

UC Irvine

UC Irvine Previously Published Works

Title

Dissociation of subtraction and multiplication in the right parietal cortex: Evidence from intraoperative cortical electrostimulation

Permalink

<https://escholarship.org/uc/item/9pp9w5bp>

Journal

Neuropsychologia, 49(10)

ISSN

0028-3932

Authors

Yu, Xiaodan
Chen, Chuansheng
Pu, Song
[et al.](#)

Publication Date

2011-08-01

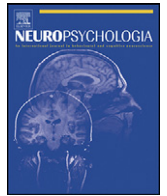
DOI

10.1016/j.neuropsychologia.2011.06.015

Copyright Information

This work is made available under the terms of a Creative Commons Attribution License, available at <https://creativecommons.org/licenses/by/4.0/>

Peer reviewed



Dissociation of subtraction and multiplication in the right parietal cortex: Evidence from intraoperative cortical electrostimulation

Xiaodan Yu^a, Chuansheng Chen^b, Song Pu^c, Chenxing Wu^d, Yongnian Li^a, Tao Jiang^d, Xinlin Zhou^{a,*}

^a National Key Laboratory of Cognitive Neuroscience and Learning, Institute of Cognitive Neuroscience and Learning, Beijing Normal University, Beijing 100875, China

^b Department of Psychology and Social Behavior, University of California, Irvine, CA 92697-7085, USA

^c Department of Neurosurgery, The First Affiliated Hospital of Harbin Medical University, Harbin, Heilongjiang 150001, China

^d Department of Neurosurgery, Beijing Tiantan Hospital Affiliated to Capital Medical University, Beijing 100050, China

ARTICLE INFO

Article history:

Received 16 November 2010

Received in revised form 28 April 2011

Accepted 14 June 2011

Available online 28 June 2011

Keywords:

Numerical processing

Intraoperative cortical electrical stimulation

Cognitive arithmetic

Glioma

ABSTRACT

Previous research has consistently shown that the left parietal cortex is critical for numerical processing, but the role of the right parietal lobe has been much less clear. This study used the intraoperative cortical electrical stimulation approach to investigate neural dissociation in the right parietal cortex for subtraction and multiplication. Results showed that multiplication (as well as picture naming) was not affected by the cortical electrical stimulation on all the targeted sites of the right parietal cortex as well as those of the right temporal cortex. In contrast, stimulation at three right parietal sites (two sites in the right inferior parietal lobule and one in the right angular gyrus) impaired performance on simple subtraction problems. This study provided the first evidence from an intraoperative cortical electrical stimulation study to show the dissociation of arithmetic operations in the right parietal cortex. This dissociation between subtraction and multiplication suggests that the right parietal cortex plays a more significant role in quantity processing (subtraction) than in verbal processing (multiplication) in numerical processing.

© 2011 Elsevier Ltd. All rights reserved.

1. Introduction

Many neuropsychological and neuroimaging studies have been devoted to revealing neural substrates of human arithmetic ability. The parietal cortex, especially the intraparietal sulcus (IPS), has been found to play a critical role in numerical processing (e.g., Ansari, Fugelsang, Dhital, & Venkatraman, 2006; Cantlon, Brannon, Carter, & Pelphrey, 2006; Chochon, Cohen, van de Moortele, & Dehaene, 1999; Cohen Kadosh et al., 2005; R. Cohen Kadosh, K. Cohen Kadosh, Kaas, Henik, Goebel, 2007; Dehaene, Spelke, Stanescu, Pinel, & Tsivkin, 1999; Eger, Sterzer, Russ, Giraud, Kleinschmidt, 2003; Fias, Lammertyn, Reynvoet, Dupont, & Orban, 2003; Kaufmann et al., 2005; see a review by Dehaene, Piazza, Pinel, & Cohen, 2003). The consistency of evidence, however, varied by hemisphere. Several lines of previous studies have consistently shown that the left parietal cortex is critical for numerical processing (e.g., Ashkenazi, Henik, Ifergane, & Shelef, 2008; Cohen Kadosh et al., 2005; Rickard et al., 2000; Takayama, Sugishita, Akiguchi, & Kimura, 1994; Warrington, 1982; Zago et al., 2008).

First, numerous studies have shown that the patients who had injuries in the parietal regions suffered from dyscalculia, but did not show significant impairments in other types of cognitive abil-

ities (e.g., Ashkenazi et al., 2008; Baldo & Dronkers, 2007; Delazer & Benke, 1997; Denes & Signorini, 2001; Van Harskamp, Rudge, & Cipolotti, 2002). For example, Denes and Signorini (2001) reported a patient with an injury in the left parietal cortex who showed dense acalculia and a specific deficit in reading numbers. His word reading and picture naming abilities were preserved. Van Harskamp et al. (2002) also reported a case of impaired single-digit subtraction due to a left parietal lobe lesion. Similar evidence also came from studies on Gerstmann's syndrome. Acalculia is a typical symptom of Gerstmann's syndrome along with other symptoms such as agraphia, finger agnosia, and left–right distinction difficulties (Gerstmann, 1940). Several studies showed that the lesions that cause acalculia among patients with Gerstmann's syndrome were typically centered in the left parietal lobe (for a review, see Dehaene et al., 2003; Mayer et al., 1999; Takayama et al., 1994).

