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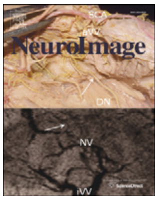

Role of distinct parietal areas in arithmetic: An fMRI-guided TMS study

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ABSTRACT

Although several parietal areas are known to be involved in number processing, their possible role in arithmetic operations remains debated. It has been hypothesized that the horizontal segment of the intraparietal sulcus (hIPS) and the posterior superior parietal lobule (PSPL) contribute to operations solved by calculation procedures, such as subtraction, but whether these areas are also involved in operations solved by memory retrieval, such as multiplication, is controversial. In the present study, we first identified the parietal areas involved in subtraction and multiplication by means of functional magnetic resonance imaging (fMRI) and we found an increased activation, bilaterally, in the hIPS and PSPL during both arithmetic operations. In order to test whether these areas are causally involved in subtraction and multiplication, we used transcranial magnetic stimulation (TMS) to create, in each participant, a virtual lesion of either the hIPS or PSPL, over the sites corresponding to the peaks of activation gathered in fMRI. When compared to a control site, we found an increase in response latencies in both operations after a virtual lesion of either the left or right hIPS, but not of the PSPL. Moreover, TMS over the hIPS increased the error rate in the multiplication task. The present results indicate that even operations solved by memory retrieval, such as multiplication, rely on the hIPS. In contrast, the PSPL seems to underlie processes that are nonessential to solve basic subtraction and multiplication problems.

Introduction

The role of the parietal lobe in mental calculation is supported by a long-lasting tradition of neuropsychological studies showing that parietal lesions often result in number processing or calculation impairments (Cipolotti and Lacy-Costello, 1995; Dehaene and Cohen, 1991, 1997; Delazer and Benke, 1997; Gerstmann, 1930; Hécaen et al., 1961; Mayer et al., 1999; McCloskey et al., 1986; Pesenti et al., 1994; Takayama et al., 1994). In the past 10 years, brain imaging results have strengthened this view but they have also suggested that distinct areas of the parietal cortex may be involved in different aspects of mental calculation (Chochon et al., 1999; Dehaene, 1999, 2009; Lee, 2000; Pesenti et al., 2000b; Piazza et al., 2006; Dehaene et al., 2003; Nieder and Dehaene, 2009). The processing of number magnitude has been assigned to the bilateral horizontal segment of the intraparietal sulcus (hIPS) and to the bilateral posterior superior parietal lobule (PSPL), a region extending from the posterior segment of the IPS to the precuneus (Dehaene et al., 2003). Functional magnetic resonance imaging (fMRI) studies showed that, in these two areas, the blood–oxygen level-dependent (BOLD) signal is modulated by the same arithmetic factors, such as problem size (Stanescu-Cosson et al., 2000), number of operands (Menon et al., 2000) and strategy (Delazer et al., 2003, 2005; Ischebeck et al., 2006). However, only the hIPS showed a selective activation during subtraction when compared to manual, visuospatial or linguistic tasks (Simon et al., 2002). Further studies showed that activation in the left and right hIPS is intrinsically related to number magnitude (Eger et al., 2009; Piazza et al., 2004, 2007). In contrast, in the PSPL, overlapping activations were found during calculation and saccade tasks (Knops et al., 2009a; Simon et al., 2002), suggesting that this area may provide a visuospatial medium for solving arithmetic problems (Dehaene, 2009; McCrink et al., 2007; Hubbard et al., 2005; Knops et al., 2009b). Although the right hemisphere was originally thought to house this visuospatial medium (Dehaene and Cohen, 1995; Zago et al., 2008), further fMRI studies revealed an equal contribution of the left and right PSPL to addition and subtraction. In some studies, a relative right hemisphere dominance was observed during addition and subtraction tasks in the context of bilateral activation (Menon et al., 2000; Zhou et al., 2007). Studies with split-brain patients suggest that the left hemisphere is sufficient to perform all arithmetic operations, whereas the right hemisphere would be endowed with basic abilities for solving small addition and subtraction problems and approximating the result of large problems (Andres et al., 2005; Gazzaniga and Smylie, 1984; Funnell et al., 2007).

Whereas several brain imaging results confirmed the involvement of the hIPS and PSPL in addition and subtraction, their contribution to multiplication remains unclear. In contrast to subtraction problems that are assumed to rely on calculation procedures, it has been proposed that the responses to multiplication problems are retrieved

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directly from long-term memory (Campbell, 1987, 1994; Dehaene, 1992; LeFevre et al., 1996; McCloskey, 1992). Retrieval-based strategies refer to the automatic activation of learned associations between a problem and its answer (Ashcraft, 1992). Some authors made the additional assumption that this memory retrieval is mediated by verbal processes (Cohen et al., 2000; Dehaene and Cohen, 1995). According to this view, the operations relying on memory retrieval would depend on a left-lateralized language network, including perisylvian and sub-cortical areas (Delazer et al., 2004; Pinel and Dehaene, 2010; Zhou et al., 2007), as well as the left angular gyrus (ANG), an area of the inferior parietal lobule known for its contribution to reading and verbal short-term memory tasks (Fiez and Petersen, 1998; Lee, 2000; Paulesu et al., 1993; Price, 1998; Simon et al., 2002; Zago et al., 2008). The left ANG is assumed to be essential only for the arithmetic problems whose result is retrieved mechanically from long-term memory (Dehaene et al., 2003). This view has received empirical support from fMRI studies contrasting retrieval versus calculation procedures (Grabner et al., 2009a), trained versus untrained problems (Delazer et al., 2003, 2005) or exact versus approximate calculation (Dehaene, 1999).

However, the view that subtraction and multiplication rely on distinct brain networks faces several discrepancies. Indeed, several brain imaging studies have evidenced an increased activation in the hIPS when solving simple multiplication problems (Chochon et al., 1999; Delazer et al., 2003; Fehr et al., 2007; Fulbright et al., 2000; Hayashi et al., 2000; Jost et al., 2009; Kazui et al., 2000; Rickard et al., 2000; Zago et al., 2001). Moreover, some studies showed that language areas were not activated and sometimes even deactivated during the retrieval of arithmetic facts (Keller and Menon, 2009; Pesenti et al., 2000b; Rickard et al., 2000; Venkatraman et al., 2005; Zago et al., 2001). Neuropsychological data also question the idea that operations solved by memory retrieval rely exclusively on language areas. Indeed, some aphasic patients are capable of solving multiplication problems which they are unable to read aloud (e.g., when presented with 8 + 5, the patient read «*two plus four*» but correctly answered *13*; Rossor et al., 1995; Warrington, 1982; Whalen et al., 2002). Finally, because brain imaging studies only provide correlative data, it is currently impossible to determine which parietal areas are causally involved in a given arithmetic operation. This issue is also difficult to address in brain-lesioned patients because of the close proximity of the aforementioned areas and the uncertainty relative to the location and size of the lesions.

The present study aimed at clarifying the contribution of the parietal lobe to arithmetic operations by combining fMRI and repetitive transcranial magnetic stimulation (rTMS). FMRI was first used to identify, in each participant, the parietal areas activated during subtraction and multiplication tasks. In a second step, rTMS was applied exactly over the same areas while participants performed the same tasks to test the causal relationship between the disrupted area and each operation. Under the assumption that the hIPS is engaged in arithmetic operations solved by calculation procedures and not in those solved by memory retrieval, this area should be more activated during subtraction than multiplication and its virtual lesion should increase response latencies (RLs) and/or error rates during subtraction only. Alternatively, the finding that rTMS over the hIPS also affects multiplication would mean that it could actually contribute to the retrieval of arithmetic problems from memory. If the two hIPS are necessary for these arithmetic operations, as suggested by neuroimaging studies, performance should be impaired by either a left or right virtual lesion. Finally, under the assumption that memory retrieval and calculation procedures are mediated by verbal and visuospatial processes, respectively, increased activity should be observed in the left ANG during multiplication whereas the right PSPL should be selectively activated during subtraction. In contrast, an absence of activation in the left ANG during multiplication would corroborate recent evidence suggesting that overlearned operations do not necessarily depend on verbal representations. Although there is a larger consensus about the activation of the PSPL during arithmetic operations solved by calculation procedures, it is still unknown whether its integrity is required to perform these operations. The right hemisphere dominance observed in some visuospatial tasks predicts a superiority of the right over the left PSPL during subtraction (Dehaene and Cohen, 1995; Zago et al., 2008), suggesting that virtual lesions of the left PSPL should be compensated by the right PSPL contribution.

