Causal role of the posterior parietal cortex for two-digit mental subtraction and addition: a repetitive TMS study

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Abstract

Although parietal areas of the left hemisphere are known to be involved in simple mental calculation, the possible role of the homologue areas of the right hemisphere in mental complex calculation remains debated. In the present study, we tested the causal role of the posterior parietal cortex of both hemispheres in two-digit mental addition and subtraction by means of neuronavigated repetitive TMS (rTMS), investigating possible hemispheric asymmetries in specific parietal areas. In particular, we performed two rTMS experiments, which differed only for the target sites stimulated, on independent samples of participants. rTMS was delivered over the horizontal and ventral portions of intraparietal sulcus (HIPS and VIPS, respectively) of each hemisphere in Experiment 1, and over the angular and supramarginal gyri (ANG and SMG, respectively) of each hemisphere in Experiment 2. First, we found that each cerebral area of the posterior parietal cortex is involved to some degree in the two-digit addition and subtraction. Second, in Experiment 1, we found a stronger pattern of hemispheric asymmetry for the involvement of HIPS in addition compared to subtraction. In particular, results showed a greater involvement of the right HIPS than the left one for addition. Moreover, we found less asymmetry for the VIPS. Taken together, these results suggest that two-digit mental addition is more strongly associated with the use of a spatial mapping compared to subtraction. In support of this view, in Experiment 2, a greater role of left and right ANG was found for addition needed in verbal processing of numbers and in visuospatial attention processes, respectively. We also revealed a greater involvement of the bilateral SMG in two-digit mental subtraction, in response to greater working memory load required to solve this latter operation compared to addition.

Keywords: two-digit operations, repetitive TMS, horizontal intraparietal sulcus, ventral intraparietal sulcus, angular gyrus, supramarginal gyrus

Abbreviations: ANG = angular gyrus; IPS = intraparietal sulcus; HIPS = horizontal intraparietal sulcus; LH = left hemisphere; MNL = mental number line; RH = right hemisphere; SMG = supramarginal gyrus; VIPS = ventral intraparietal sulcus

1. Introduction

Mental calculation is a fundamental ability involved in a wide range of daily activities. For this reason, understanding its brain underpinnings is a pivotal topic in cognitive science. However, while it is clear that mental calculation is connected to several cognitive processes, information about cerebral areas involved in different calculation processes is still relatively limited. Indeed, despite several attempts to investigate the causal role of brain regions involved in simple mental calculation (e.g., Andres et al., 2011; Della Puppa et al., 2015b; Maurer et al., 2015; Salillas et al., 2012), few studies have addressed this issue on more complex mental calculation (e.g., De Smedt et al., 2009; Grabner et al., 2015). This issue is particularly important because of a crucial difference between simple and complex mental calculation that is not merely quantitative. Simple mental calculation, in fact, is mostly based on rote verbal memory, underpinned by the left angular gyrus (ANG) associated with the verbal processing of numbers (e.g., Dehaene et al., 2003). In contrast, complex mental calculation is solved via procedures requiring a stronger recruitment of quantity systems (e.g., Feher et al., 2007; Menon et al., 2000) underpinned by the bilateral horizontal portion of intraparietal sulcus (HIPS) (Dehaene et al., 2003).

Recently, behavioral studies observed that attentional shifts implied by arithmetic operations influence the speed to detect a target presented on the left or right of the screen, specifically when participants solve one-digit subtractions and two-digit additions, respectively (Masson & Pesenti, 2014; 2015). They have also shown the so-called operational momentum effect, a bias in over- and under-estimating the results of addition and subtraction, respectively, especially for two-digit additions (Lindemann and Tira, 2015). The idea is that ancient neural circuits, such as for example, multimodal parietal areas involved in saccadic and attentional control, are "recycled" for arithmetic calculation (Dehaene and Cohen, 2007). This hypothesis received further support from neuropsychological studies. Importantly, patients with left neglect (and right parietal lesions) present deficits in the mental number line (MNL) (e.g., Vuilleumier et al., 2004; Zorzi et al., 2002;

see also Benavides-Varela et al., 2014) consisting of a horizontal representation of numerical magnitude in which larger numbers are associated with the right side of the line and smaller numbers with the left side.

First neuroimaging investigations of mathematical functions (Dehaene et al., 1999; Pesenti et al., 2000) indicated a pivotal role of the left hemisphere (LH) in calculation, with little specification about the contribution of the right hemisphere (RH). However, a recent meta-analysis on functional magnetic resonance imaging (fMRI) studies (Arsalidou and Taylor, 2011) revealed a much more complex story. The meta-analysis revealed that addition, subtraction, and multiplication differentially recruited prefrontal and parietal regions in the LH and RH: neural activity was dominant in the LH for addition, mainly bilateral for subtraction, and in the RH for multiplication. In particular, Rosenberg-Lee and colleagues (2011) showed that multiplication evoked a greater activation of the right posterior intraparietal sulcus (IPS) compared to addition, suggesting that these operations recruit different brain processes, therefore challenging the idea that both would rely on a strategy based on memory retrieval. In addition, the relative recruitment of the right IPS (including HIPS) was related to the processing of order information in the context of mental arithmetic (Knops and Willems, 2014). More importantly, fMRI studies have demonstrated that bilateral frontal and parietal regions are differently engaged during simple and complex calculation operations (Fehr et al., 2007, 2008; Hamid et al., 2011; Menon et al., 2000; Zhang et al., 2005). In particular, the inferior parietal lobule, including the ANG, the supramarginal gyrus (SMG), and the IPS, shows stronger activation in response to increasing calculation difficulty (Vansteensel et al., 2014; Wu et al., 2009). Moreover, an involvement of the right ANG and SMG has been observed in visuospatial attention and working memory in complex calculation (Zago et al., 2001).

However, it should be noted that the results from both neuropsychological and neuroimaging studies cannot definitely clarify the causal role of the LH and RH in mental calculation. On the one hand, most of neuropsychological studies have a limited spatial resolution since cerebral lesions are usually wider compared to the cerebral areas revealed by neuroimaging studies. On the other hand, neuroimaging studies adopt a correlational approach and, thus, they do not provide proof of the causal role of a specific cerebral region in the process.

In order to overcome these drawbacks, transcranial magnetic stimulation (TMS) would be a more appropriate approach, because it can be used to investigate the causal role of specific areas in mental arithmetic with high spatial resolution. TMS studies have shown that specific RH areas are involved in specific simple mental arithmetic operations (for a review see Salillas and Semenza, 2015). For example, it has been shown that the efficiency in performance for simple multiplications not only involves HIPS but also depends on a motion-sensitive area, i.e., the ventral region of the intraparietal sulcus (VIPS) of the RH (Salillas et al., 2009; Salillas et al., 2012). Using navigated repetitive TMS (rTMS) for preoperative mapping of calculation function, a more recent study found that one-digit addition-related areas were predominantly localized in the LH, while one-digit subtraction-related ones were localized in the RH (Maurer et al., 2015).