Second, repetitive transcranial magnetic stimulation (rTMS) studies showed that stimulation in the left parietal cortex could induce dyscalculia (e.g., Andres, Seron, & Olivier, 2005; Knops, Nuerk, Sparing, Foltys, & Willmes, 2006; Sandrini, Rossini, & Miniussi, 2004). Andres and colleagues (2005) found significant increases in RTs when subjects were comparing digits following an rTMS-induced disruption in the left posterior parietal cortex. Sandrini et al. (2004) also found that subjects' performance on a number-comparison task was significantly slowed down when trains of repetitive TMS were delivered to their posterior parietal scalp site overlying the left inferior parietal lobule.

* Corresponding author. Tel.: +86 10 58806154; fax: +86 10 58806154.

E-mail address: zhou.xinlin@bnu.edu.cn (X. Zhou).

Third, intraoperative cortical electrical stimulation (IES) studies also confirmed the importance of the left parietal lobe in number processing (e.g., Duffau et al., 2002; Roux, Boukhatem, Draper, Sacko, & Demonet, 2009; Whalen, McCloskey, Lesser, & Gordon, 1997). The intraoperative cortical electrical stimulation approach is used before the removal of glioma to help doctors avoid dissecting key functional brain regions (e.g., motor, language). Researchers have used this method to localize brain functions. For example, placing a single electrode on a site in the left inferior parietal region near the angular gyrus, Whalen et al. (1997) found that multiplication performance was disrupted much more than was addition performance when stimulation was delivered to the site (27% vs. 87%) (Whalen et al., 1997). Duffau et al. (2002) also used intraoperative cortical electrical stimulation and found a dissociation of simple subtraction and multiplication in the left parietal cortex. They found a functional site for multiplication in the inferior part of the AG, a functional site for subtraction in the superior part immediately below the intraparietal sulcus, and a functional intermediary area (overlapping of the two previous sites) for both multiplication and subtraction.

Fourth, split-brain studies also showed the importance of the left hemisphere in numerical processing (e.g., Cohen & Dehaene, 1996; Funnell, Colvin, & Gazzaniga, 2007; Gazzaniga & Smylie, 1984; Seymour, Reuter-Lorenz, & Gazzaniga, 1994). Gazzaniga and Smylie (1984) reported two brain-bisected patients whose left brain was capable of simple mathematical tasks, whereas their right hemisphere performed poorly. These results have been further confirmed by a series of experiments by Funnell et al. (2007) on split-brain patients.

In contrast to the consistent role of the left parietal lobe in number processing as reviewed above, the role of the right parietal lobe has been less consistent. Some studies suggest that the right parietal lobe might be involved in numerical processing (e.g., Cattaneo, Silvanto, Pascual-Leone, & Battelli, 2009; Chochon et al., 1999; R. Cohen Kadosh, K. Cohen Kadosh, Schuhmann, et al., 2007; Göbel, Walsh, & Rushworth, 2001; Keller & Menon, 2009; Menon, Rivera, White, Glover, & Reiss, 2000; Venkatramana, Ansari, & Chee, 2005). First, fMRI studies showed number-induced activation in the brain regions around the right IPS (e.g., Chochon et al., 1999; Venkatramana et al., 2005). Second, studies with the rTMS technique showed that the right parietal cortex was involved in number processing (e.g., R. Cohen Kadosh, K. Cohen Kadosh, Schuhmann, et al., 2007; Göbel et al., 2001). In fact, an rTMS study by R. Cohen Kadosh, K. Cohen Kadosh, Schuhmann, et al. (2007) found that automatic magnitude processing was impaired only when the right IPS activity was disrupted by rTMS. Third, patient data from several studies were also consistent with the notion that the right parietal cortex is involved in number processing (e.g., Dehaene & Cohen, 1997; Vuilleumier, Ortigue, & Brugger, 2004). For example, Dehaene & Cohen (1997) reported a patient MAR whose simple arithmetic processing was affected by damages in the right inferior parietal lobule. Deficits of numerical processing (e.g., bisection of number intervals) have also been demonstrated in unilateral spatially neglecting patients with right-hemispheric lesions (e.g., Vuilleumier et al., 2004; Zorzi, Priftis, & Umiltà, 2002). Fourth, studies on the numerical processing of split-brain patients showed that these patients could complete number comparison tasks regardless whether the numbers appeared in their right visual field or their left visual field (e.g., Cohen & Dehaene, 1996; Colvin, Funnell, & Gazzaniga, 2005).

