Balancing the two hemispheres in simple calculation.

Evidence from direct cortical electrostimulation.

Semenza C. [1,2], Salillas. E.[3], Di Pellegrin S[1] and Della Puppa A.[4]

[1] Neuroscience Department and Centre for Cognitive Neuroscience, University of Padova, Italy.

[2] IRCCS San Camillo Hospital Foundation, Neuropsychology Unit, Lido-Venice, Italy

[3] Basque Center on Cognition, Brain and Language, Donostia, Spain

[4] Department of Neurosurgery, University Hospital of Padova, Italy

ABSTRACT

How do the parietal lobes contribute to simple calculation? Clinical and neuroimaging methods, which are based mainly on correlational evidence, have provided contrasting results so far. Here we used direct cortical electrostimulation during brain surgery to causally infer the role of the left and right parietal lobes in simple calculation. Stimulation provoked errors for addition and multiplication in different parietal areas on both hemispheres. Crucially, an innovative qualitative error analysis unveiled the functional contrast of the two parietal lobes. Right or left stimulation led to different types of substitution errors in multiplication, unveiling the function of the more active hemisphere. While inhibition of the left hemisphere led mainly to approximation errors, right hemisphere inhibition enhanced retrieval within a stored repertory. These results highlight the respective roles of each hemisphere in the network: rote retrieval of possible solutions by the left parietal areas and approximation to the correct solution by the right hemisphere. The bilateral orchestration between these functions guarantees precise calculation.

Keywords: approximation; exact calculation; parietal lobe; hemispheric complementarity; brain mapping.

INTRODUCTION

How do the parietal lobes contribute to simple calculation? The traditional view, based on lesion studies and corroborated by neuroimaging (Dehaene and Cohen, 1995; Dehaene et al, 2003), is that, in mathematically educated people, one-digit addition and multiplication are retrieved by verbal rote mechanisms (Ashcraft, 1995; Domahs and Delazer, 2005; Verguts and Fias, 2005; Grabner et al, 2009) in the left angular gyrus (lAG) with the contribution of the horizontal portion of the left intraparietal sulcus (lHIPS). This view has been completed by further studies suggesting the additional involvement, closely related to the demands imposed by arithmetic fact retrieval, of the medial frontal cortex (e.g. Jost et al, 2011). Importantly, clinical cases show that arithmetical fact impairments can be operation-specific, indicating that each type of operation is separately sustained in the brain. Different patterns of preservation and impairment have indeed been reported for each simple operation (e.g. Grafman et al, 1989; McCloskey et al, 1991; Dagenbach and McCloskey, 1992; Girelli et al, 1993; McNeil and Warrington, 1994; Hittmair-Delazer et al, 1994; Dehaene and Cohen, 1997; Cipolotti and De Lacy Costello, 1995; van Harskamp and Cipolotti, 2001, see Cipolotti and van Harskamp, 2001, and Cappelletti, 2015, for reviews). An operation that is selectively impaired in one patient may thus be spared in another patient, who may be instead impaired in another operation. Such pattern, called "double dissociation", cannot be explained in terms of a generic, across-the-board, impairment due to a generalized shortcoming of cognitive resources. All reported cases follow left hemisphere lesions, except for one case of a left-handed patient with a right hemisphere lesion (Dehaene and Cohen, 1997).

Recent neuroimaging (Arsalidou and Taylor, 2011) and brain stimulation studies (Salillas and Semenza, 2015) suggest that a view emphasizing the role of the left hemisphere may need some updating. In fact, several investigations provide new evidence of an involvement of the right parietal lobe in one-digit addition and multiplication. For example, fMRI data (Rosenberg-Lee et al, 2011; Price et al, 2013) provide evidence that simple multiplication is primarily processed in the right parietal lobe. Transcranial magnetic stimulation (TMS) also reveals that, in addition to the lAG and the lHIPS, the right HIPS also contributes to both addition and multiplication (Andres et al, 2011; Salillas et al, 2012); moreover, the right ventral intraparietal sulcus (rVIPS) is also shown to play a role in multiplication (Salillas et al, 2012). Finally, clinical group studies on people with damage to the right hemisphere also regularly report problems with arithmetical facts. These findings have been neglected in literature; only recently has some evidence been produced that these errors result from specific deficits rather than deriving from a generic loss of cognitive sources (Benavides-Varela et al, 2014).

Despite the accumulation of apparently contrasting results highlighting an involvement of both hemispheres in simple arithmetic, no study has focused on the actual role of each hemisphere. This issue is crucial since it might conciliate current neuroimaging, TMS data and recent clinical findings on the brain basis of this fundamental math process.