Material and methods

Participants

Ten French-speaking males (mean age and S.D.: 21 ± 2 years), right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971), gave their informed consent to participate to both the fMRI and TMS experiments. They had normal vision and none of them had experienced a neurological disease or mathematical disabilities. They were screened for risk factors by a neurologist before each experiment (Keel et al., 2001). The TMS experiment took place within 10 months following the acquisition of fMRI data. All procedures were approved by the Biomedical Ethical Committee of the Université catholique de Louvain.

fMRI experiment

Tasks and stimuli

Single Arabic digits between 3 and 9 were displayed in black on a white background in the centre of a computer screen (maximum visual angle: 5°). Participants were instructed to subtract mentally the presented digit from 11 or 13, or to multiply it by 3 or 4, and to provide the response verbally. Instructions emphasized both speed and accuracy. The arithmetic problems were chosen to equate the average RL and error rate across the two operations while keeping the set of digits identical in the visual display. Ties (i.e., problems including similar digits: 3×3) or problems including digits 2 or 5 were not included because they may benefit from a distinct access in memory or may be decomposed into multiple additions (Campbell and Graham, 1985; De Brauwer et al., 2006; LeFevre et al., 1996, 2004). In the reference condition, participants were asked to read aloud uppercase letters (C, D, F, G, H, J) displayed in the same format as Arabic digits (see Fig. 1A).

fMRI protocol

High-resolution anatomical images were first acquired for each participant using a T1-weighted 3D turbo fast field-echo sequence with an inversion recovery prepulse (TE = 4.6 ms, TR = 9.1 ms, Flip angle = 8°, Field of view (FOV) = 220 × 197 mm, 150 contiguous axial slices of 1 mm, voxel size = 0.81 × 0.95 × 1 mm, SENSE factor = 1.4). This was followed by 4 runs of functional data acquisition. Functional images were acquired with a 3.0 Tesla magnetic resonance imager and an 8-channel phased array head coil (Achieva, Philips Medical Systems) as series of blood-oxygen-sensitive T2*-weighted echo-planar image volumes (GRE-EPI). Each run consisted of 132 volumes and was preceded by 4 dummy scans to allow for magnetic saturation effects. Acquisition parameters were: TE = 50 ms, TR = 2500 ms, Flip angle = 90°, FOV = 220 × 220 mm, 36 slices acquired in an ascending interleaved sequence, slice thickness = 3.5 mm with no interslice gap, SENSE factor (parallel imaging) = 2.5. Head movement was limited by foam padding within the head coil and a restraining band across the forehead.

We used a block-design paradigm with short blocks of 5 trials (1 digit/letter every 3500 ms for a total duration of 17500 ms), interleaved with 10000 ms fixation periods, to optimize the signal-to-noise ratio while controlling speech-related head motion artefacts. Indeed, the peak of the BOLD signal is expected to occur 6 s after the

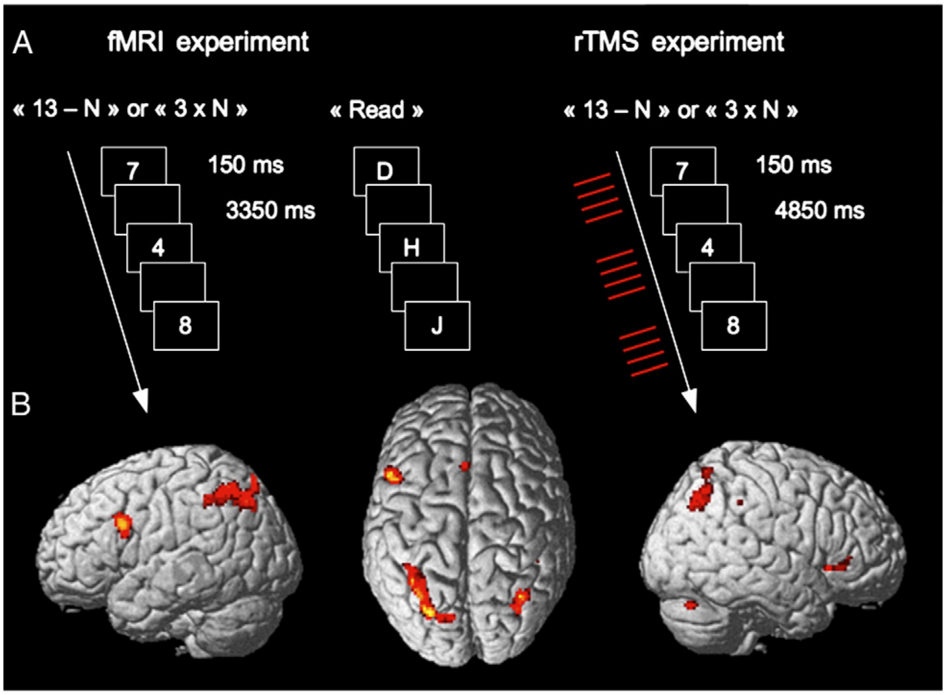

Fig. 1. Experimental procedure. (A) Time course of stimulus presentation. In the fMRI experiment, a reading task was used as a reference condition. In the TMS experiment, 4 pulses (red) were delivered with a 10 Hz frequency 100 ms after stimulus onset. (B) Regions showing increased activity during subtraction and multiplication, as revealed by a conjunction analysis of the two arithmetic tasks (images are displayed with a threshold set at $p<0.001$ uncorrected; minimal cluster size (k) = 10 voxels). A neuronavigation system was used to position the TMS coil over the site showing maximal activation in the left/right hIPS or PSPL in each individual.

stimulus display, whereas the speech-induced head movements should be observed within 3500 ms after the stimulus display. Therefore, at the level of one trial, the time course of the BOLD signal was desynchronized from the time course of head movement artefacts and the event-related response should not be affected (Birn et al., 1999). However, as the number of trials increases, artefacts are more likely to overlap with the BOLD response. Simulations of this interaction showed that a 17500 ms block, including no more than 5 trials, offers a good compromise between a low sensitivity to artefacts and a high signal-to-noise ratio (Birn et al., 2004).

Experimental procedure

Subtraction and multiplication were tested separately in 4 runs following an ABBA order in half of the participants and a BAAB in the others. Each run included 6 blocks of the same arithmetic task interleaved with 6 blocks of letter reading. In each block, 5 different numbers/letters were presented, in a random order, for 150 ms with a 3500 ms inter-stimulus interval (ISI; see Fig. 1A). Each digit/letter was presented 5 times in each run. The stimulus display was controlled by E-prime 2.0 (Schneider et al., 2002) and verbal responses were recorded by a digital recorder. The recorder was placed in an anechoic box, outside the scanner room. The auditory signal was conveyed to the anechoic box through a 10 m plastic tube connected to an oxygen mask placed over the participant's mouth. Before the experiment, participants were trained to produce audible responses while keeping bucco-laryngo-facial movements to a minimum. Accordingly, during data acquisition, head movements did not exceed a 1 mm displacement or 1 degree rotation along the x, y and z axes.

Data analysis

Data were processed and analyzed using Statistical Parametric Mapping (SPM2, Welcome Department of Cognitive Neurology, London, UK, <http://www.fil.ion.ac.uk/spm>). Functional images were (1) corrected for slice acquisition delays, (2) re-aligned to the first scan of the first run (closest to the anatomical scan) to correct for within- and between-run motion, (3) coregistered with the anatomical scan, (4) normalized to the MNI template using an affine fourth degree β-spline interpolation transformation and a voxel size of $2\times2\times2$ mm^3 after the skull and bones had been removed with a mask based on the individual anatomical images, and (5) spatially smoothed using an 8-mm FWHM Gaussian kernel. Condition-related changes in regional brain activity were estimated for each participant by a general linear model in which the responses evoked by each condition of interest were modeled by a standard hemodynamic response function. The contrasts of interest were first computed at the individual level to identify the cerebral regions significantly activated by subtraction or multiplication. Significant cerebral activations for the critical contrasts (subtraction *versus* letter reading; multiplication *versus* letter reading; multiplication *versus* subtraction; subtraction *versus* multiplication) were then examined at the group level in random-effect analyses using one-sample t-tests and analyses of variance (ANOVA) with the statistical threshold set at $p<0.05$ (FWE corrected at the cluster level) and extending to at least 150 contiguous voxels (k).