Although a large number of studies have implicated the right parietal cortex in number processing, many other studies have failed to come to the same conclusion. For example, Gazzaniga and Smylie (1984) demonstrated that split-brain patients' right brain performed poorly on simple arithmetic tasks. A number of rTMS studies showed that stimulation in the left parietal cortex, but not

that in the right parietal cortex, disrupted numerical processing (e.g., Andres et al., 2005; Sandrini et al., 2004). In addition, most reports on acquired dyscalculia came from patients with injuries to the left parietal regions (e.g., Ashkenazi et al., 2008; Baldo & Dronkers, 2007; Delazer & Benke, 1997; Denes & Signorini, 2001; van Harskamp et al., 2002; see Dehaene & Cohen, 1997, for an exception).

One possible reason for the consistencies of evidence for the right parietal cortex's involvement in number processing is that it may depend on the type of number processing. It is possible that the right hemisphere's role in number processing is limited to tasks that strongly rely on the manipulation of numerical magnitude (such as addition, subtraction, and number comparison) (e.g., Cohen & Dehaene, 1996; R. Cohen Kadosh, K. Cohen Kadosh, Schuhmann, et al., 2007). For number processing that involves less magnitude processing such as multiplication, the right parietal cortex may be less involved. Consistent with this conjecture, two recent fMRI studies (Prado et al., in press; Zhou et al., 2007) found that addition or subtraction problems elicited greater activations in the right intraparietal sulcus than did multiplication problems.

In the current study, we used the intraoperative cortical electrical stimulation approach to further investigate neural dissociation in the right parietal cortex for subtraction and multiplication. To our knowledge, no study has used the intraoperative cortical stimulation approach to investigate the role of the right parietal cortex in numerical processing. Previous studies only examined the left parietal cortex (e.g., Duffau et al., 2002; Roux et al., 2009; Whalen et al., 1997). Given previous imaging findings of a neural dissociation in the right parietal region mentioned above (Prado et al., in press; Zhou et al., 2007), we expected that subtraction, but not multiplication, would be affected when the right parietal lobe was stimulated.

2. Methods

2.1. Case description

HHL, a 41-year-old man with 12 years of formal education, was operated for a low-grade glioma in the right temporal cortex. The surgical approach to the lesion was determined by T1- and T2-weighted MR images, supported by information from intraoperative ultrasonography (e.g., Fig. 1). The glioma had been causing partial seizures. He was right-handed (assessed by the Edinburg inventory) with normal eyesight. Before the experiment, he gave written informed consent for the experiment after the procedures (including behavioral and intraoperative procedures) were fully explained to him. This study was approved by the IRBs of both Tiantan Hospital and the State Key Laboratory of Cognitive Neuroscience and Learning at Beijing Normal University. The glioma resection was conducted in May 2008. By the time of writing this manuscript, the patient had recovered from the glioma and held a regular administrative job.

2.2. Procedure

2.2.1. Pre- and post-operative cognitive tests

Before the surgery and 18 days after the operation, the patient completed four cognitive tests, including a simple reaction time test, single-digit subtraction, Stroop-like number comparison, and a verbal working memory (digit span) test. The two arithmetic tests (single-digit subtraction and number comparison) were used to examine whether he suffered from dyscalculia. All the four cognitive tests are available in the website "<http://www.dweipsy.com>".

In the simple reaction time test, the patient responded by pressing a key quickly once a dot appeared on the screen. The patient pressed "Q" for the session measuring the left hand's reaction time and "P" for the session for the right hand's reaction time. The target stimulus was presented randomly within 15° angle of view and it vanished once the patient pressed the key. The interval between reaction and next stimulus changed randomly between 1500 and 3000 ms. The test lasted approximately 4 min, including 8 practice trials and 40 experimental trials.

We used a standard verification paradigm in the single-digit subtraction task, in which a subtraction equation was presented in the center of the screen and two alternative answers right below the equation. The patient needed to choose the right answer and press the corresponding key. The patient pressed "Q" with the left hand if the correct answer was on the left side or "P" with the right hand if the correct answer was on the right side. This test lasted 3 min.