A recent addition to the above-reported evidence came from investigations using intraoperative direct cortical electrostimulation (DCE), where positive sites were found for addition and multiplication in cortical as well as subcortical locations in the right parietal areas (Della Puppa et al, 2013, 2014). The purpose of DCE is to gather precise information about the brain localization of functions that must be spared while removing tissues affected by pathology. When possible (in a limited number of cases), neurosurgeons check the functions that might depend upon the area that is being operated. Electrodes are applied directly to the cortex after removing part of the skull bone under local anaesthesia. It is possible for the patient to be alert during the operation and to interact with the operating team. The patient's errors in tasks sustained by stimulated areas reveal the locations of these functions so that such areas can be spared in the operation whenever possible.

Previous studies on simple math with DCE had concerned almost exclusively the left parietal cortex (Whalen et al, 1997; Duffau et al, 2002; Kurimoto et al, 2006; Roux et al, 2009; Pu et al, 2011; Yu et al, 2011), contrasting with only two reports (Yu et al, 2011; Della Puppa et al, 2014), whereby positive sites were found in the right parietal area. In all these studies the classification of errors was missing, and no comparison was ever made between the two hemispheres.

The present study compared DCE findings in the left and the right parietal lobe. The analysis of errors that was applied here to DCE findings may reveal differences that could reflect the specific role of each hemisphere. Thus, inhibiting one of the hemispheres by DCE should provoke the predominance of the contralateral function, reflected in the properties of errors. As will be shown, while the left hemisphere seems to predominantly work by retrieving solutions from stored memory, the right hemisphere may contribute in indicating the approximate numerical interval of the solution.

MATERIALS AND METHODS

Participants

Nine people, six females and three males, undergoing resection of a glioma in the parietal lobe (four on the left and five on the right side) participated in this investigation. The location of the glioma for each patient is shown in Figure 1. Figure 2 shows the tumour overlap between the nine patients. In all patients the tumour was located in or near the parietal lobe.

Patients were from 42 to 69 years old (mean = 50.66). Their education ranged from 5 to 13 years (mean = 8.88). Inclusion criteria were: tumour located only in the parietal lobe and full right-handedness assessed through the Italian version of the Edinburgh Handedness Inventory. Exclusion criteria were: preoperative impairment of numeral processing performance and preoperative motor impairment. Informed consent was obtained from all patients and their families. The study was carried out with the approval of the local ethical committee, and informed consent was obtained according to the Declaration of Helsinki.

Preoperative and postoperative assessment

Preoperative clinical examination was normal in all cases. No linguistic impairments in spontaneous speech, word generation, repetition, picture naming, reading or writing were detected (Aachener Aphasia Test; DO-80 picture-naming test). Visual-spatial functions, executive functions, memory, praxis and general cognitive functions as assessed by specific tests were intact. No signs of depression or pathological anxiety were detected, as evaluated with the EORTC QLQ-C30 and HADS tests. The assessment of calculation skills according to the norms reported in Semenza et al (2014) showed normal performance. Over the two days prior to surgery, patients were informed in detail about the procedure of stimulation, familiarized with the stimulus devices and trained to perform naming and calculation tasks. In the preoperative assessment all patients performed at ceiling with the same tasks they later performed during the operation. Failure to perform at ceiling in these tasks was a reason for exclusion from this investigation. In the postoperative cognitive assessment all the patients again showed normal performance on all the tasks.

Intra-operative calculation tasks

A speech therapist was always present in the operating room in order to administer the tests and detect the mistakes. Language and sensory-motor functions were mapped first.

Numerical stimuli were presented visually, in Arabic digits, using a computer system with a display screen. Multiplication and addition were studied. Two different types of calculation tasks were administered to the patient: single-digit addition with a single operand (e.g. 4+7; 8+6; 5+7) and single-digit multiplication with a single operand (e.g. 8x4; 5x6; 9x7). Each operation had to be solved within the four-second time of the stimulation and was presented in the middle of the screen without the equals sign; the patient's response was oral. The patient was unaware of when electrical stimulation was being performed. The administration procedure was as follows: a block of 14 addition problems was presented to the patient in random order using the electro-stimulation in an alternate fashion, and this was repeated three times. Sites were marked with tags as functional for calculation when an error was detected in at least two out of three repeated stimulations. A total of 21 trials with and 21 trials without stimulation were administered. Afterwards, three blocks of 15 multiplication problems were administered with the same procedure, for a total of 22 test problems with and 23 without stimulation.

Surgical Strategy

The surgical strategy was preoperatively planned on the basis of T1-weighted MRI images after gadolinium administration. Tumour removal was carried out using these functional landmarks as boundaries of the resection. A tailored craniotomy was carried out on the basis of neuro-navigation data through a linear incision. As a consequence of this, the parietal cortex was never completely exposed. Conversely, in all cases, sensory-motor areas were partially exposed to determine the intensity of stimulation. The cortical incision procedure was customized according to neuro-navigation and cortical mapping data.