With the same goal, recent studies conducted with direct cortical electrostimulation (DCE) found a role of specific RH areas in simple addition and multiplication (Della Puppa et al., 2013; Della Puppa et al., 2015a; Della Puppa et al., 2015b; Duffau et al., 2002; Roux et al., 2009; Semenza et al., 2016) and subtractions (Yu et al., 2011). Finally, by means of a technique similar to rTMS and DCE (i.e., transcranial direct current stimulation, tDCS) and focusing on the acquisition of mathematical knowledge, Grabner and colleagues (2015) demonstrated that the left posterior parietal cortex is causally involved in arithmetic learning of two-digit operations.

In the present study, we aimed to test the causal role of specific LH and RH parietal areas in two-digit mental addition and subtraction using rTMS. In particular, unlike Grabner and colleagues (2015), the present study evaluated not only the left, but also, crucially, the right posterior parietal cortex. Furthermore, rTMS stimulation, which has a higher spatial resolution than tDCS (Priori et al., 2009), allowed us to disentangle the contribution of the specific areas within the posterior parietal cortex of both hemispheres. More importantly, the present study and the Grabner and colleagues' (2015) one investigate different cognitive processes. Indeed, in our case, rTMS stimulation was administered to interfere with the genuine calculation process of complex operations, while in Grabner and colleagues' study (2015), tDCS stimulation was administered to modulate the learning process of complex operations.

We performed two rTMS experiments, which differed only for the target sites stimulated, on independent samples of participants who resolved mentally complex additions and subtractions and provided the result verbally. In Experiment 1, rTMS was delivered over HIPS and VIPS of each hemisphere. After having tested the role of the HIPS and VIPS in the two-digit mental arithmetic, a second experiment was carried out in order to evaluate the causal role of ANG and SMG of each hemisphere. We predict a bilateral contribution of the posterior parietal cortex, with some specialization. Consistently with the idea that two-digit additions determine attentional shift along the MNL compared to two-digit subtraction (Masson and Pesenti, 2014; 2015; Lindemann and Tira, 2015), we expect to find a greater rightward asymmetry for the involvement of HIPS, especially during complex additions, due to the fact that the right HIPS is involved not only in the quantity system (e.g., Feher et al., 2007; Menon et al., 2000), but also in processing the order information along the MNL (Knops and Willems, 2014). We also expect to find the involvement of VIPS, especially during complex additions, as this area underpins the use of the MNL (Salillas et al., 2009, 2012). On the contrary, finding particular functional asymmetries for the involvement of ANG and SMG in both operations would not be expected, given the contribution of these two areas to more general cognitive processes involved in the calculation (Dehaene et al., 2003; Zago and Tzourio-Mazoyer, 2002). However, given the importance of left and right ANG in verbal processing and visuospatial attention, respectively, and the fact that addition is a more automatic operation than subtraction, we expect to find the involvement of ANG especially for additions. Opposite hypotheses can be made for the lateralization of ANG involvement in solving complex operations:

leftward and rightward asymmetries for the involvement of ANG in solving complex operations would indicate the importance of verbal processing and visuospatial attention mediated by this area, respectively. Moreover, a greater involvement of SMG might be predicted for subtractions, given the higher cognitive demands posed by solving complex subtractions compared to additions.

2. Experiment 1

2.1. Method

2.1.1. Participants

Ten native Italian participants (three males; mean age = 25.27 years, *SD* = 4.79 years) took part in this study. The sample size was chosen based on an a-priori power analysis (G*Power 3 software; Faul et al., 2009) for *F* tests (see Ambrosini et al., 2013; Montefinese et al., 2015a; Montefinese et al., 2015b). This analysis revealed that our sample size was large enough to detect a significant (α = .05) interaction corresponding to an effect size of ≈ .1 (η^2_p) with a statistical power ($1 - \beta$) of .80. Participants had normal or corrected-to-normal vision and reported no history of neuropsychiatric illness or epilepsy, and had no contraindication to rTMS (Rossi et al., 2009; Wassermann, 1998). The procedure was approved by the local Ethics Committee (IRCCS San Camillo Hospital Foundation, Venice, Italy) and performed in accordance with the ethical standards of the Declaration of Helsinki for human studies (World Medical Association, 2013). All participants gave written informed consent and were reimbursed for travel expenses and time taken to participate in the study.

2.1.2. Apparatus and stimuli

rTMS was delivered through a Magstim Rapid² stimulator through a 70 mm figure of eight coil (The Magstim Company Limited, Whitland, UK). To identify stimulation sites in both hemispheres we used a frameless stereotaxic neuronavigation system (SofTaxic Optic©, EMS; Bologna, Italy). Before the experiment, a T1-weighted MR scan was obtained from each participant using a Philips

Achieva 1.5 T scanner (Philips Medical Systems, Best, The Netherlands). Stimulation points were then localized on the participant's scalp by coregistering the reference scalp locations to individual MR images using an optical tracking system (Polaris Vicra, NDI, Waterloo, Canada), running a SofTaxic software. The localization procedure was performed at the beginning of each experimental session. Firstly, we identified the rTMS stimulation sites on the basis of the coordinates derived from the literature on participant's MRI in order to localize approximately the rTMS stimulation sites. Next, in order to control for inter-individual differences in brain anatomy, we refined manually the localization of the rTMS stimulation site according to individual anatomical landmarks. The stimulation sites were marked on a tightly fitting Lycra cap worn by participants, and the coil, perpendicular to the scalp surface, was kept in position by an articulated metallic arm for the duration of the experimental session.

The participants sat comfortably in a sound- and light-attenuated room, facing a 17-in LCD computer monitor (resolution: 640×480 pixels; refresh rate: 60 Hz) at a distance of 57 cm, and their heads were stabilized by means of a chin and head rest. The presentation of stimuli was controlled by the E-Prime software (Schneider et al., 2002) and participants' vocal responses were recorded by an external microphone to the computer placed on the table in front of them.