The audio recordings collected during the fMRI experiment were filtered, using a specific noise cancellation tool to separate the verbal responses from the MR noise (Cusack et al., 2005). A trigger signal controlled by E-prime allowed us to detect the beginning of each block in the audio recordings and to measure RLs with respect to the onset of each stimulus. The mean RL of correct trials and the error rate were compared between the two arithmetic tasks using paired t-tests after removing outlier RL>3 S.D. (1.4 ± 1%) and trials where audio recordings could not be filtered appropriately (0.9 ± 1.5%).

TMS experiment

Tasks and stimuli

Tasks and stimuli were the same as in the first experiment, except for the reference condition (letter reading) which was specific to the fMRI design. Instructions emphasized both speed and accuracy.

TMS protocol

Based on the results of our fMRI experiment, we focussed on four stimulation sites, located in the hIPS and PSPL of each hemisphere. The coordinates of the TMS sites were defined individually by selecting, in each region, the voxel showing the maximal increase of activity in the single-participant analysis testing the conjunction of the t-contrasts between each operation and letter reading (see Fig. 1B). During the TMS experiment, the stimulation sites were localized on-line on the participant's scalp through a neuronavigation system that allowed us to visualize the coil position with respect to the projection of each site onto the individual MRI with a spatial accuracy close to the mm (Noirhomme et al., 2004). The vertex was used as a control site. In each trial, four TMS pulses were delivered during 300 ms, at a 10 Hz frequency and an intensity of 65% of the stimulator output, by means of a Magstim Rapid stimulator through a 35-mm inner diameter figure-of-eight coil (Magstim Company, Whitland, UK).

Experimental procedure

The five TMS sites (left and right hIPS, left and right PSPL, vertex) were tested in separate runs, following a random order, with the constraint that each site should be assigned twice to each position in the sequence across the 10 participants. Within each run, 4 blocks of subtraction problems and 4 blocks of multiplication problems were presented alternatively, with half of the participants starting with subtraction problems. These blocks were interleaved with fixation periods of 5000 ms. The arithmetic task was cued at the beginning of each block (e.g. "multiply by 3") and participants were asked to perform the same task with 10 digits presented successively. The digits were displayed for 150 ms, with an ISI of 5000 ms, and rTMS was applied 100 ms after the digit onset (see Fig. 1A). The display device was the same as in the fMRI experiment. A microphone was used to record verbal responses and RLs were measured on-line by E-prime.

Data analysis

The behavioural data collected during the TMS experiment were analysed with SPSS after removing, on a subject-by-subject basis, trials in which the microphone failed to trigger (1 ± 2%) or in which the RL exceeded the individual mean RL ± 3 S.D. (2 ± 1%). In the first part of the analysis, the data collected for the left and right homologue sites were pooled together before computing the mean RL and error rate for each task and each site, irrespective to hemispheric lateralization, the vertex being undefined in terms of left or right localization. An ANOVA was conducted on these values with TASK (subtraction vs. multiplication) and SITE (vertex vs. hIPS vs. PSPL) as within-subject factors. In order to investigate hemispheric lateralization, we performed a second ANOVA with TASK (subtraction vs. multiplication), SITE (hIPS vs. PSPL) and HEMISPHERE (left vs. right) as within-subject factors. The Greenhouse–Geisser procedure was used to correct the degrees of freedoms when the sphericity assumption was violated. Paired t-tests were used for post-hoc comparisons (one-tailed, $p<0.05$ corrected for multiple comparisons using the stepwise Bonferroni–Holm procedure; Holm, 1979).

Results

fMRI experiment

Behavioural data failed to reveal a significant difference of performance between multiplication (mean RL ± SD: 810 ± 257 ms and 1.7 ± 1.3% errors) and subtraction (mean RL ± SD: 903 ± 260 ms, $t(9)=1.7$, *ns*; and 2 ± 0.9% errors, $t(9)=1.4$, *ns*). Concerning functional data, the contrast between each arithmetic task and the letter reading task revealed similar activations for subtraction and multiplication in the parietal and frontal lobes (see Table 1). A conjunction analysis of these contrasts confirmed that the parietal lobe was involved in both arithmetic operations. Increased activation was observed in the bilateral PSPL and in the left hIPS (see Fig. 1B). A small cluster was also found in the right hIPS at an uncorrected level ($p<.001$). Subtraction and multiplication also recruited common areas in the left inferior frontal gyrus (IFG), the left supplementary motor area (SMA), the right insula and the right cerebellum. Results did not show any region that was more activated during subtraction than multiplication, whereas additional activations were found bilaterally in the middle (MTG) and superior (STG) temporal gyrii during multiplication (see Fig. 2). There was no evidence for an increased activation in the ANG during multiplication when compared to letter reading or subtraction, even at an uncorrected level ($p<.001$). To ensure that this absence of activation was not due to the reference condition used in the present study, we also looked at the contrast between multiplication and fixation blocks but this contrast also failed to reveal an activation of the ANG.

TMS experiment

In the vertex condition used as a baseline, subtraction and multiplication led to comparable RLs (894 ± 265 ms and 909 ± 284 ms; $t(9)=0.4$, *ns*) and error rates (4 ± 4.6% and 1 ± 2.1%; $t(9)=1.9$, $p<0.1$). The individual coordinates of the stimulation sites are shown in Table 2 and their location is represented on a glass brain in Fig. 3. The first ANOVA, with SITE (hIPS *vs.* PSPL vs. vertex) and OPERATION (subtraction *vs.* multiplication) as within-subject factors, revealed a main effect of SITE ($F(2,18)=4.26$, $p<.03$). As shown in Fig. 3, TMS over the hIPS (1007 ± 296 ms) induced a RL increase when compared to the vertex (900 ± 266 ms; $t(9)=2.6$, $p<0.05$) and PSPL conditions (950 ± 269 ms; $t(9)=2.2$, $p<0.05$). There was no RL difference between the vertex and PSPL conditions ($t(9)=1.2$, $p<0.2$). The OPERATION had no effect on RL ($F<1$) and there was no interaction between SITE and OPERATION ($F<1$). In order to test the hemispheric lateralization of the hIPS contribution, we conducted a second ANOVA with SITE (hIPS *vs.* PSPL), OPERATION (subtraction vs. multiplication) and HEMISPHERE (left *vs.* right) as within-subject factors. Results confirmed the main effect of SITE ($F(1,9)=5.7$, $p<0.04$) but this effect did not interact with HEMISPHERE ($F<1$), suggesting an equal contribution of the left and right hIPS to arithmetic tasks (see Table 3). All other main effects and interactions were not significant (all p-values > 0.1).

The 2 × 3 ANOVA performed on the error rate revealed no effect of OPERATION ($F(1,9)=1.2$, $p<0.3$) but a main effect of SITE ($F(2,18)=6.5$, $p<0.01$) and a SITE by OPERATION interaction ($F(2,18)=4.7$, $p<0.05$). This interaction indicated that the effect of SITE was significant for multiplication only ($F(2,18)=11.4$, $p<0.005$; see Fig. 3). Indeed,

Table 1

Table of coordinates (x, y, z), normalized to the MNI sample, T-values of the peak voxel (** corrected $p<0.05$; * uncorrected $p<0.001$) for each area showing increased activity during subtraction and/or multiplication.

Contrast	*x*	*y*	*z*	*T*-value	Brain area
[Multiply and Subtract]	−28	−70	42	4.48^{**}	L PSPL
	−34	−56	52	4.21^{**}	L hIPS
	−50	12	28	4.19^{**}	L IFG (part opercularis)
	−2	20	54	3.34^{*}	L SMA
	32	−64	42	3.87^{**}	R PSPL
	36	−74	−28	3.68^{*}	R Cerebellum Crus I
	38	30	−2	3.46^{*}	R Insula
	42	−40	40	3.42^{*}	R hIPS
[Multiply vs. Subtract]	−52	−24	12	4.01^{**}	L STG
	−62	−18	12	3.87^{**}	L STG
	−62	−12	−4	3.98^{**}	L MTG
	−56	−2	−4	3.54^{**}	L STG
	60	−4	−6	4.32^{**}	R STG
	66	−26	12	4.25^{**}	R STG
	68	−12	6	3.81^{**}	R STG
[Subtract vs. Multiply]	–	–	–	–	none