Intraoperative mapping

The study entailed continuous electro-encephalography, electro-corticography and multi-channel electro-myography recordings. Cortical and sub-cortical mapping was performed by means of a bipolar stimulator. The operating surgeon performed both cortical anatomical mapping (sulci/gyri identification) and tumour site assessment with the aid of MRI neuro-navigation. Lettered tags were positioned on the cortical surface to draw the sub-cortical location of the tumour. Then, a functional cortical map was obtained using the method described by Duffau et al (2005). A 5 mm-spaced tips bipolar probe delivering a biphasic current was applied on the cortex for a period of four seconds (pulse frequency of 60 Hz, single pulse phase duration of 0.3 ms). The current intensity was determined with progressive increases by 0.5 mA (from a baseline of 1 mA) until a sensory-motor response was obtained. Every patient was stimulated using the same method with the exact same parameters. A sensory-motor mapping was performed, and numbered tags were positioned on the cortical surface. In a second stage, patients were asked to perform counting and picture naming. In a third stage, calculation task tests were administered. All sites functional for calculation were marked with tags ("+" for addition and "x" for multiplication). Each cortical site (5×5 mm) of the whole cortex exposed by the bone flap was tested 3 times. Both the superior and the inferior parietal gyri were stimulated in all the patients. All sites functional for calculation were spared during tumour resection.

In picture naming, positive sites were found only in left hemisphere patients, who either omitted the answer or produced another word (semantic or phonetic paraphasia). None of these sites was later found positive for addition or multiplication.

Data analysis on addition and multiplication

A site was considered positive if the patient committed errors in at least two out of three tests under DCE stimulation (Duffau et al, 2005). Thus, a first descriptive analysis implied the observation of positive sites in the different cortical parietal areas, distinguishing the angular gyrus (AG), the supramarginal gyrus (SMG), the horizontal intra-parietal sulcus (HIPS), the ventral part of the intra-parietal sulcus (VIPS), the superior parietal lobule and subcortical areas for each operation. This allowed the contrast between arithmetic operations within and across left and right parietal sites.

Secondly, a qualitative analysis of errors was performed on the whole pool of errors for multiplication. One patient (LD), who was receiving surgery on the left hemisphere, was excluded from this analysis because a simplified version of the items was used. This analysis was focused on the quantification of retrieval (table-related and operand errors) vs. non-retrieval errors. Operand errors refer to those errors implying a solution in the multiplication table of one of the operands (e.g. 8 x 7 = 64); Table-related errors are errors that are a valid product outside of the multiplication table of any of the operands (e.g. 8 x 7 = 81). McCloskey et al. (1991) explain these errors as due to interference during the retrieval of arithmetic operations that are verbally learned by rote and stored in memory as an associative network. The authors further classify all other errors as non-table/non-retrieval errors. A second classification aimed at the detection of the use of approximation. Thus, errors were classified as close to or far from the correct solution. A maximum deviation of up to 9 was considered an approximation in multiplication, where the maximum solution was 81 (9 x 9 = 9). For addition problems, the proportional maximum deviation of 2 was used because the maximum possible solution was 18 (9 + 9). All errors were classified as close or far, thus leading to six different categories: Operand, Operand close, Table, Table close, Non-Table and Non-Table close.

A descriptive analysis was carried out for all errors. The probability of each type of error for each patient was calculated as the number of errors for each category divided by the total number of errors for that patient. The reported proportions for each category reflect the average of the probability across patients. Three different analyses were performed: 1) First, two Z tests contrasted the probability of retrieval (operand plus operand close, table close and table far) vs. non-retrieval (non-table close plus non-table far errors), one test for each hemisphere or group of patients. 2) Next, two Z tests contrasted the probability of close errors (table close plus non-table close errors) vs. far errors (table far plus non-table far), one test for each hemisphere. Operand errors were excluded from these last tests. 3) Operand close errors were taken as the best indication of a retrieval process, and a new Z test contrasted the difference in the probability of this error type between the two hemispheres. Z tests were performed on the averaged probability for each category, over the total number of errors for each disrupted hemisphere (RH: 21 errors; LH: 11 errors) for the first analysis (1) and excluding operand errors for the second analyses (RH: 10 errors; LH: 7 errors; (2)). For the third analysis, performed on operand errors, Z tests were calculated on the proportions over the total amount of errors for each hemisphere, including operand errors (RH: 21 errors; LH: 11 errors; (3)).

Finally, for addition, the qualitative analysis was restricted to the observation of approximation errors in the two hemispheres. In the first analysis, a Z test contrasted the probability of using approximation (i.e. close errors) between hemispheres, over the total amount of errors in each hemisphere (RH: 10 errors; LH: 12 errors). Secondly, the actual deviation from the correct solution was more closely analysed, and a t-test was performed on the array of deviations between the two groups of patients. This t-test contrasted the two hemispheres in terms of the absolute value of deviation of all errors.