The problems were presented in column format and were well within foveal vision (horizontal visual angle < 4°). The operations were presented in white (24-point monospace Courier New font) on a black background. The stimuli set was derived from a pilot experiment on an independent sample of fifteen participants (mean age: 23.65, *SD* = 3.26 years). Participants were asked to mentally solve two-digit additions and subtractions presented at the center of the screen in separate blocks and provided the result verbally with a modality of presentation of the stimuli and procedure that were equal to the rTMS experiments ones, except for the rTMS stimulation (see section 2.1.3 and Fig. 1 for further details). The vocal responses were treated as those of the rTMS experiments (see section 2.1.5 for the details). The stimulus set included all of the possible combinations of operations with two-digit operands and result, but with some restrictions to minimize the occurrence of confounds. In particular, we selected two-digit additions and subtractions without carrying/borrowing, in order to limit the use of automatic retrieval processes of arithmetic facts and eliminate the confound given by the greater difficulty of the two-digit arithmetic operations requiring carrying/borrowing. To match low-level stimulus properties, subtraction stimuli were created by reversing the operands/result of the addition stimuli. In line with previous studies (Avancini et al., 2014; Galfano et al., 2004), we discarded operations with repeated operands (e.g., 23 + 23), operands with either identical units or teens between operands/result (e.g., 23 + 53; 23 + 26 for the addition; 76 – 53 = 23; 49 - 26 = 23 for the subtraction), since they have a privileged memory access compared to other operations (Campbell and Gunter, 2002). Moreover, operations containing "0" and "1" digits in the operands or result (e.g., 37 – 21, 42 + 20) were not included in the stimulus set, because they involve rule-based problems (Jost et al., 2004; McCloskey et al., 1991). This resulted in 102 distinct operations for each of the two orders of operands. Both the first operand for addition (and result for subtraction) and the second operand ranged from 23 to 75. The result for addition (and first operand for the subtraction) was from 47 to 98. To select the stimuli as similar as possible in terms of performance across the operations, we performed a regression analysis on participants' log-transformed vocal response times (vRTs) for both operations. This analysis showed a positive linear correlation between addition and subtraction ($r = .191$, $p < .0087$, $R^2 = .037$). We chose to select the stimuli with at most one error in both operations and those with smaller residuals in order to optimize the number of trials with correct responses for the analysis, since a worsening of performance rTMS-dependent is expected. The final set of stimuli was constituted by 80 total operations (40 distinct operations for addition and subtraction) for which the same relation between the operations was observed ($r = .823$, $p < .0001$, $R^2 = .677$) for the Experiment 1 and 2. A further set of 20 stimuli was selected for the practice session.

The first operand for addition (and result for subtraction) ranged from 23 to 74, the second operand from 23 to 75, and the result for addition (and first operand for the subtraction) ranged from 57 to 98.

2.1.3. Procedure

Participants had to mentally solve two-digit additions and subtractions, and provide the result verbally during the presentation of the operation. We explicitly asked participants to solve the operations in canonical order (from units to tens) to limit the use of different strategies.

The problems were presented one at a time at the center of the screen for 8000 ms with an inter-trial interval (a white hash symbol in 24-point Courier New font on a black background) of 500 ms. Additions and subtractions were presented in separate blocks following an ABBA order in half of the participants and a BAAB in the others when the experimental sessions did not include the rTMS stimulation over vertex (Andres et al., 2011). Otherwise, the presentation of addition and subtraction blocks follows and ABBA AB order in half of the participants and a BAAB BA in the others. The trial order within each block was randomized across participants. After twelve practice trials for each operation, participants performed five experimental blocks for each operation (presented in random order across participants). Each block comprised 40 two-digit operations, repeated among the operation blocks.

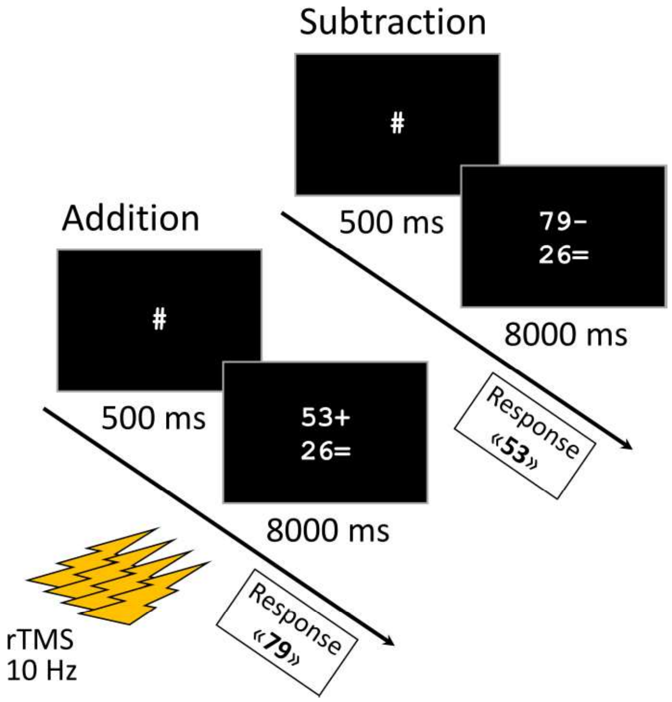

Fig. 1. Time-course of a trial for both rTMS experiments. Note that the timeline for the pilot study is the same as that in the Experiment 1 and 2, except for the rTMS stimulation.

2.1.4. rTMS protocol

Since the excitability threshold of the primary motor cortex may not represent the excitability of non-motor areas of the brain (Robertson et al., 2003), and the thresholds of the latter are difficult to determine, we chose to use a fixed stimulation intensity (Ciavarro et al., 2013; Vesia et al., 2010). In accordance with a previous study on calculation-related activity on parietal cortex (Andres et al., 2011), we decided to use a fixed stimulation intensity of 65% of the maximal output of the stimulator. In each trial, the rTMS train consisted of four pulses (10 Hz) delivered at 100 ms following the onset of the stimulus. Consistent with a previous study (Andres et al., 2011), we chose this rTMS stimulation protocol to interfere with the normal activity of the stimulated target sites as compared to the control site and, thus, induce a performance decline (i.e., a vRTs slowing).

For Experiment 1, the rTMS was delivered over the horizontal and ventral intraparietal portions of sulcus (HIPS and VIPS, respectively) of both hemispheres. The HIPS site (see Fig. 2) was taken by a meta-analysis on neuroimaging studies (Dehaene et al., 2003) examining the role of

HIPS in different arithmetic tasks (Dehaene et al., 2003), and is comparable to the site stimulated by TMS studies on simple mental calculation (Andres et al., 2011; Salillas et al., 2012), suggesting its main role in quantity representation and support the processing of order information in mental arithmetic (Knops and Willems, 2014). In contrast, the VIPS site (see Fig. 2) was found in TMS studies impairing participants' performance in motion perception (Salillas et al., 2009), number comparison (Salillas et al., 2009), and simple calculation (Salillas et al., 2012) tasks, suggesting its role in sustaining use of the MNL.

The four target sites (left- and right-HIPS, left- and right-VIPS) were tested in two separate sessions. This was done to avoid stimulating homologue areas and areas belonging to the same hemisphere in the same session in order to prevent distance- and connectivity-dependent rTMS effects between the cortical areas. In each session, we stimulated either the HIPS or the VIPS in one hemisphere as target sites, as well as the other area in the opposite hemisphere (e.g., the right-HIPS and left-VIPS). For both target sites, participants performed one addition and one subtraction block. The vertex was used as a control site and baseline condition and was stimulated in one of the two sessions. The rTMS stimulation over vertex occurred in the first session for half of the participants and in the second session for the other half, in a counterbalanced order across participants. Thus, each session was composed of either six or four operation blocks. The rTMS stimulation of control and target sites as well as the order of presentation of operation blocks was counterbalanced across sessions and participants. The online rTMS train frequency, intensity, and duration were well within safe limits (Rossi et al., 2009; Wassermann, 1998).