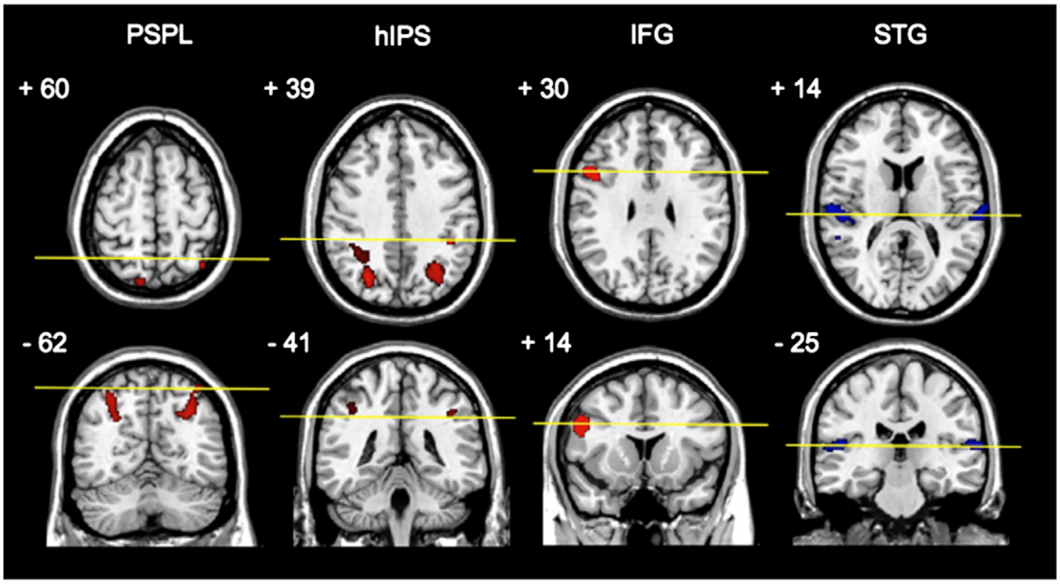

Fig. 2. FMRI experiment. Axial and coronal views of the brain regions showing increased activity during mental arithmetic. In each column, the yellow line crossing the axial view indicates the plane corresponding to the coronal view below and vice versa. Red clusters represent the parietal and frontal areas involved in subtraction and multiplication. The bilateral posterior superior parietal lobe (PSPL), the horizontal segment of the left intraparietal sulcus (hIPS) and the left inferior frontal gyrus (IFG) survived a corrected threshold of $p<0.05$ in a conjunction analysis ($k=150$). Voxels showing increased activity during both arithmetic operations were also found in the right hIPS but only at an uncorrected threshold of $p<0.001$. Blue clusters include perisylvian areas of the superior (STG) and middle temporal lobe showing more activity during multiplication than subtraction (corrected $p<0.05$, $k=150$). No brain region was more activated during subtraction than multiplication.

the participants answered multiplication problems less accurately when TMS was applied over the hIPS (6 ± 4.3%) than over the vertex (1 ± 2.1%; $t(9)=5.3$, $p<0.001$) or PSPL (1.5 ± 1.5%; $t(9)=2.9$, $p<0.05$), these two conditions being not different from each other ($t(9)=.6$, *ns*). Eighty-seven percent of incorrect answers were *operand-related* (i.e., the erroneous answer is a correct response for another problem sharing an operand with the one presented; e.g., $4\times8=24$); 4% were *table* errors (i.e., the erroneous answer is a correct response for a problem sharing no operand with the one presented; e.g., $3\times8=28$), and 9% were *non-table* errors (i.e., the erroneous answer is not a possible arithmetic response; e.g., $4\times6=26$). For the subtraction problems, no difference was observed between the vertex (4 ± 4.6%), hIPS (3.6 ± 3.6%) and PSPL conditions (4.3 ± 3.4%; $F<1$). Overall, 70% of incorrect answers to subtraction problems were distant of one unit from the correct answer and the remaining were within the range of the correct answer ± 3 units. The $2\times2\times2$ ANOVA testing hemispheric lateralization showed a main effect of SITE ($F(1,9)=9.4$, $p<0.01$) and a marginal interaction between SITE and OPERATION ($F(1,9)=4.6$, $p<0.06$), but these effects were not modulated by HEMISPHERE (all p-values >.1; see Table 3).

Table 2

Normalized MNI coordinates (x, y, z) of the TMS sites selected as a function of the fMRI activations revealed at the single-subject level by the conjunction of the subtraction and multiplication tasks. Individual coordinates of the peak voxel are provided for the bilateral intraparietal sulcus (hIPS) and posterior superior parietal lobule (PSPL). The threshold was set at $p<0.01$ (uncorrected for multiple comparisons), except for participants 3, 7 and 10 where identification of the stimulation sites required setting the threshold at $p<0.1$.

Subject	Left hemisphere						Right hemisphere					
	hIPS			PSPL			hIPS			PSPL		
	x	*y*	*z*	*x*	*y*	*z*	*x*	*y*	*z*	*x*	*y*	*z*
1	−40	−54	56	−18	−74	56	42	−44	48	20	−72	64
2	−30	−46	44	−16	−70	60	48	−36	64	16	−72	62
3	−36	−50	48	−18	−74	58	54	−32	54	20	−74	60
4	−34	−42	40	−32	−68	48	42	−58	60	24	−78	52
5	−34	−54	54	−20	−70	48	34	−42	40	16	−78	54
6	−50	−40	56	−14	−76	56	34	−60	46	14	−68	64
7	−28	−52	44	−30	−64	32	50	−40	64	30	−70	40
8	−40	−36	54	−40	−60	60	52	−36	62	30	−60	58
9	−38	−56	52	−28	−66	54	42	−56	58	38	−68	58
10	−42	−46	38	−24	−70	46	42	−50	42	24	−70	42
Mean	−37	−48	49	−24	−69	52	44	−45	54	23	−71	55
S.D.	6	7	7	8	5	9	7	10	9	8	5	9

Discussion

The primary goal of the present study was to test the contribution of the parietal lobe to the solving of subtraction problems, which are assumed to require the manipulation of numerical quantities, and multiplication problems, which are thought to be directly retrieved from memory. In order to go beyond the correlative nature of the available data, we used fMRI to identify the parietal sites showing a significant increase during subtraction and multiplication and then applied TMS over these sites to interfere on-line with the solving of arithmetic problems. Because a causal relationship between the hIPS and magnitude processing had been demonstrated in several other TMS studies (Andres et al., 2005; Cappelletti et al., 2007; Dormal et al., 2008; Knops et al., 2006; Sandrini et al., 2004), we expected to impair the performance in subtraction after hIPS stimulation. Under the assumption that multiplication problems are retrieved from memory without accessing the magnitude of the numbers, they should remain unaffected when TMS is applied over the hIPS.

FMRI results revealed common hIPS areas for subtraction and multiplication, at the exact coordinates of the left ($x=-37$, $y=-48$, $z=49$) and right ($x=44$, $y=-45$, $z=54$) sites identified as the core substrate of number magnitude processing in a recent meta-analysis (Dehaene et al., 2003). The finding that TMS applied over these sites induces a similar RL increase during subtraction and multiplication provides unquestionable evidence that the hIPS is necessary to perform both types of arithmetic operations. The slight increase of multiplication errors when TMS was applied over the hIPS is remarkable if one considers that the disruptive effects of TMS in cognitive tasks are generally limited to RL (Robertson et al., 2003). The absence of an increased error rate in subtraction could be due to the