RESULTS

Distribution of positive sites.

Table 1 and Figure 3 report the distribution of positive sites (numerical processing interferences) for addition and multiplication. Overall, a total of 18 positive sites (4 for addition and 14 for multiplication) were found in the right hemisphere patients and 20 (6 for addition and 14 for multiplication) in the left hemisphere patients. No individual site was found positive for both addition and multiplication. Overall, functional sites for these tasks were located in all parietal regions explored by electrostimulation on both hemispheres: the angular gyrus (AG), supramarginal gyrus (SMG), horizontal intraparietal sulcus (HIPS) and superior parietal lobule. Moreover, electrostimulation to subcortical areas detected distinct interference sites for both addition and multiplication in both hemispheres. Multiplication sites seem to be more anterior on the left hemisphere (i.e. in the SMG) with respect to addition sites, which seem to be distributed more posteriorly (i.e. in the AG). Multiplication sites appear to be more close together in the left than in the right hemisphere: while only multiplication sites were found in the left SMG, both addition and multiplication sites were found in the right SMG. Sites that were positive only for multiplication were found bilaterally in the HIPS. Subcortical functional sites were also found on both sides for multiplication and on the right side for addition. No omission/commission errors were made during surgery without stimulation.

Qualitative analysis of errors.

The averaged probability of commission errors (i.e. mistaken solutions) under right hemisphere stimulation was 0.16 for addition and 0.19 for multiplication. The averaged probability of committing an error under left hemisphere stimulation was 0.19 for addition and 0.25 for multiplication. Considering both omission and commission errors, the averaged probability of error under right hemisphere stimulation was 0.24 for addition and 0.34 for multiplication. The probability of any error under left hemisphere stimulation was 0.3 for both addition and multiplication. Thus, although disruption of the left parietal areas tends to provoke more calculation errors, especially for addition, many errors were also found after right hemisphere disruption. Importantly, the quality of commission errors differed (all errors are described in supplemental tables S1, S2 and S3).

For multiplication (Figure 4), errors were classified according to the presence or absence of fact retrieval (McCloskey et al, 1991). "Operand" errors thus refer to those errors implying a solution in the multiplication table of one of the operands (e.g. 8 x 7 = 64); "table-related" errors are errors that are a valid product outside of the multiplication table of any of the operands (e.g. 8 x 7= 81). Contrarily, "non-table" errors are errors that are not a product in any multiplication table, and thus arithmetic fact retrieval does not mediate their production (e.g. 8 x 7 = 83). Besides this classification, given solutions were classified as close to or far from the correct solution as a means to measure the use of approximation. Erroneous solutions with a maximal difference of 9 from the correct solution were classified as close (i.e. an index of the use of approximation), and all other distances were considered far. For operand solutions, however, solutions that were close to the correct one were considered the best indicator of retrieval, since they comprised the retrieval of one of the closest solutions in the multiplication table of any of the operands (i.e. 2 x 3 = 8, or 9).

With RH disruption by DCE, the probability of committing retrieval errors (72% out of 21 errors) significantly differed from the probability of committing non-retrieval errors (28% of 21 errors). This seems to indicate the predominance for the use of retrieval when right parietal areas are inhibited (Z=2.85 p=0.004 one-tailed retrieval > non retrieval, p=0.002). During RH stimulation approximation, close errors were equally probable (27% of 10 errors) to far errors (15% of 10 errors), with no significant difference (Z=0.66 p=0.5 one-tailed p=0.25). Contrarily, under LH disruption by DCE, the likelihood of close errors (53% of 7) significantly differed from that of far errors (11% of 7). This may indicate a predominance of the use of approximation when left parietal areas are inhibited (Z=1.7 p=0.09 one tailed close > far p=0.04). The proportion of retrieval errors (53% of 11 errors) did not differ from the proportion of non-retrieval errors (47% of 11) after LH stimulation. Finally, operand close errors were predominant during RH stimulation (39% of 21) and significantly more likely to result during RH stimulation than during LH stimulation (5.6% of 11 errors) (Z=2.05 p=0.04 one-tailed RH>LH p=0.02). These errors are the best indication of the use of retrieval during multiplication, while the right parietal areas are inhibited by DCE.

