9	18	E		28	9	9	81	E	265,23	185,35	152,73	135,75

Table 2. Mean Talairach coordinates and standard deviations for TMS stimulation in Experiment 2.

	X	Y	Z	sdX	sdY	sdZ
lVIPS	-26.6	-84.3	33.3	2.6	3.8	4.3
rVIPS	26.5	-83.8	33.1	3.1	2.7	4.8
lHIPS	-44.1	-49.6	46.2	2.9	4.2	3.2
rHIPS	44.9	-50.0	48.4	2.0	2.5	2.6

Table 3. Effects of SOA in Experiment 2. RTs and (SD) depending on site of stimulation, hemisphere, Visual field for each SOA.

ADDITION	SOA	**CONTRALATERAL**		**IPSILATERAL**	
		LH	RH	LH	RH
HIPS	150	1220.9 (584.3)	1257.5 (588.5)	1180.8 (576.9)	1191.1 (503.3)
	200	1329.5 (616.2)	1295.4 (565.3)	1093.8 (410.5)	1209.6 (558.7)
	250	1233.6 (565.9)	1255.7 (536.6)	1147.2 (474.1)	1284.7 (609.1)
	300	1304.7 (593.5)	1380.6 (576.4)	1143.2 (464.1)	1215.8 (518.3)
VIPS	150	1312.9 (531.6)	1136.1 (486.8)	1144.4 (366.6)	1205.7 (512.3)
	200	1217.7 (546.3)	1260.8 (533.5)	1256.7 (446.8)	1228.5 (508.1)
	250	1219.8 (509.1)	1141.7 (473.3)	1212.3 (437.5)	1269.5 (513.5)
	300	1207.4 (44404)	1170.1 (512.4)	1237.2 (387.3)	1217.9 (471.4)

MULTIPLICATION	SOA	CONTRALATERAL		IPSILATERAL	
		LH	RH	LH	RH
HIPS	150	1603.9 (382.8)	1462.9 (470.8)	1396.8 (453.3)	1423.7 (499.6)
	200	1514.4 (502.9)	1422.8 (586.7)	1422.2 (445.3)	1437.1 (649.5)
	250	1527.9 (349.1)	1485.1 (586.9)	1411.8 (527.9)	1389.7 (675.1)
	300	1586.8 (508.7)	1404.8 (472.2)	1324.3 (476.1)	1590.3 (639.5)
VIPS	150	1327.5 (488.6)	1455.7 (509.4)	1356.5 (278.6)	1176.6 (424.4)
	200	1391.5 (609.3)	1506.7 (445.3)	1368.9 (521.8)	1176.3 (422.7)
	250	1441.4 (547.4)	1575.7 (663.9)	1451.1 (479.2)	1185.3 (424.9)
	300	1371.1 (513.9)	1445.2 (530.9)	1396.8 (447.1)	1250.5 (397.6)

Figure 1. Sites of TMS-induced interference. a) right and left VIPS b) right and left HIPS c) central control regions d) bidimensional representation of the TMS stimulation sites obtained through the FasTrak Polhemus neuronavigation system.

Figure 2. RTs as a function of site of stimulation for Experiment 1. RTs (ms.) for addition (a) and multiplication (b) under TMS directed at the VIPS, HIPS, and central control regions in the RH and LH for the easy and hard items with 95 % confidence intervals.

Figure 3. RTs as a function of site of stimulation for Experiment 2. RTs (ms.) for addition (a) and multiplication (b) under TMS directed to HIPS and VIPS in the RH and LH for ipsilateral or contralateral stimuli presentation. RTs are plotted with 95% confidence interval.