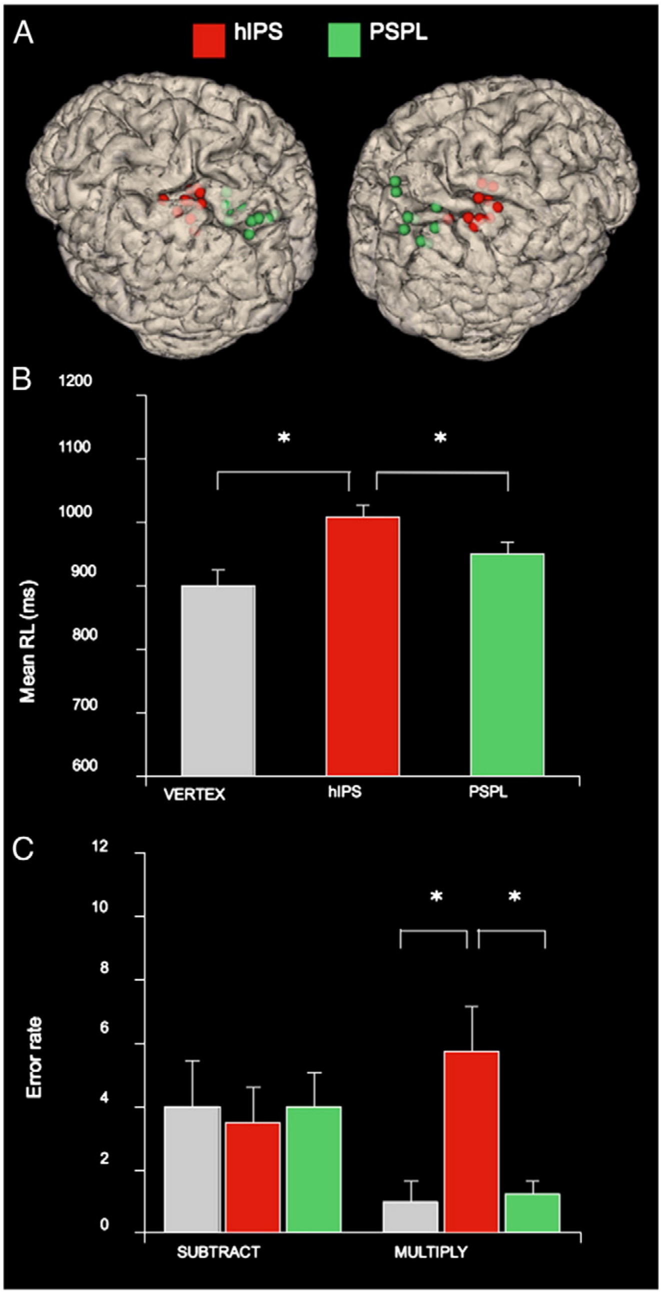

Fig. 3. TMS experiment. (A) The stimulation sites of each participant are represented on two lateral views of a glass brain. Spheres are centred on the normalized MNI coordinates of individual stimulation points in the hIPS (red) and PSPL (green). (B) Mean RL as a function of the TMS site. (C) Mean error rate as a function of the arithmetic task and the TMS site. Error bars show within-subject corrected standard errors (Loftus and Masson, 1994) and asterisks signal significant differences between conditions (*$p<0.05$ corrected for multiple comparisons).

Table 3
Summary of the mean RL (ms) and error rate (%) in each condition (± S.E. corrected for within-subject designs; Loftus and Masson, 1994).

Operation	Left hemisphere		Right hemisphere		Vertex
	hIPS	PSPL	hIPS	PSPL	
Multiplication	1014 ± 103	966 ± 103	1058 ± 123	944 ± 87	909 ± 90
	8.5 ± 2	1.5 ± 0.8	3 ± 1.5	1 ± 0.7	1 ± 0.7
Subtraction	1007 ± 86	950 ± 75	963 ± 81	941 ± 92	894 ± 84
	4 ± 1.5	4.5 ± 2	3 ± 1.1	3.5 ± 1.3	4 ± 1.5

smaller size of the correct responses (all responses <10) when compared to multiplication (12<responses<36), but the comparison of the error rates in the baseline condition contradicts this view as errors were more frequent in subtraction than multiplication. We propose that multiplication showed a greater vulnerability to TMS than subtraction because the retrieval of the correct response is constrained by the interference of other responses belonging to the same table. Several behavioural studies showed that competitive answers are automatically activated in memory during the solving of multiplication problems (Campbell, 1987; Campbell and Clark, 1989; Campbell and Graham, 1985). In line with this view, we found a high proportion of *operand-related* and *table-related* errors in the multiplication task. We assume that, in this task, the disruptive effects of TMS resulted in a lack of activation of the correct answer leading occasionally to the selection of a competitive answer.

Our results underline the crucial role of the left hIPS in arithmetic but they also indicate a contribution of the right hIPS, suggesting that the two homologue areas play complementary roles. Indeed, because either a left or right hIPS lesion was sufficient to slow down RLs, it is reasonable to assume that both hIPS provide inputs to the process of solving arithmetic problems. Previous fMRI and split-brain patient studies highlighted the bilateral involvement of the hIPS in subtraction (Chochon et al., 1999; Funnell et al., 2007; Lee, 2000). Although several fMRI results converge to a bilateral involvement of the hIPS in multiplication (Chochon et al., 1999; Delazer et al., 2003), this operation was most often associated to a left hemisphere dominance (Funnell et al., 2007; Gazzaniga and Smylie, 1984; Rickard et al., 2000; Zhou et al., 2007; Zago et al., 2001), which is congruent with a slightly higher error rate after left than right hIPS virtual lesions.

Together with the finding that solving addition problems is also slowed down by hIPS stimulation (Gobel et al., 2006), our results suggest that this region plays a central role in solving arithmetic operations, including those that rely on memory retrieval. It is worth noting that speed and accuracy in the multiplication task were within the range of performance observed when using retrieval-based strategies (LeFevre et al., 1996), which makes it unlikely that our participants solved these problems by means of calculation procedures. Hence, the absence of dissociation between subtraction and multiplication after TMS over the hIPS suggests that its role in arithmetic is not restricted to the use of calculation procedures. An alternative theory proposes that basic subtraction and multiplication problems are stored in distinct memories and that their retrieval requires prior access to the magnitude representation of the operands (McCloskey, 1992). This view accounts for the selective difficulties of acalculic patients but does not make any prediction regarding the cerebral architecture of arithmetic operations (Dagenbach and McCloskey, 1992). One possibility is that the hIPS contributes to guide memory retrieval of arithmetic results in remote areas by determining the most plausible answer with respect to the magnitude of the numbers. The set of superior and middle temporal areas activated during multiplication, in the present study, are plausible candidates for storing semantic knowledge of arithmetic problems since their lesion was found to cause the loss of multiplication abilities in several patients (Lampl et al., 1994; Sandrini et al., 2003; Van Harskamp et al., 2005; see also Delazer et al., 2006). However, the present study does not allow us to answer this question because bilateral superior temporal activation, close to the auditory cortex, may also be explained by the greater phonological complexity of multiplication results (i.e., two-digit numbers) when compared to subtraction results (i.e., one digit). Another possibility is that distinct memories of subtraction and multiplication problems are implemented in intermingled neuronal networks within the hIPS and that the retrieval of the correct response is performed under the executive control of frontal areas, such as the inferior frontal gyrus which was activated by both operations in the present study (Kazui et al., 2000). In line with the idea that direct memory retrieval may underlie both operations, it is worth noting that RLs and error rates were roughly equivalent in the subtraction and multiplication tasks. A non-significant 100 ms difference was observed between the RLs gathered in the multiplication and subtraction tasks in the fMRI experiment. Although results of statistical analyses may suggest a lack of power in this experiment ($\eta^2 = 0.24$, $0.2 < \text{Pw} < 0.3$), the comparison of baseline RLs in the TMS experiment clearly indicates that there was no reliable RL difference between arithmetic operations ($\eta^2 = 0.02$, $\text{Pw} < 0.1$). Thus, although the set of subtraction problems used in this study is usually not considered as being retrieved from memory, we cannot exclude the possibility that they could also benefit from a representation in long-term memory. Yet, it is worth noting that this possibility in fact strengthens rather than weakens our claim that the hIPS is involved in arithmetic operations solved by memory retrieval. This finding may indicate that the left and right hIPS contribute to the automatic retrieval of learned associations between two numbers and their product/difference rather than to magnitude processing. In order to reconcile these two interpretations, we propose that the hIPS mediates successful memory retrieval by contributing to the generation and maintenance of an integrated representation of number magnitude and retrieved information. In agreement with fMRI studies suggesting a role of the hIPS in episodic memory retrieval (Wagner et al., 2005; Vilberg and Rugg, 2008, 2009), this area could act as an episodic buffer for learned associations between numbers and arithmetic results (Baddeley, 2000).