Because all addition errors can be an alternative sum of any of the operands and therefore a classification in terms of retrieval is not applicable, the analysis of errors for addition was focused in the use of approximation (Figure 5). The disruption of the RH by DCE implied a lower proportion of approximation errors (83% of 10 errors) than disruption of the LH, as 100% of errors were close errors (out of 10, Z=1.48 p=0.14 one-tailed RH<LH p=0.06). A second analysis considered the direction and actual deviation from the correct solution. After stimulation of each hemisphere, a higher proportion of the errors implied an underestimation in relation to the correct response (65%). However, this tendency became stronger under LH stimulation (70% of 12 errors, Z= 1.78; p=0.07 one-tailed underestimation > overestimation p=0.036 vs. 60% of errors under RH stimulation (n.s.)). Crucially, interference on the RH led to a higher overall absolute deviation from the correct solution than disruption on the LH (RH:1.7 vs. LH:1.4; t=2.45, p=0.04, one-tailed p=0.02).

Finally, in order to observe the inter-individual variability for LH vs. RH patterns of commission errors, a hierarchical cluster analysis (Ward's method using Squared Euclidean Distance) was performed based on two variables reflecting the extreme case of errors: 1) operand errors (probability of operand error plus probability of operand close error for each patient), reflecting retrieval and 2) pure approximation (the mean between the probability for non-table close errors in multiplication and the probability for close errors in addition, for each patient), reflecting approximation without any retrieval. This cluster analysis correctly classified 6 out of 8 patients in two groups. One of the two misclassified patients was SM, for whom mainly subcortical stimulation was performed. Hence, two clusters were obtained: cluster 1 that grouped all the LH patients (VF, PI and BA) and RH patients GL and SM, and cluster 2 that grouped RH patients PG, CP and CF (see the resulting dendogram in Supplemental material Figure 1S and further analyses in Figure 2S).

DISCUSSION

This study used DCE to understand the respective roles of the two hemispheres in simple calculation. In agreement with recent literature, both parietal lobes contribute to simple addition and multiplication. DCE allowed further specification of what each hemisphere does.

The newest and most interesting results come from the analysis of errors, which seems to suggest that the two hemispheres play complementary roles. Importantly, while the proportion of omission errors was small, commission errors were frequently found for both hemispheres. Commission errors are of special interest in neuropsychology insofar that they may reveal the functional systems working to compensate the disruption of normally working systems. The errors found in this study were very specific in type, and no site was in fact found positive for both addition and multiplication. Indeed, it would not be easy to attribute the errors to generic problems of attention, vision or language. The contrast between retrieval and approximation was not empirically manipulated; however a distinctive pattern of spontaneous errors appeared. Such a systematic pattern cannot be accounted for by generic visual or attentional factors. These factors should affect errors equally when stimulating any one of the two hemispheres. No overlap was found with naming sites; thus no errors made after left hemisphere stimulation were likely to be due to language problems. However, if we consider retrieval errors as interference from items that are related in an arithmetic memory network, they could be interpreted as a sort of “arithmetic paraphasia” similar to the interference occurring between semantically related items during picture naming. Indeed, the memory network that was being targeted is a core learned arithmetic network, a crucial component of the math system located in the left hemisphere, from which the stored result for a given simple operation may be retrieved.

Literature on calculation offers a clear, theoretically based and empirically supported distinction for the interpretation of the present results. A crucial distinction between retrieval and non-retrieval multiplication errors is in fact relevant in this study. An unequal distribution in such errors was found when comparing the results of interference to the right and left parietal areas. While interference on the right parietal areas provoked an overwhelming proportion of retrieval errors, interference on the left was about as likely to provoke non-retrieval errors as retrieval errors. Thus interference on the left provokes a heavy use of approximation, as reflected by the high proportion of errors close to the solution.

These results can be interpreted as reflecting different contributions to calculation of the right and left parietal areas. Based on the idea of interhemispheric inhibition/interference between the left and right parietal lobes (Cappelletti et al, 2007; Cohen-Kadosh et al, 2010), interference on the right hemisphere would leave more space to the action of the left hemisphere; errors thus tend to reflect left hemisphere predominance in the search for a solution through retrieval. Conversely, interference on the left tend to result in enhanced right hemisphere processing, which is reflected in a different type of error guided by approximation. The findings for addition, whereby overestimation and overall deviation from the correct solution is larger when the right hemisphere is interfered with, converge with this view. On this logic, retrieval errors are committed by the left hemisphere when choosing from a stored repertory of solutions of table problems. In contrast, non-retrieval, often approximation, errors are committed by the right hemisphere using its own type of competence. A hypothesis in this sense had been put forward (Dehaene, 2009), but no direct empirical evidence had been provided before the present study. Indeed, storing table knowledge and approximation are functions that, overall, are respectively attributed to the left and the right hemisphere. These issues constitute the grounds of a presently ongoing debate. The evidence collected with DCE seems to suggest that simple multiplication is performed with the critical, more or less simultaneous, contribution of the two hemispheres, each one according to its own capacity. In this context, approximation and retrieval are thus not separate operations occurring when required as such and sustained by different areas, as was previously assumed in the literature. They are rather critical processing components dynamically concurring in the same task. DCE unbalances this dynamic according to a right or a left stimulation. These findings open the way to further studies aiming at highlighting the dynamic interplay of the two hemispheres.