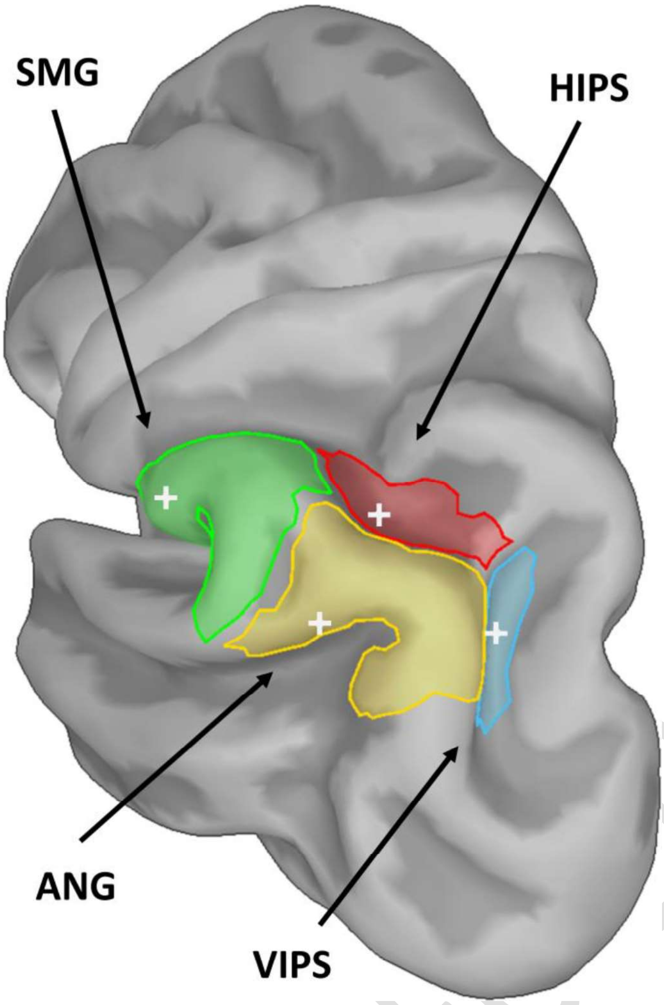

Fig. 2. rTMS sites rendered over a standard brain. White crosses represent the mean Talairach coordinates across participants as follows: Horizontal Intraparietal Sulcus (HIPS) (in red): x = −39, y = −47, z = 48; Ventral Intraparietal Sulcus (VIPS) (in light blue): x = −26, y = −75, z = 31; Angular Gyrus (ANG) (in yellow): x = −49, y = −59, z = 31; Supramarginal Gyrus (SMG) (in green): x = −54, y = −31, z = 30.

2.1.5. Data analysis

Vocal response times were measured from the onset of the stimulus to the beginning of the vocal response by means of a sound capture device (contained in E-Prime). Responses were recorded in WAV files, which were later analyzed using CheckVocal (Protopapas, 2007).

We discarded all trials with incorrect or missing responses (3% of the trials). We logarithmically transformed the vRTs of correct responses to satisfy the assumption of normality for the analyses. To obtain measures of central tendency that were as robust as possible against aberrant observations, we applied a robust estimation of central tendency for each condition of interest, which is robust to non-normality and sample size (Ambrosini and Vallesi, 2016; Rousseeuw and Verboven, 2002), as implemented by the *mloclogist* and *madc* functions in the LIBRA Matlab library (Verboven and Hubert, 2005, 2010). For all the analyses, the dependent variable was the difference in vRTs between rTMS over target site (left- or right-HIPS, left- or right-VIPS) and rTMS over control site (vertex). Firstly, a series of one-sample, one-tailed *t*-tests against zero were carried out to analyze the rTMS effect for each target site. These tests were corrected for multiple comparisons using the Holm-Bonferroni correction. Secondly, to test the different involvement of each site in additions and subtractions, we performed a by-items repeated measures analysis of variance (ANOVA) with Operation (Addition, Subtraction), Hemisphere (LH, RH) and Area (HIPS, VIPS) as within-items factors. Difference scores were analyzed and Duncan's post-hoc test was performed to interpret interactions.

In order to test whether the practice effect biased participants' performances, we then conducted linear mixed-effect modelling, as implemented by the function *lmer* from the lme4 library (version 0.999999-0; Bates, Maechler, & Bolker, 2012) in R (version 2.15.2; R Core Team, 2012). This allowed us to account for random and fixed effects at the within- and between-subject levels, providing more efficient estimates of the experimental effects and a better protection against capitalization on chance, or Type I error (Baayen et al., 2008; Quené and Van den Bergh, 2008). The experimental effects included the effects of the Operation factor (Addition, Subtraction), those of the Hemisphere (LH, RH) and of the Area (HIPS, VIPS), the interactions between them, and a linear function of the time throughout the experiment. The effect of this covariate (i.e., the factor time), which accounts for potential confounding longitudinal effects of fatigue or familiarization across participants, was modelled by a parameter representing the session number vector zero-centered (cSession) to remove the possible spurious correlation between the by-subjects random intercepts and slopes. We determined the simplest best (final) linear mixed-effect models to fit our dependent variables by using a log-likelihood ratio test (for a detailed description of the procedure, see Montefinese et al., 2014) according to standard procedures (Baayen et al., 2008; Quené and Van den Bergh, 2008). In the model building process the order of entry of successive variables was based on theoretical motivation. First, we determined the random part of the model, then the inclusion of the effects of main theoretical interest described above. We then fitted the final model after excluding outliers, which were identified as observations for which the standardized residual exceeded the value of ±3 (.94% and .80% of analyzed trials, respectively for Experiments 1 and 2). For fixed effects we reported the estimated coefficient (b), the p values (p_{MCMC}) and upper and lower highest posteriori density intervals ($\mathrm{HPD}_{95\%}$) estimated on the basis of the posterior distribution of the corresponding parameters, obtained through Markov Chain Monte Carlo (MCMC) sampling (10000 samples) supported by the *pvals.fnc* function of the language R package (version 1.4; Baayen et al., 2008).

2.2. Results

One-sample *t*-tests on rTMS mean effects (target site – vertex) showed that the rTMS interference was significantly different from zero for all sites (all $ts_{(39)} \geq 1.923$, $ps \leq .031$, $ds \geq .304$). These results suggest that all stimulated sites are involved in two-digit mental additions and subtractions. Table 1 shows the participants' accuracy for both addition and subtraction.

Table 1. Accuracy (proportion of correct responses) for both addition and subtraction from Experiment 1.