Our results also shed light on another critical issue related to the contribution of the PSPL to arithmetic. Although the PSPL was often found activated, together with the hIPS, in number comparison and arithmetic tasks (Pesenti et al., 2000b; Simon et al., 2002; Zago et al., 2001), its exact contribution remains obscure. In the present study, subtraction and multiplication led to a comparable increase of the BOLD signal in the left and right PSPL, refuting the simple view that the right PSPL plays a dominant role in providing a visuo-spatial medium to arithmetic operations (Dehaene and Cohen, 1995). The results of previous fMRI and TMS studies rather suggest that the parietal areas involved in arithmetic and visuo-spatial tasks overlap in each hemisphere (Simon et al., 2002; Pelgrims et al., 2009). Using multi-voxel pattern analysis, a recent fMRI study revealed the existence of a common neural code for leftward saccades and subtraction operations and for rightward saccades and addition operations in the bilateral PSPL (Knops et al., 2009a). It has therefore been proposed that the initial function of the PSPL in orienting attention could be “recycled” to perform attention shifts towards the left or right side of a mental numerical continuum, providing the intuition of removing or adding quantities (Hubbard et al., 2005). The idea that the PSPL contribution to addition and subtraction is shaped by specific neuronal properties for coding space is consistent with the introspective reports of embedded representations of number and space made by synaesthetes and mathematicians (Galton, 1880; Seron et al., 1992; Ward et al., 2009). However, the relevance of these number and space interactions for arithmetic is questioned by the total absence of calculation impairments, in the present study, when TMS was applied over parietal sites (left : $x = -24$, $y = -69$, $z = 52$; right : $x = 23$, $y = -71$, $z = 55$) whose location strictly coincides with previous reports of PSPL activation in arithmetic tasks (Dehaene et al., 2003; Knops et al., 2009a; Pesenti et al., 2000b). The PSPL activation may be reminiscent of a specific stage in the development where visuospatial processes offer a start-up tool to represent intuitively addition and subtraction operations (McCrink and Wynn, 2009). Recent findings showed that children have a similar intuitive knowledge of multiplication operations before they get trained with these operations (McCrink and Spelke, 2010). Yet, once exact arithmetic abilities have been acquired, this approximate system is no longer essential for solving arithmetic problems, meaning that its role is at best limited to the monitoring of calculation procedures through estimation. Indeed, fMRI results showed that, in adults, the bilateral activation of the PSPL is typically larger when participants are required to approximate the result of arithmetic operations than when they are instructed to retrieve the exact answer (Dehaene, 1999). Although this approximate system is not sufficient to compensate the loss of arithmetic abilities following a lesion of the hIPS, it may help narrowing the range of potential responses, as suggested by the performance of patient NAU who had lost arithmetic abilities but could still chose the closest answer out of two choices (Dehaene and Cohen, 1991). Hence, our results show that if the PSPL can be diverted from its initial function in orienting attention to allow the emergence of culturally-defined abilities such as calculation, this process does not necessarily imply that arithmetic knowledge is grounded in spatial representations (Knops et al., 2009a). This conclusion is corroborated by the finding that neglect patients may experience similar difficulties to bisect numerical intervals and physical lines due to their visuospatial deficit, whereas assessment of their arithmetic abilities has not revealed any impairment so far (Pia et al., 2009; Vuilleumier et al., 2004; Zorzi et al., 2002). The same conclusion was reached in the study of a patient with visual agnosia who had no deficit in arithmetic, despite major difficulties for processing visual representations, including the shape of Arabic numbers, from long-term memory (Pesenti et al., 2000a). Future TMS studies should nevertheless explore the possibility that the PSPL plays a functional role when arithmetic operations are performed on stimuli that cannot be mapped onto numerical symbols (e.g., sets of dots) or when they imply to multiply, add or subtract large numbers, which involves storing and manipulating operands and intermediate results on a visuo-spatial short-term medium (Göbel et al., 2006; Hitch, 1978; Zago et al., 2001).

Furthermore, it is worth underlining the absence of increased activity in the left ANG, even when multiplication was compared to fixation, which contradicts the hypothesis that arithmetic operations learned by drill depend on a left-lateralized language network involving the ANG. As advocated in the Introduction, the relationship between the left ANG and the retrieval of overlearned arithmetic problems is mainly based on the results of direct contrasts between these problems and problems requiring calculation procedures (Dehaene, 1999; Grabner et al., 2009a; Lee, 2000). In the absence of further information about the percent signal change relative to a non-arithmetic control task, it is difficult to decide whether the activation of the ANG in these studies reflects increased activity during retrieval or decreased activity during calculation. Indeed, in brain imaging studies where multiplication was compared to a non-arithmetic control task, the ANG was found de-activated during operations solved by memory retrieval (Rickard et al., 2000; Zago et al., 2001; Keller and Menon, 2009). Moreover, two case studies indicate that a lesion of the left ANG is neither a sufficient nor a necessary condition to observe a deficit in multiplication (van Harskamp et al., 2002; van Harskamp et al., 2005). Therefore, we argue that, in previous fMRI studies, the ANG activation could reflect unspecific processes related to the cognitive load of the task. This assumption is supported by recent fMRI findings showing similar activations in the ANG while retrieving the solution of arithmetic or figural-spatial problems (Grabner et al., 2009b) and by connectivity studies suggesting that the ANG integrates a default-mode network which is typically associated to greater activity during resting states than during a cognitive task (Keller and Menon, 2009; Uddin et al., 2010). This could explain why activation of the ANG is systematically reported in studies contrasting problems solved through automatic retrieval *versus* calculation procedures.

Contrary to previous studies (Gobel et al., 2006; Grabner et al., 2009a; Rusconi et al., 2005; Stanescu-Cosson et al., 2000), our fMRI and TMS experiments were designed to allow the recording of verbal responses. This protocol provided us with an on-line measurement of the participant's performance, which is lacking in studies using silent naming of the result. It is also reasonable to assume that this production task put stronger demands on the retrieval of the correct answer than verification tasks (Dehaene, 1999; Delazer et al., 2003, 2005). Previous behavioural and neuropsychological data indicated that production and verification tasks are driven by different memory processes and they clearly favoured a familiarity-based over a retrieval-based model in verification tasks (Campbell and Tarling, 1996; Lochy et al., 2004). Therefore, privileging the use of production tasks to assess arithmetic performance in future research could highlight the contribution of brain regions that were undetected in previous fMRI studies (e.g., the middle and superior temporal areas), and improve the discrimination between brain regions related to the retrieval of an arithmetic result and those potentially related to other aspects of the performance (e.g., the ANG).

Conclusion

Using neuronavigated TMS, we evidenced for the first time that the integrity of the hIPS is required to perform arithmetic operations. Moreover, we showed that the hIPS contributes to the solving of both subtraction and multiplication problems, in contrast with the view that the brain networks underlying these operations are entirely separated. Our results also suggest that the PSPL underlies secondary processes which are not crucial to solve basic arithmetic problems.

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References

Andres, M., Seron, X., Olivier, E., 2005. Hemispheric lateralization of number comparison. Cogn. Brain Res. 25, 283–290.

Ashcraft, M.H., 1992. Cognitive arithmetic: a review of data and theory. Cognition 44, 75–106.

Baddeley, 2000. The episodic buffer: a new component of working memory? Trends Cogn. Sci. (Regul. Ed.) 4, 417–423.

Birn, R.M., Bandettini, P.A., Cox, R.W., Shaker, R., 1999. Event-related fMRI of tasks involving brief motion. Hum. Brain Mapp. 7, 106–114.

Birn, R.M., Cox, R.W., Bandettini, P.A., 2004. Experimental designs and processing strategies for fMRI studies involving overt verbal responses. Neuroimage 23, 1046–1058.

Campbell, J.I.D., 1987. Network interference and mental multiplication. J. Exp. Psychol. Learn. Mem. Cogn. 13, 109–123.

Campbell, J.I.D., 1994. Architectures for numerical cognition. Cognition 53, 1–44.

Campbell, J.I.D., Clark, J.M., 1989. Time course of error priming in number-fact retrieval: evidence for excitatory and inhibitory mechanisms. J. Exp. Psychol. Learn. Mem. Cogn. 15, 920–929.

Campbell, J.I., Graham, D.J., 1985. Mental multiplication skill: structure, process, and acquisition. Can. J. Psychol. 39, 338–366.

Campbell, J.I.D., Tarling, D.P.M., 1996. Production, verification, and error priming in cognitive arithmetic. Mem. Cognit. 24, 156–172.

Cappelletti, M., Barth, H., Fregni, F., Spelke, E.S., Pascual-Leone, A., 2007. rTMS over the intraparietal sulcus disrupts numerosity processing. Exp. Brain Res. 179, 631–642.

Chochon, F., Cohen, L., Moortele, P.F.V.D., Dehaene, S., 1999. Differential contributions of the left and right inferior parietal lobules to number processing. J. Cogn. Neurosci. 11, 617–630.

Cipolotti, L., Lacy-Costello, A.L., 1995. Selective impairment for simple division. Cortex 31, 433–449.

Cohen, L., Dehaene, S., Chochon, F., Lehéricy, S., Naccache, L., 2000. Language and calculation within the parietal lobe: a combined cognitive, anatomical and fMRI study. Neuropsychologia 38, 1426–1440.

Cusack, R., Cumming, N., Bor, D., Norris, D., Lyzenga, J., 2005. Automated post-hoc noise cancellation tool for audio recordings acquired in an MRI scanner. Hum. Brain Mapp. 24, 299–304.