Further results complement earlier observations. Multiplication sites appear to be sparser on the right than on the left, where they appear to be closer together within each patient. Moreover, multiplication sites seem to be more anterior on the left hemisphere (i.e. in the SMG) with respect to addition sites, which seem to be distributed more posteriorly (i.e. in the AG). Only for multiplication were positive sites found bilaterally in the HIPS. Subcortical functional sites were also found on both sides for multiplication and on the right side for addition.

We discovered that multiplication and addition sites are differently distributed between the SMG and the AG on the left. These findings contradict the commonly accepted notion that multiplication is mainly located in the AG, rather than more anteriorly in the SMG, as was found in our study. The location of addition sites located more posteriorly with respect to the multiplication sites in the AG is also novel and requires confirmation.

Importantly, no individual site was found positive for both addition and multiplication. This finding is important insofar that it constitutes evidence of the operation-specificity of positive sites. This means that disturbances of simple calculation found when disrupting the functioning of the right hemisphere can hardly be attributed to a generic lack of resources due to brain damage. The traditional literature on acalculia indeed occasionally reports errors even in one-digit calculation after right hemisphere lesions. However, these findings have never been commented upon, possibly because of the assumption that they could be attributed to a generic brain damage effect.

Positive sites for calculation in subcortical areas were found in both hemispheres. However, further research is needed to understand the role of specific subcortical pathways that unfortunately could not be clearly identified in these operations.

Addition and multiplication thus entail not completely overlapping parietal substrates. Exact calculation, in turn, is not a function reduced to an isolated verbal left hemisphere network: it rather requires the joint coordination of bilateral parietal areas with specific contributions from each hemisphere. The precise analysis of the errors elicited by DCE shows to be a crucial source of information for the functional characteristics of the stimulated sites.

Acknowledgements

This work was supported by the Italian Ministry of Health (grant RF-2009-1530973); by the University of Padua (grant Progetto d'Ateneo CPDA131328 and Progetto strategico NEURAT) to CS, and by the Spanish Ministry of Science and Innovation (grant PSI2014-53351) to ES and by financial assistance as a Severo Ochoa Center of Excellence SEV-2015-0490 to the BCBL (ES). The authors declare no competing financial interests. CS and ES equally contributed to this paper.

Correspondence and request for materials should be addressed to Carlo Semenza MD, Department of Neuroscience, University of Padova, via Giustiniani 5, 35128 Padova, Italy (carlo.semenza@unipd.it) or to Elena Salillas PhD, Basque Center on Cognition, Brian and Language, Paseo Mikeletegi 69, 20009 San Sebastián-Donostia, Spain (e.salillas@bcbl.eu).

REFERENCES

Andres M, Pelgrims B, Michaux N, Olivier E, Pesenti M. 2011. Role of distinct parietal areas in arithmetic: an fMRI-guided TMS study. Neuroimage. 54(4): 3048- 3056.

Arsalidou M, Taylor MJ. 2011. 2+2=4? Meta-analyses of brain areas needed for numbers and calculations. Neuroimage. 54: 2382–2393.

Ashcraft MH. 1995. Cognitive psychology and simple arithmetic: a review and summary of new directions. Math Cogn. 1(1): 3-34.

Benavides-Varela S, Pitteri M, Priftis K, Passarini L, Meneghello F, Semenza C. 2014. Right-hemisphere (spatial?) acalculia and the influence of neglect. Frontiers in Human Neurosciences, 8:644, 1-9.

Cappelletti M. 2015.The neuropsychology of acquired number and calculation disorders. In: Cohen Kadosh R, Dowker A, editors. Oxford Handbook of Numerical Cognition. Oxford Univ. Press, Oxford.

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

Cipolotti L, De Lacy Costello A, 1995. Selwctive impairment for simple division. Cortex. 31: 433-449.

Cipolotti L, van Harskamp NJ. 2001. Disturbances of number processing and calculation. In: Berndt RS, editor. Handbook of Neuropsychology. Elsevier.

Cohen Kadosh R, Soskic S, Iuculano T, Kanai R, Walsh V. 2010. Modulating neuronal activity produces specific and long lasting changes in numerical competence. Curr Biol. 20: 2016-2020.

Dagenbach D, McCloskey M. 1992. The organization of arithmetical facts in memory. Evidence from a brain.damaged patient. Brain Cog. 20: 345-366.

Dehaene S, Cohen L. 1995. Towards and 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. Cognitive Neuropsych. 20: 487–506.

Dehaene S. 2009. Origins of mathematical intuition. The case of arithmetic. Ann N Y Acad Sci. 1156: 232-259.