	Addition		**Subtraction**	
	M	*SD*	*M*	*SD*
Hemisphere				
LH	.973	.164	.968	.177
RH	.978	.148	.959	.199
Area				
HIPS	.980	.140	.963	.190
VIPS	.970	.171	.964	.187
Vertex	.985	.122	.963	.190
Interaction				
LH-HIPS	.980	.140	.958	.178
LH-HIPS	.965	.184	.968	.178
RH-VIPS	.980	.140	.958	.202
RH-VIPS	.975	.156	.960	.196

LH = Left Hemisphere; RH = Right Hemisphere; HIPS = Horizontal Intraparietal Sulcus; VIPS = Ventral Intraparietal Sulcus.

The by-items ANOVA revealed a number of significant effects. First, we found a main effect for Hemisphere factor ($F_{(1, 39)} = 8.921$, p =.0049, $\eta^2_p = .186$) with a greater rTMS effect over the RH (*M* = .082, *SD* = .055) compared to the LH (*M* = .060, *SD* = .052). The two-way interaction between Hemisphere and Area was also significant ($F_{(1, 39)} = 15.572$, $p < .0001$, $\eta^2_p = .285$). This interaction was explained by the fact that the hemispheric asymmetry of rTMS effect for HIPS (Right-Left difference = .054, *SD* = .070) was greater than that found for VIPS, for which an opposite trend was observed (Right-Left difference: -.009, *SD* = .069). Indeed, post-hoc analyses revealed that while the rTMS effect was higher for right than left HIPS (Left = .042, *SD* = .069; Right = .096, *SD* = .062; p = .0001), no significant lateralization was found for VIPS (Left = .077, *SD* = .049; Right = .068, *SD* = .069; p = .4355); in addition, the rTMS effect for right HIPS was higher than that found for the right VIPS (p = .0223) and both the left and right VIPS showed higher rTMS effects as compared to that found for the left HIPS (respectively, p = .0051 and .0269).

Importantly, the Hemisphere by Area interaction was further qualified by the three-way interaction between Operation, Hemisphere, and Area factors ($F_{(1, 39)} = 4.545$, $p = .0394$, $\eta^2_p = .285$). As shown in Fig. 3, the greater asymmetric rTMS effect over HIPS described above was significantly higher for Addition (HIPS = .079, *SD* = .090; VIPS = -.017, *SD* = .081; HIPS – VIPS difference: .097, *SD* = .130) compared to that found for Subtraction (HIPS = .029, *SD* = .099; VIPS = 0, *SD* = .105; HIPS – VIPS difference: .130, *SD* = .153). Indeed, post-hoc analyses showed that while for Subtraction none of the pairwise comparisons were significant (all *p*s > .1104), for Addition the rTMS effect was higher for right than left HIPS (respectively, *M* = .102 and .022, *SD* = .079 and .073; *p* = .0001), but no significant lateralization was found for VIPS (right VIPS = .061, *SD* = .089; left VIPS = .076, *SD* = .074; *p* = .3361); moreover, the rTMS effect for right HIPS was higher than that found for the right VIPS (*p* = .0284) and both the left and right VIPS showed higher rTMS effects as compared to that found for the left HIPS (respectively, *p* = .0026 and .0198). There were no other significant main effects or interactions (all *p*s ≥ .1812).

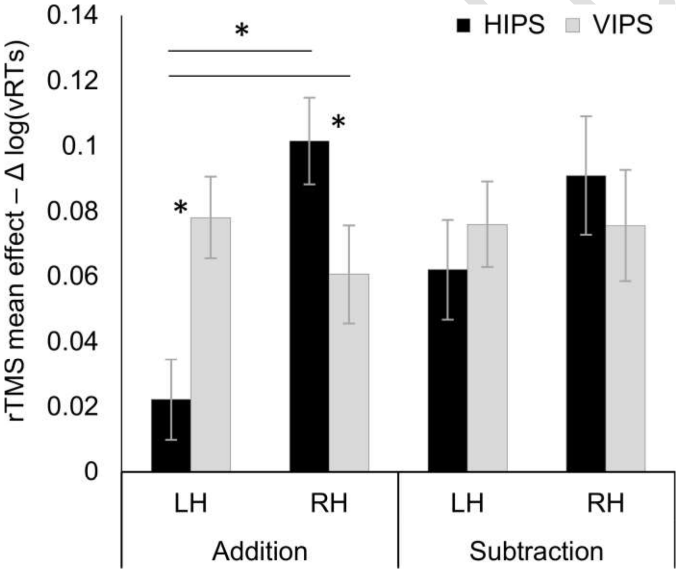

Fig. 3. rTMS effect mean is shown as a function of Operation (Addition, Subtraction), Hemisphere (Left Hemisphere, LH and Right Hemisphere, RH) and Area (Horizontal Intraparietal Sulcus, HIPS, and Ventral Intraparietal sulcus, VIPS) factors. Error bars indicate within-items standard error of the mean (Morey, 2008). * = $p < .05$.

These results were corroborated by the linear mixed-effects model analysis, controlling for the participants' practice effect (cSession factor). The final model included two parameters for the random effects of Subjects and Trials in the random part and the parameters for the fixed effects of cSession, Operation, Hemisphere, and Area in the fixed part, as well as the parameters for the interactions of interest. The effect of cSession factor was significant ($b = -.014$, $p_{\text{MCMC}} = .0001$), suggesting that the rTMS effect decreased linearly with the increase of the number of sessions performed by participants. We also found a main effect of Operation ($b = .053$, $p_{\text{MCMC}} = .0136$) as well as an Operation by Area interaction ($b = -.070$, $p_{\text{MCMC}} = .0176$). Importantly, also the highest order three-way interaction was significant ($b = .087$, $p_{\text{MCMC}} = .0368$), confirming results showed by the ANOVA. There were no other significant main effects or interactions (all $p_{\text{MCMC}}s \geq .3376$). The parameters and the corresponding statistics of the final trimmed model are shown in Table 2.

Table 2. Estimated parameters and statistics of mixed-effects modelling of data from Experiment 1.

	Estimate	$\text{Mean}_{\text{MCMC}}$	$\text{HPD95}_{\text{lower}}$	$\text{HPD95}_{\text{upper}}$	p_{MCMC}
Intercept	0.0546	0.0552	-0.039	0.1440	0.2076
cSess	-0.0143	-0.0143	-0.0182	-0.0106	0.0001
Addition	0.0526	0.0525	0.0119	0.0934	0.0136
RH	-0.0013	-0.0014	-0.0418	0.0400	0.9504
HIPS	-0.0076	-0.0077	-0.0492	0.0326	0.7122
Addition:RH	-0.0302	-0.0300	-0.0886	0.0267	0.3096
Addition:HIPS	-0.0700	-0.0699	-0.1285	-0.0127	0.0176
RH:HIPS	0.0284	0.0285	-0.0287	0.0867	0.3422
Addition:RH:HIPS	0.0874	0.0872	0.0092	0.1720	0.0368

MCMC = Markov Chain Monte Carlo, HPD= Highest Posteriori Density, cSess = zero-centered vector for the Session effect, RH = Right Hemisphere, HIPS = Horizontal Intraparietal Sulcus

3. Experiment 2

3.1. Method

3.1.1. Participants

Another sample of ten native Italian participants (three males; mean age = 28.11 years, *SD* = 5.19 years) took part in this study. The sample size was chosen based on an a-priori power analysis as described for Experiment 1. Participants had normal or corrected-to-normal vision and reported no history of neuropsychiatric illness or epilepsy, and had no contraindications to rTMS (Rossi et al., 2009; Wassermann, 1998). The procedure was approved by the local Ethics Committee (IRCCS San Camillo Hospital Foundation, Venice, Italy) and performed in accordance with the ethical standards of the Declaration of Helsinki for human studies (World Medical Association, 2013). All gave written informed consent and were reimbursed for travel expenses and time taken to participate in the study.