Dagenbach, D., McCloskey, M., 1992. The organization of arithmetic facts in memory: evidence from a brain-damaged patient. Brain Cogn. 20, 345–366.

De Brauwer, J., Verguts, T., Fias, W., 2006. The representation of multiplication facts: developmental changes in the problem size, five, and tie effects. J. Exp. Child Psychol. 94, 43–56.

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

Dehaene, S., 1999. Sources of mathematical thinking: behavioral and brain-imaging evidence. Science 284, 970–974.

Dehaene, S., 2009. Origins of mathematical intuitions. Ann. NY Acad. Sci. 1156, 232–259.

Dehaene, S., Cohen, L., 1991. Two mental calculation systems: a case study of severe acalculia with preserved approximation. Neuropsychologia 29, 1045–1074.

Dehaene, S., Cohen, L., 1995. Towards an anatomical and functional model of number processing. Math. Cogn. 1, 83–120.

Dehaene, S., Cohen, L., 1997. Cerebral pathways for calculation: double dissociation between rote verbal and quantitative knowledge of arithmetic. Cortex 33, 219–250.

Dehaene, S., Piazza, M., Pinel, P., Cohen, L., 2003. Three parietal circuits for number processing. Cogn. Neuropsychol. 20, 487.

Delazer, M., Benke, T., 1997. Arithmetic facts without meaning. Cortex 33, 697–710.

Delazer, M., Domahs, F., Bartha, L., Brenneis, C., Lochy, A., Trieb, T., Benke, T., 2003. Learning complex arithmetic—an fMRI study. Cogn. Brain Res. 18, 76–88.

Delazer, M., Domahs, F., Lochy, A., Karner, E., Benke, T., Poewe, W., 2004. Number processing and basal ganglia dysfunction: a single case study. Neuropsychologia 42, 1050–1062.

Delazer, M., Ischebeck, A., Domahs, F., Zamarian, L., Koppelstaetter, F., Siedentopf, C., Kaufmann, L., Benke, T., Felber, S., 2005. Learning by strategies and learning by drill—evidence from an fMRI study. Neuroimage 25, 838–849.

Delazer, M., Benke, T., Trieb, T., Schocke, M., Ischebeck, A., 2006. Isolated numerical skills in posterior cortical atrophy—an fMRI study. Neuropsychologia 44, 1909–1913.

Dormal, V., Andres, M., Pesenti, M., 2008. Dissociation of numerosity and duration processing in the left intraparietal sulcus: a transcranial magnetic stimulation study. Cortex 44, 462–469.

Eger, E., Michel, V., Thirion, B., Amadon, A., Dehaene, S., Kleinschmidt, A., 2009. Deciphering cortical number coding from human brain activity patterns. Curr. Biol. 19, 1608–1615.

Fehr, T., Code, C., Herrmann, M., 2007. Common brain regions underlying different arithmetic operations as revealed by conjunct fMRI-BOLD activation. Brain Res. 1172, 93–102.

Fiez, J.A., Petersen, S.E., 1998. Neuroimaging studies of word reading. Proc. Natl Acad. Sci. USA 95, 914–921.

Fulbright, R.K., Molfese, D.L., Stevens, A.A., Skudlarski, P., Lacadie, C.M., Gore, J.C., 2000. Cerebral activation during multiplication: a functional MR imaging study of number processing. AJNR Am. J. Neuroradiol. 21, 1048–1054.

Funnell, M.G., Colvin, M.K., Gazzaniga, M.S., 2007. The calculating hemispheres: studies of a split-brain patient. Neuropsychologia 45, 2378–2386.

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

Gazzaniga, M.S., Smylie, C.S., 1984. Dissociation of language and cognition. A psychological profile of two disconnected right hemispheres. Brain 107 (Pt 1), 145–153.

Gerstmann, J., 1930. Syndrome of finger agnosia, disorientation for right and left, agraphia and acalculia. Arch. Neurol. Psychiatry 44, 398–408.

Gobel, S., Rushworth, M., Walsh, V., 2006. Inferior parietal RTMS affects performance in an addition task. Cortex 42, 774–781.

Göbel, S.M., Calabria, M., Farnè, A., Rossetti, Y., 2006. Parietal rTMS distorts the mental number line: simulating spatial neglect in healthy subjects. Neuropsychologia 44, 860–868.

Grabner, R.H., Ansari, D., Koschutnig, K., Reishofer, G., Ebner, F., Neuper, C., 2009a. To retrieve or to calculate? Left angular gyrus mediates the retrieval of arithmetic facts during problem solving. Neuropsychologia 47, 604–608.

Grabner, R.H., Ischebeck, A., Reishofer, G., Koschutnig, K., Delazer, M., Ebner, F., Neuper, C., 2009b. Fact learning in complex arithmetic and figural-spatial tasks: the role of the angular gyrus and its relation to mathematical competence. Hum. Brain Mapp. 30, 2936–2952.

Hayashi, N., Ishii, K., Kitagaki, H., Kazui, H., 2000. Regional differences in cerebral blood flow during recitation of the multiplication table and actual calculation: a positron emission tomography study. J. Neurol. Sci. 176, 102–108.

Hécaen, H., Angelergues, R., Houiller, S., 1961. Les variétés cliniques des acalculies au cours des lésions rétrorolandiques: approche statistique du problème. Rev. Neurol. 2, 85–103.

Hitch, G.J., 1978. The role of short-term working memory in mental arithmetic. Cogn. Psychol. 10, 302–323.

Holm, S., 1979. A simple sequentially rejective multiple test procedure. Scand. J. Stat. 6, 65–70.

Hubbard, E.M., Piazza, M., Pinel, P., Dehaene, S., 2005. Interactions between number and space in parietal cortex. Nat. Rev. Neurosci. 6, 435–448.

Ischebeck, A., Zamarian, L., Siedentopf, C., Koppelstätter, F., Benke, T., Felber, S., Delazer, M., 2006. How specifically do we learn? Imaging the learning of multiplication and subtraction. Neuroimage 30, 1365–1375.

Jost, K., Khader, P., Burke, M., Bien, S., Rösler, F., 2009. Dissociating the solution processes of small, large, and zero multiplications by means of fMRI. Neuroimage 46, 308–318.

Kazui, H., Kitagaki, H., Mori, E., 2000. Cortical activation during retrieval of arithmetical facts and actual calculation: a functional magnetic resonance imaging study. Psychiatry Clin. Neurosci. 54, 479–485.

Keel, J.C., Smith, M.J., Wassermann, E.M., 2001. A safety screening questionnaire for transcranial magnetic stimulation. Clin. Neurophysiol. 112, 720.

Keller, K., Menon, V., 2009. Gender differences in the functional and structural neuroanatomy of mathematical cognition. Neuroimage 47, 342–352.

Knops, A., Nuerk, H., Sparing, R., Foltys, H., Willmes, K., 2006. On the functional role of human parietal cortex in number processing: how gender mediates the impact of a "virtual lesion" induced by rTMS. Neuropsychologia 44, 2270–2283.

Knops, A., Thirion, B., Hubbard, E.M., Michel, V., Dehaene, S., 2009a. Recruitment of an area involved in eye movements during mental arithmetic. Science 324, 1583–1585.

Knops, A., Viarouge, A., Dehaene, S., 2009b. Dynamic representations underlying symbolic and nonsymbolic calculation: evidence from the operational momentum effect. Atten. Percept. Psychophys. 71, 803–821.

Lampl, Y., Eshel, Y., Gilad, R., Sarova-Pinhas, I., 1994. Selective acalculia with sparing of the subtraction process in a patient with left parietotemporal hemorrhage. Neurology 44, 1759.

Lee, K., 2000. Cortical areas differentially involved in multiplication and subtraction: a functional magnetic resonance imaging study and correlation with a case of selective acalculia. Ann. Neurol. 48, 657–661.

LeFevre, J., Bisanz, J., Daley, K.E., Buffone, L., Greenham, S.L., Sadesky, G.S., 1996. Multiple routes to solution of single-digit multiplication problems. J. Exp. Psychol. Gen. 125, 284–306.

LeFevre, J., Shanahan, T., Destefano, D., 2004. The tie effect in simple arithmetic: an access-based account. Mem. Cognit. 32, 1019–1031.

Lochy, A., Domahs, F., Delazer, M., 2004. A case-study of access deficit to stored multiplication facts: discrepancy between explicit and implicit tasks. Cortex 40, 153–154.