Della Puppa A, De Pellegrin S, Salillas E, Grego A, Lazzarini A, Vallesi A. 2014. Functional mapping of left parietal areas involved in simple addition and multiplication. A single-case study of qualitative analysis of errors. J Neuropsychol. 9(2): 330-335.

Della Puppa A, De Pellegrin ST, D'Avella E, Gioffrè G, Munari M, Saladini M, Salillas E, Scienza R, Semenza C. 2013. Right parietal cortex and calculation processing. Intra-operative functional mapping of multiplication and addition. J Neurosurg. 27(6): 680-90.

Domahs F, Delazer M. 2005. Some assumptions and facts about arithmetic facts. Psychol Sci. 47: 96–111.

Duffau H, Denvil D, Lopes M, Gasparini M, Cohen L, Capelle L, Van Effenterre V. 2002. Intraoperative mapping of the cortical areas involved in multiplication and subtraction: An electrostimulation study in a patient with a left parietal glioma. J Neurol Neurosurg Psychiatry. 73: 733–738.

Duffau H, Gatignol P, Mandonnet E, Peruzzi P, Tzourio-Mazoyer N, Capelle L. 2005. New insights into the anatomo-functional connectivity of the semantic system: a study using cortico-subcortical electrostimulations. Brain. 128: 797–810.

Grabner R, Ischebeck A, Reishofer G, Koschutnig K, Delazer M, Ebner F, Neuper C. 2009. 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.

Girelli L, Hittmair-Delazer M, Semenza C, Denes G. 1996. The representation of arithmetical facts: evidence from two rehabilitation studies. Cortex. 32: 49-66.

Grafman J, Kampen D, Rosemberg J, Salazar A, Boller F. 1989. Calculation ability in a patient with a virtual left hemisphere hemispherectomy. Behav Neurol: 2; 183-194.

Hittmair-Delazer M, Semenza C, Denes G. 1994. Concepts and facts in calculation. *Brain*. 117: 715-728.

Jost K, Khader PH, Burke M, Bien S, Rösler F. 2011. Frontal and Parietal Contributions to Arithmetic Fact Retrieval: A Parametric Analysis of the Problem-Size Effect. Hum Brain Mapp. 32: 51–59.

Kurimoto M, Asahi T, Shibata T, Takahashi C, Nagai S, Hayashi N, Matsui M, Endo S. 2006. Safe removal of glioblastoma near the angular gyrus by awake surgery preserving calculation ability. Neurol Med Chir (Tokyo). 46(1): 46-50.

McCloskey M, Harley W, Sokol SM. 1991. Models of arithmetic fact retrieval: An evaluation in light of findings from normal and brain-damaged subjects. J Exp Psychol Learn Mem Cogn. 3: 377–397.

McNeil J, Warrington EK. 1994. A dissociation between addition and subtraction with written calculation. Neuropsychologia. 32, 717-728.

Price GR, Mazzocco MM, Ansari D. 2013. Why mental arithmetic counts: brain activation during single digit arithmetic predicts high school math scores. J Neurosci. 33: 156–163.

Pu S, Li YN, Wu CX, Wang YZ, Zhou XL, Jiang T. 2011. Cortical areas involved in numerical processing: An intraoperative electrostimulation study. Stereotact Funct Neurosurg. 89 (1): 42–47.

Rosenberg-Lee M, Chang TT, Young CB, Wu S, Menon V. 2011. Functional dissociations between four basic arithmetic operations in the human posterior parietal cortex: A cytoarchitectonic mapping study. Neuropsychologia. 49 (9): 2592–2608.

Roux FE, Boukhatem L, Draper L, Sacko O, Demonet JF. 2009. Cortical calculation localization using electrostimulation. J Neurosurg. 110 (6): 1291–1299.

Salillas E, Semenza C, Basso D, Vecchi T, Siegal M. 2012. Single pulse TMS induced disruption to right and left parietal cortex on addiction and multiplication. Neuroimage. 59: 3159–3165.

Salillas E, Semenza C. 2015. Mapping the Brain for Math. Reversible inactivation by direct cortical electrostimulation and transcranial magnetic stimulation. In: Cohen Kadosh R, Dowker A, editors. Oxford Handbook of Numerical Cognition. Oxford Univ. Press, Oxford.

Semenza C, Meneghello F, Arcara G, Burgio F, Gnoato F, Facchini S, Benavides-Varela S, Clementi M, Butterworth B. 2014. A new clinical tool for assessing numerical abilities in neurological diseases: Numerical Activities of Daily Living. Front. Aging Neurosci. 6: 112, 1-8.

van Harskamp NJ, Cipolotti L. 2001. Selective impairments in addition, subtraction and multiplication: implications for the orgnization of arithmetical facts. Cortex, 37, 363-388.