3.1.2. Apparatus and stimuli

The experimental apparatus and the stimuli set were the same as for Experiment 1.

3.1.3. Procedure

The procedure was the same as for the Experiment 1.

3.1.4. rTMS protocol

The rTMS protocol was the same as for the Experiment 1, except for the stimulated target sites. In particular, for Experiment 2, the rTMS was delivered over the ANG and SMG of both hemispheres. The ANG site (see Fig. 2) was chosen based on the peak response in arithmetic tasks with strong verbal component in a meta-analysis on neuroimaging studies (Dehaene et al., 2003). In contrast, the SMG site (see Fig. 2) was taken from an fMRI study (Price et al., 2013) showing a fine-grained relation between brain activation in this region during a calculation task and a participants' greater engagement of calculation strategies involving the quantity processing.

3.1.5. Data analysis

The recorded responses were measured and analyzed in the same way as in Experiment 1. There were 3.55% trials with incorrect or no responses. We logarithmically transformed the vRTs of the correct responses and calculated a robust estimation of central tendency (e.g., Verboven & Hubert, 2010). As for Experiment 1, we performed one-sample *t*-tests (one-tailed) to test the rTMS effect for each target site. We also assessed the effect of interest factors by means of a by-items repeated measures ANOVA as detailed for Experiment 1 (see section 2.1.5). Finally, we tested the participants' practice effect, by conducting linear mixed-effect modelling (see section 2.1.5 for further details).

3.2. Results

One-sample *t*-tests on rTMS mean effects (target site – vertex) showed that the rTMS interference was significantly different from zero for all sites (all $ts_{(39)} \geq 1.770$, $ps \leq .042$, $ds \geq .280$). As for Experiment 1, results suggest that all of the stimulated sites are involved in the two-digit mental additions and subtractions. Table 3 shows the participants' accuracy for both addition and subtraction.

Table 3. Accuracy (proportion of correct responses) for both addition and subtraction from Experiment 2.

	Addition		**Subtraction**	
	M	*SD*	*M*	*SD*
Hemisphere				
LH	.976	.152	.946	.226
RH	.975	.156	.960	.196
Area				
ANG	.979	.144	.948	.223
SMG	.973	.164	.959	.199
Vertex	.988	.111	.955	.208
Interaction				
LH-ANG	.983	.131	.940	.238
LH-SMG	.970	.171	.953	.213
RH-ANG	.975	.156	.955	.208
RH-SMG	.975	.156	.965	.184

LH = Left Hemisphere; RH = Right Hemisphere; ANG = Angular Gyrus; SMG = Supramarginal Gyrus.

The by-items ANOVA revealed a number of significant effects. We found a Hemisphere effect ($F_{(1, 39)} = 22.158$, $p < .0001$, $\eta^2_p = .362$) with a greater rTMS effect over the RH (*M* = .075, *SD* = .069) compared to the LH (*M* = .045, *SD* = .063).

The two-way interaction between Hemisphere and Area was also significant ($F_{(1, 39)} = 8.762$, $p = .0052$, $\eta^2_p = .183$). This interaction was explained by the fact that the hemispheric asymmetry of rTMS effect for SMG (Right-Left difference: .056, *SD* = .065) was greater than that found for ANG (Right-Left difference: .004, *SD* = .072). Indeed, post-hoc analyses revealed that while the rTMS effect was significantly higher for right than left SMG (Left = .028, *SD* = .069; Right = .084, *SD* = .082; $p = .0002$), no significant lateralization of rTMS effect was found for ANG (Left = .062, *SD* = .074; Right = .066, *SD* = .076; $p = .7436$). The rTMS effect for right SMG was also significantly higher than that found for right ANG ($p = .0101$), and both the left and right ANG showed higher rTMS effects as compared to that found for the left SMG (respectively, $p = .0100$ and .0058) (see Figure 4).

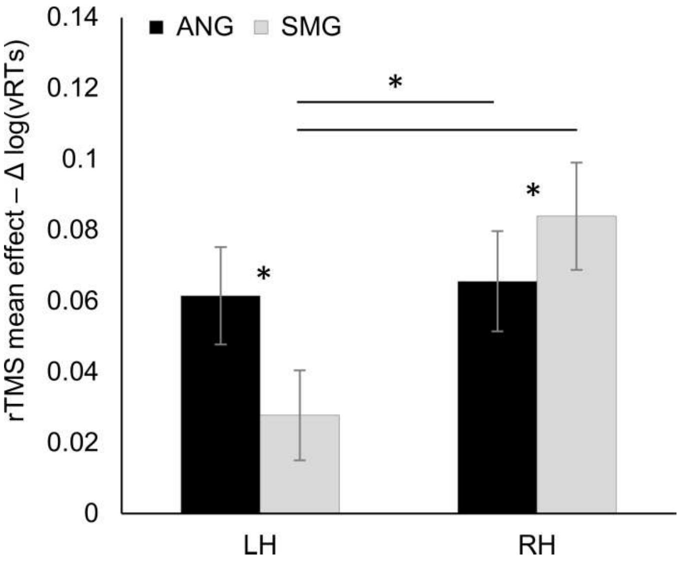

Fig. 4. rTMS effect mean is shown as a function of Hemisphere (Left Hemisphere, LH and Right Hemisphere, RH) and Area (Angular Gyrus, ANG and Supramarginal Gyrus, SMG) factors. Other conventions are as for Fig. 3.

The two-way interaction between Operation and Area was also significant ($F_{(1, 39)} = 5.350$, $p = .0261$, $\eta^2_p = .121$). This interaction was based on the fact that ANG and SMG showed opposite operation-related differential rTMS effects (Addition-Subtraction difference for ANG: $M = .029$, $SD = .114$, and SMG: $M = -.006$, $SD = .088$). Indeed, post-hoc analyses revealed that while the rTMS effect was significantly higher for ANG in Addition than Subtraction (Addition = .078, $SD = .079$; Subtraction = .049, $SD = .094$; $p = .0176$), an opposite trend for higher rTMS effect in Subtraction than Addition was observed for SMG (Addition = .053, $SD = .070$; Subtraction = .059, $SD = .091$; $p = .5508$). The rTMS effect for ANG in Addition was also significantly higher than that found for SMG ($p = .0306$) (see Fig. 5). There were no other significant main effects or interactions (all *p*s > .2213).