Loftus, G.R., Masson, M.E., 1994. Using confidence intervals in within-subject designs. Psychon. Bull. Rev. 1, 476–490.

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

McCloskey, M., 1992. Cognitive mechanisms in numerical processing: evidence from acquired dyscalculia. Cognition 44, 107–157.

McCloskey, M., Sokol, S.M., Goodman, R.A., 1986. Cognitive processes in verbal-number production : inferences from the performance of brain-damaged subjects. J. Exp. Psychol. Gen. 115, 307–330.

McCrink, K., Spelke, E.S., 2010. Core multiplication in childhood. Cognition 116, 204–216.

McCrink, K., Wynn, K., 2009. Operational momentum in large-number addition and subtraction by 9-month-olds. J. Exp. Child Psychol. 103, 400–408.

McCrink, K., Dehaene, S., Dehaene-Lambertz, G., 2007. Moving along the number line: operational momentum in nonsymbolic arithmetic. Percept. Psychophys. 69, 1324–1333.

Menon, V., Rivera, S.M., White, C.D., Glover, G.H., Reiss, A.L., 2000. Dissociating prefrontal and parietal cortex activation during arithmetic processing. Neuroimage 12, 357–365.

Nieder, A., Dehaene, S., 2009. Representation of number in the brain. Annu. Rev. Neurosci. 32, 185–208.

Noirhomme, Q., Ferrant, M., Vandermeeren, Y., Olivier, E., Macq, B., Cuisenaire, O., 2004. Registration and real-time visualization of transcranial magnetic stimulation with 3-D MR images. IEEE Trans. Biomed. Eng. 51, 1994–2005.

Oldfield, R., 1971. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9, 97–113.

Paulesu, E., Frith, C.D., Frackowiak, R.S.J., 1993. The neural correlates of the verbal component of working memory. Nature 362, 342–345.

Pelgrims, B., Andres, M., Olivier, E., 2009. Double dissociation between motor and visual imagery in the posterior parietal cortex. Cereb. Cortex 19, 2298–2307.

Pesenti, M., Seron, X., Van der Linden, M., 1994. Selective impairment as an evidence for mental organisation of arithmetic facts : BB, a case of preserved subtraction? Cortex 30, 661–671.

Pesenti, M., Thioux, M., Samson, D., Bruyer, R., Seron, X., 2000a. Number processing and calculation in a case of visual agnosia. Cortex 36, 377–400.

Pesenti, M., Thioux, M., Seron, X., Volder, A.D., 2000b. Neuroanatomical substrates of Arabic number processing, numerical comparison, and simple addition: a PET study. J. Cogn. Neurosci. 12, 461–479.

Pia, L., Corazzini, L.L., Folegatti, A., Gindri, P., Cauda, F., 2009. Mental number line disruption in a right-neglect patient after a left-hemisphere stroke. Brain Cogn. 69, 81–88.

Piazza, M., Izard, V., Pinel, P., Le Bihan, D., Dehaene, S., 2004. Tuning curves for approximate numerosity in the human intraparietal sulcus. Neuron 44, 547–555.

Piazza, M., Mechelli, A., Price, C.J., Butterworth, B., 2006. Exact and approximate judgements of visual and auditory numerosity: an fMRI study. Brain Res. 1106, 177–188.

Piazza, M., Pinel, P., Le Bihan, D., Dehaene, S., 2007. A magnitude code common to numerosities and number symbols in human intraparietal cortex. Neuron 53, 293–305.

Pinel, P., Dehaene, S., 2010. Beyond hemispheric dominance: brain regions underlying the joint lateralization of language and arithmetic to the left hemisphere. J. Cogn. Neurosci. 22, 48–66.

Price, C., 1998. The functional anatomy of word comprehension and production. Trends Cogn. Sci. 2, 281–288.

Rickard, T.C., Romero, S.G., Basso, G., Wharton, C., Flitman, S., Grafman, J., 2000. The calculating brain: an fMRI study. Neuropsychologia 38, 325–335.

Robertson, E.M., Théoret, H., Pascual-Leone, A., 2003. Studies in cognition: the problems solved and created by transcranial magnetic stimulation. J. Cogn. Neurosci. 15, 948–960.

Rossor, M.N., Warrington, E.K., Cipolotti, L., 1995. The isolation of calculation skills. J. Neurol. 242, 78–81.

Rusconi, E., Walsh, V., Butterworth, B., 2005. Dexterity with numbers: rTMS over left angular gyrus disrupts finger gnosis and number processing. Neuropsychologia 43, 1609–1624.

Sandrini, M., Miozzo, A., Cotelli, M., Cappa, S., 2003. The residual calculation abilities of a patient with severe aphasia: evidence for a selective deficit of subtraction procedures. Cortex 39, 85–96.

Sandrini, M., Rossini, P.M., Miniussi, C., 2004. The differential involvement of inferior parietal lobule in number comparison: a rTMS study. Neuropsychologia 42, 1902–1909.

Schneider, W., Eschmann, A., Zuccolotto, A., 2002. E-Prime Reference Guide. Psychology Software Tools, Pittsburgh, PA.

Seron, X., Pesenti, M., Noël, M., Deloche, G., Cornet, J., 1992. Images of numbers, or "when 98 is upper left and 6 sky blue". Cognition 44, 159–196.

Simon, O., Mangin, J.F., 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.

Stanescu-Cosson, R., Pinel, P., van de Moortele, P., Le Bihan, D., Cohen, L., Dehaene, S., 2000. Understanding dissociations in dyscalculia: a brain imaging study of the impact of number size on the cerebral networks for exact and approximate calculation. Brain 123, 2240–2255.

Takayama, Y., Sugishita, M., Akigushi, I., Kimura, J., 1994. Isolated acalculia due to left parietal lesion. Arch. Neurol. 21, 286–294.

Uddin, L.Q., Supekar, K., Amin, H., Rykhlevskaia, E., Nguyen, D.A., Greicius, M.D., Menon, V., 2010. Dissociable connectivity within human angular gyrus and intraparietal sulcus: evidence from functional and structural connectivity. Cereb. Cortex 20 (11), 2636–2646.

van Harskamp, N.J., Rudge, P., Cipolotti, L., 2002. Are multiplication facts implemented by the left supramarginal and angular gyri? Neuropsychologia 40, 1786–1793.

van Harskamp, N., Rudge, P., Cipolotti, L., 2005. Does the left inferior parietal lobule contribute to multiplication facts? Cortex 41, 742–752.

Venkatraman, V., Ansari, D., Chee, M.W., 2005. Neural correlates of symbolic and non-symbolic arithmetic. Neuropsychologia 43, 744–753.

Vilberg, K.L., Rugg, M.D., 2008. Memory retrieval and the parietal cortex: a review of evidence from a dual-process perspective. Neuropsychologia 46, 1787–1799.

Vilberg, K.L., Rugg, M.D., 2009. An investigation of the effects of relative probability of old and new test items on the neural correlates of successful and unsuccessful source memory. Neuroimage 45, 562–571.

Vuilleumier, P., Ortigue, S., Brugger, P., 2004. The number space and neglect. Cortex 40, 399–410.

Wagner, A.D., Shannon, B.J., Kahn, I., Buckner, R.L., 2005. Parietal lobe contributions to episodic memory retrieval. Trends Cogn. Sci. (Regul. Ed.) 9, 445–453.

Ward, J., Sagiv, N., Butterworth, B., 2009. The impact of visuo-spatial number forms on simple arithmetic. Cortex 45, 1261–1265.

Warrington, E.K., 1982. The fractionation of arithmetical skills: a single case study. Q. J. Exp. Psychol. A Hum. Exp. Psychol. 34, 31.

Whalen, J., McCloskey, M., Lindemann, M., Bouton, G., 2002. Representing arithmetic table facts in memory: evidence from acquired impairments. Cogn. Neuropsychol. 19, 505.

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.

Zago, L., Petit, L., Turbelin, M., Andersson, F., Vigneau, M., Tzourio-Mazoyer, N., 2008. How verbal and spatial manipulation networks contribute to calculation: An fMRI study. Neuropsychologia 46, 2403–2414.

Zhou, X., Chen, C., Zang, Y., Dong, Q., Chen, C., Qiao, S., Gong, Q., 2007. Dissociated brain organization for single-digit addition and multiplication. Neuroimage 35, 871–880.

Zorzi, M., Priftis, K., Umilta, C., 2002. Brain damage: neglect disrupts the mental number line. Nature 417, 138–139.