Verguts T, Fias W. 2005. Interacting neighbors: A connectionist model of retrieval in single-digit multiplication. Mem Cognit. 33: 1–16.

Whalen J, McCloskey M, Lesser RP, Gordon B. 1997. Localizing Arithmetic Processes in the Brain: Evidence from a Transient Deficit During Cortical Stimulation. J Cogn Neurosci. 9 (3): 409–417.

Yu X, Chen C, Pu S, Wu C, Li Y, Jiang T, Zhou X. 2011. Dissociation of subtraction and multiplication in the right parietal cortex: Evidence from intraoperative cortical electrostimulation. Neuropsychologia. 49: 2889–2895.

Table 1. Positive sites for each patient. A site was considered positive if the patient committed at least two out of three errors under DCE stimulation. A: Addition M: Multiplication.

Patient	Angular Gyrus	Supramarginal Gyrus	HIPS	Superior Lobule	Subcortical
RIGHT					
GL	1A	1M	1M	-	
CP	1M	1M	1M	1M	
CF	-	1M 1A	-	-	2M 1A
PG	1M	1M	-	-	
SM	-	-	-	1M	2M 1A
LEFT					
BA	-	1M	1M	2A	
PI	-	1M	1M	1A	
VF	3A	2M	1M	-	
LD	2M	1M	1M	1M	2M

FIGURE CAPTIONS

Figure 1. Structural images for the nine patients showing the location of the tumour. *Right hemisphere patients*: in GL the tumour was cortically bounded by the superior parietal lobule, AG and SMG, and it extended to invade the IPS and dorsal postcentral gyrus. In CP it was located in the dorsal part of the precentral gyrus, colliding anteriorly with the superior frontal lobule, inferiorly with the middle frontal gyrus, and posteriorly with the postcentral gyrus and parietal areas. CF showed a tumour in the superior parietal lobule, bounded inferiorly by the inferior parietal areas and anteriorly by the postcentral gyrus. In PG, the tumour was located in the inferior parietal lobule and postcentral gyrus and bounded by the IPS, ANG and SMG. In SM it was located in the precentral gyrus and was bounded posteriorly by the postcentral and then superior parietal lobule. *Left hemisphere patients*: in BA the tumour was located between the postcentral gyrus and the superior parietal lobule, bounded inferiorly by the inferior parietal areas and IPS. In PI the tumour invaded the superior part of the central sulcus and the precentral and postcentral gyry, and it was bounded posteriorly by the superior parietal lobule. VF had the most subcortically extended tumour, located below the postcentral and parietal areas. Patient LD had a previous right hemisphere lesion and showed the largest tumour of all patients, in the left hemisphere, extending within and subcortically below the parietal lobe.

Figure 2. **Tumour overlap between the nine patients.** Structural images from each patient were normalized to an ICBM152_2016 template using SPM8. Tumours were then drawn in each slice using the normalized image and overlapped in the template T1 using MRIcron.

Figure 3. Stimulation points for each patient. A) Cortical reconstruction for each patient (cortical reconstruction and volumetric segmentation was performed with the Freesurfer image analysis suite (http://surfer.nmr.mgh.harvard.edu/)). Stimulation points were located using anatomical landmarks and the relative location of the sensorimotor stimulation. Images are oriented to match the orientation of the photo (except for patient SM), which was taken after stimulation and tagging was performed. For patients BA and PI, the photo was taken before the last positive site on SMG an SPL were found, respectively. They are thus not localized in the surface. **B)** Cortical surfaces and stimulation points for each patient were projected on an ICBM152_2016 template using the FreeSurfer module of Brainstorm (http://neuroimage.usc.edu/brainstorm). The tumour was drawn slide by slide and coloured in black (note that tumours are usually not recognized by FreeSurfer during surface reconstruction when they occupy cortical areas; therefore, an empty space usually appears in the cortex, which unequivocally indexes the tumour location in the cortex). In all figures: superior parietal lobe - light pink; IPS - violet; ANG - dark blue; SMG - light blue.

Figure 4. A qualitative analysis of errors reveals inter-hemispheric differences in the contribution to multiplication. A) Plots in percentages of the proportion of errors for each error category when the right hemisphere was stimulated. **B)** Plots in percentages of the proportion of errors for each error category when the left hemisphere was stimulated. **C)** All retrieval vs. non-retrieval errors collapsed. These are the proportions where statistics were conducted. **D)** Plots of collapsed close vs. far errors for each hemisphere.

Figure 5. **Analysis of errors reveals inter-hemispheric differences in the use of approximation during addition. A)** The relative use of approximation between the two hemispheres. **B)** Errors ordered from maximum overestimation to maximum underestimation on the X-axis and the actual deviation of each error for each hemisphere on the Y-axis. **C)** The mean absolute deviation for each of the hemispheres. Error bars represent standard error.