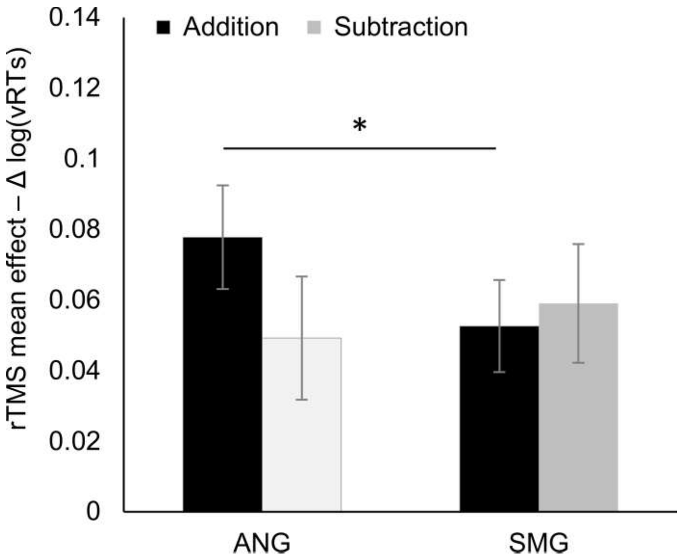

Fig. 5. rTMS effect mean is shown as a function of Operation (Addition, Subtraction) and Area (Angular Gyrus, ANG and Supramarginal Gyrus, SMG) factors. Other conventions are as for Fig. 3.

As for Experiment 1, these results were corroborated by linear mixed-effects model analysis. The main effect of Operation was not significant (p_{MCMC} = .3325). The effect of cSession (*b* = -0.012, $p_{\mathrm{MCMC}} < .0001$), Hemisphere (*b* = 0.031, p_{MCMC} = .0009), and Area (*b* = -.029, p_{MCMC} = .0228) factors were significant. Importantly, also the Area by Operation interaction was significant (*b* = .038, p_{MCMC} = .0432). This result confirmed and extended those found in the ANOVA by showing that the rTMS effect was significantly higher for SMG in Subtraction. The parameters and the corresponding statistics of the final trimmed model are shown in Table 4.

Table 4. Estimated parameters and statistics of mixed-effects modeling of data from Experiment 2.

	Estimate	$\mathrm{Mean}_{\mathrm{MCMC}}$	$\mathrm{HPD95}_{\mathrm{lower}}$	$\mathrm{HPD95}_{\mathrm{upper}}$	p_{MCMC}
Intercept	0.0605	0.0606	-0.0125	0.1364	0.0998
cSess	-0.0121	-0.0121	-0.0154	-0.0091	0.0001
RH	0.0313	0.0314	0.0131	0.0498	0.0012
Subtraction	-0.0129	-0.0129	-0.0383	0.0138	0.329
SMG	-0.0294	-0.0297	-0.0555	-0.0046	0.0228
Subtraction:SMG	0.0375	0.0376	0.0029	0.0769	0.0432

MCMC = Markov Chain Monte Carlo, HPD = Highest Posteriori Density, cSess = zero-centered vector for the Session effect, RH = Right Hemisphere, SMG = Supramarginal Gyrus

4. Discussion

This study used rTMS to examine the role of HIPS, VIPS, ANG, and SMG of each hemisphere in solving complex arithmetic operations, which require manipulation of magnitude and calculation procedures. In particular, participants solved two-digit additions and subtractions presented visually and provided the result verbally.

We found a significant effect of rTMS over all of the stimulated target sites, suggesting that each area is involved to some degree in both operations. These results could be due to the fact that solving complex calculations requires magnitude coding and MNL manipulation processes complemented by more general cognitive processes such as verbal processing, working memory, visuospatial attention, and cognitive control, not specific to the number domain.

4.1. Right hemisphere in two-digit mental operations

We found that the rTMS interference was stronger over the RH in both Experiment 1 and 2, suggesting that it has a critical role in solving two-digit addition and subtraction. This result could be due to the nature of the calculation strategy used in this study. Indeed, simple calculation (i.e., one-digit addition and subtraction) rely on verbal retrieval strategies of learned associations between a problem and its outcome and, thus, they involve mostly the LH (Dehaene et al., 1999; Pesenti et al., 2000). Conversely, complex calculation (i.e., two-digit addition and subtraction) relies on a visuospatial strategy, as calculating the result of an arithmetic operation implies attention shifting to the left or right side of the MNL (Masson and Pesenti, 2014, 2015), and, thus, they also involve the RH (Feher et al., 2007; Menon et al., 2000). This idea fits with studies on patients with right parietal damage who present deficits in both the numerical and spatial bisection tasks (Cappelletti et al., 2007b; Zorzi et al., 2002) and rTMS studies which simulated these deficits in healthy participants (Fierro et al., 2006; Göbel et al., 2006a). The adoption of these spatial strategies to compute results of a given operation might explain the involvement of areas traditionally attributed to visuospatial attention during internal number processing with no overt or covert attentional orienting components. We also suggest that the role of the RH is not limited to approximate calculation (Knops et al., 2009; McCrink et al., 2007; Pinhas and Fischer, 2008) and numerical judgments (Andres et al., 2005), but is also crucial for complex calculation.

4.2. Horizontal and ventral portions of intraparietal sulcus in two-digit mental operations

In Experiment 1, we found that solving complex operations was significantly disrupted by rTMS over the areas within the IPS of each hemisphere (both bilateral HIPS and VIPS), as highlighted by one-sample *t* tests. These results are consistent with previous studies, which showed a bilateral activation of the IPS as number size and problem complexity increased, due to greater difficulty in retrieving arithmetic facts from memory and increasing reliance on visuospatial strategies (Molko et al., 2003; Stanescu-Cosson et al., 2000; Zago et al., 2008; Zhou et al., 2007). At the same time, these results are in contrast to those of another rTMS study, which revealed no role for the right IPS in two-digit mental addition (Göbel et al., 2006b). This discrepancy might be due to the fact that, while Göbel and colleagues used a verification result task, we used a verbal production task, without cued results. In fact, it is reasonable to posit that the lack of rTMS effect over the right IPS in Göbel et al.'s study might be attributed to the fact that verification tasks, as compared to production tasks, rely on a plausibility or familiarity judgment, rather than on the computation of the correct result (see Andres et al., 2011). In particular, a role for bilateral HIPS in arithmetic operations was expected, since its involvement in coding the abstract magnitude meaning of numbers is well known in the literature (Dehaene et al., 2003). These results are consistent with previous TMS studies, which showed a causal link between HIPS and quantity processing (Andres et al., 2005; Cappelletti et al., 2007a; Dormal et al., 2008; Knops et al., 2006; Sandrini et al., 2004) as well as between HIPS and simple mental calculation (Andres et al., 2011; Salillas et al., 2012).

Importantly, the two-way interaction between hemisphere and area found in Experiment 1 showed a significant greater involvement of the right HIPS, as compared to both the left one and the bilateral VIPS in solving complex operations. This result might be explained by an observation by Knops and Willmes (2014), who postulated a specific functional role of right IPS, including HIPS, which was stimulated in our study. Indeed, according to the authors, this region might not only represent numerical magnitude, like the left HIPS, but also enhance the serial position information on the spatially oriented MNL in mental arithmetic. Conversely, our results suggest a more bilateral involvement for VIPS, which corresponds to human vIPS (Shulman et al., 1999) and to the junction of intraparietal and transverse occipital sulci (Wojciulik and Kanwisher, 1999). VIPS is a sensory motion-sensitive area (Nieder, 2004), which acts in conjunction with the HIPS to operate over the MNL (Salillas et al., 2009; Salillas et al., 2012). In particular, as pointed out by Salillas and colleagues, VIPS would support attention shifts along the MNL in number comparison (Salillas et al., 2009) and also in simple calculation tasks (Salillas et al., 2012). Our results are in line with this view, extending the role of VIPS in number processing to complex mental calculation.

However, the pattern just described was more evident for addition compared to subtraction, as emerged from the higher order interaction found in Experiment 1. For the reasons described above, this result suggests that complex addition is more reliant on visuospatial strategies such as shifting along the MNL during solving of this operation. This might be due to the fact that we used operations with large numbers. Indeed, the set of stimuli we used for two-digit addition and subtraction might have decreased the effect of the operands for subtraction in line with the results by Masson and colleagues (2014). These authors found leftward and rightward attentional shifts specifically when participants solved one-digit subtractions and two-digit additions, respectively, and interpreted this result as an effect of semantic associations learned from experience (see Masson & Pesenti, 2014; 2015). Thus, in our case it is possible that solving complex subtractions involved attentional shifts (to the left) to a lesser extent than addition because all the numbers involved in our two-digit problems were large. In addition, in support of the involvement of attentional shift for complex mental additions, Lindemann and Tira (2015) observed an operational momentum effect especially for two-digit addition. Furthermore, Anelli and colleagues (2014) found that rightward body motions triggered mainly addition outcomes, while the leftward ones did not trigger the subtraction outcomes. As a consequence, it is reasonable to posit that complex mental addition would be more strongly associated to the use of a spatial strategy compared to, especially, large complex subtractions, which would explain the stronger role of regions within the IPS in computing addition results, which is suggested by our results. However, this account is highly speculative and merits further investigation.

4.3. Supramarginal and angular gyri in the two-digit mental operations

Regarding the role of SMG in complex operations, the interaction between hemisphere and area we found in Experiment 2 showed that the asymmetry (i.e., RH > LH) of the rTMS interference was stronger over the SMG as compared to the ANG, for which no significant lateralization of rTMS effects was found. This result is consistent with the proposed role of the right SMG as a critical area in mediating both working memory and shifts of spatial attention. Indeed, it has been shown that part of the right SMG presented an increased activity in response to increased visual working memory load (Silk et al., 2010). In line with this working memory account, the linear mixed model analysis also showed a significant two-way interaction between operation and area (Experiment 2), revealing a stronger involvement of SMG for subtraction compared to addition. These results are in line with the literature about the involvement of SMG in increasing difficulties of arithmetic operations (Hamid et al., 2011; Menon et al., 2000). Indeed, despite the fact that subtraction represents the inverse arithmetic process of addition (Campbell, 2008), subtraction operations are relatively less automated and difficult to solve compared to addition (Campbell, 2005; Rosenberg-Lee et al., 2011).

We also found a stronger involvement for the ANG in addition compared to subtraction (Experiment 2). In the literature activation of the ANG has been shown for exact calculation (Dehaene et al., 1999; Zago and Tzourio-Mazoyer, 2002) as well as during the retrieval of arithmetic facts (Pesenti et al., 2000; Zago et al., 2001). Furthermore, the bilateral deactivation of ANG was found to be related to poorer maths performance (Rosenberg-Lee et al., 2011; Wu et al., 2009) and individual competence (Grabner et al., 2007). However, despite this evidence, the specificity of the ANG for numerical processing is still debatable (see review by Seghier, 2013). In particular, the left ANG has been classically considered as the site for the retrieval of more automatic arithmetic operations, which could explain the greater role that ANG played in additions. This would happen because addition is a more automatic operation than subtraction. Indeed, it is taught at school to a greater extent (Barrouillet et al., 2008) and is used more frequently in daily life (Kong et al., 2005). The role of the right ANG in calculation is more controversial than that of the left ANG, although activations in the right ANG are very stable and frequent in relation to calculation. For example, a recent meta-analysis showed that the right ANG is involved in visuospatial attention when calculations are being solved (Arsalidou and Taylor, 2011). Moreover, damage to the right ANG can cause left neglect (Hillis et al., 2005; Mort et al., 2003), and this same region has an important role in exogenous saccadic orienting (Mort et al., 2003). Thus, the role of right ANG, especially for addition, would support the idea above mentioned of a greater use of a spatial strategy in addition. This idea is further supported by studies showing that gestures and spatial mapping can support arithmetic learning (Goldin-Meadow et al., 2009; Wiemers et al., 2014) and that participants with greater mathematical expertise use mostly a visuospatial strategy (Marghetis et al., 2014).

5. Conclusions

For the first time our investigation draws causal inferences on the role of the posterior parietal cortex of each hemisphere in complex mental calculation. Consistent with the idea that the brain networks subserving spatial attention are "reused" for numerical processing, we showed that two-digit mental addition and subtraction causally involve RH and LH cerebral areas of posterior parietal cortex to some degree. In particular, we showed that HIPS, VIPS, ANG, and SMG of each hemisphere contribute to solving of both subtraction and addition problems, suggesting that the brain networks underlying these operations are not entirely separated. Importantly, a stronger pattern of hemispheric asymmetry for the HIPS has been found for addition compared to subtraction. In particular, results showed a greater involvement of the right HIPS than the left one, suggesting that the right HIPS is associated with the processing of order information along the MNL in complex mental calculation. We also found less asymmetry for the VIPS, which supports the use of the MNL. Together, these results suggest that the two-digit mental addition is more strongly associated with the use of a spatial mapping compared to subtraction. In support of this view, a greater role of left and right ANG has been found for addition, which is needed in verbal processing of numbers and in visuospatial attention processes. We also revealed a greater involvement of the bilateral SMG in performing two-digit mental subtraction compared to addition, in response to greater working memory load. In light of these findings, we provide a detailed view on causal role of parietal areas of the right hemisphere in solving complex mental additions and subtractions.

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