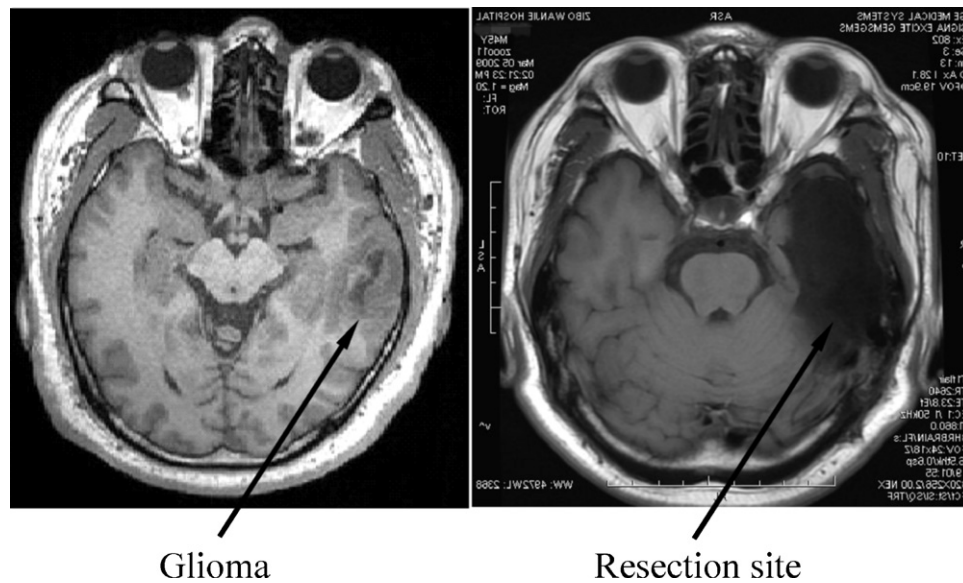


Fig. 1. Pre-operative horizontal image showing a glioma at the right temporal lobe (left) and post-operative horizontal image (right). The right of each image corresponds to the right brain.

Stroop-like number comparison was used to measure the patient's numerical processing ability especially in a situation in which irrelevant information needs to be suppressed. In this task, two numbers were presented on the screen. These

numbers varied in physical size and numerical magnitude (e.g., 3^7). The patient needed to judge which number was bigger in numerical magnitude while ignoring their differences in physical size. He was asked to press the "Q" key if he thought the left one was bigger than the right one and press the "P" key if he thought the right one was bigger. The stimulus's vision angle was approximately 2° . The test had 10 practice trials and 90 experimental stimuli which were divided into three groups. After each group, the patient had a 10 s rest to avoid fatigue. The physical size of the number pairs had three conditions: congruent with numerical magnitude, incongruent with numerical magnitude, and neutral (the two numbers were of the same physical size). This task lasted about 4 min.

To test the patient's forward and backward memory span, we presented a series of digits, one digit at a time for 1 s on the screen. The patient was asked to remember the order of the digits and report them at the end of each series. The test began with 3 items (digits) and increased gradually until the patient failed to report them correctly three times consecutively. The test lasted about 10 min.

2.2.2. Pre-operative training

Two days prior to surgery, the patient was informed in detail about the monitoring procedure of the intraoperative stimulation. He was familiarized with the stimulus materials and trained to perform the naming and calculation tasks. Pictures he could not name were removed from the final stimulus pool. Therefore, the training before operation guaranteed that the patient could normally accomplish the naming and calculation tasks.

2.2.3. Cortical stimulation during operation

Before the removal of the glioma, tests of picture naming, simple subtraction and simple multiplication were administered while the right temporal cortex and right parietal cortex were electrically stimulated. The cortex of the surgical field was divided into 47 sites (about every 1 cm between sites). The large number of stimulation sites was used so that we could study the roles of all the available regions (the inferior parietal lobule, right angular gyrus and superior temporal gyrus) in simple arithmetic. The stimulation-site density was based on previous studies (e.g., Duffau, 2007; Duffau et al., 2002). After locating the tumor boundaries, sterilized paper with printed numbers were placed on the cortical surface to mark the 47 stimulation sites. A 5 mm spaced tips bipolar stimulator probe was used to deliver a biphasic current for at most 4 s on each site. The stimulation stopped once the patient made a correct response. The maximal current was 6 mA.

The picture naming task was carried out firstly to detect sites where stimulation would induce speech arrest. For example, a picture of an elephant was presented in the center of the screen, and the patient was asked to name it during stimulation. The sites showing speech arrest were then excluded in the subsequent arithmetic tasks (simple subtraction and multiplication).

In the simple subtraction and multiplication tasks, stimuli were presented in the center of the screen, and the patient had to orally report the answer within 4 s.

For simple subtraction, both of the two operands were not more than 10 (e.g., 10-2, 8-3, 7-4, 10-5, ...), and for single-digit multiplication, at least one operand was less than 6 (e.g., 4×7 , 3×5 , 2×8 , 5×6 , ...) to ensure that all the equations could be solved by the patient within the 4 s time limit.

Each stimulation site was tested with these two operations. There were 3 blocks for each operation, which were alternated (i.e., subtraction, multiplication, subtraction, multiplication, subtraction, and multiplication). Each block covered all stimulation sites. Each site within a block had either 2 or 3 trials: One trial was presented without stimulation (to check if the patient was able to solve the problem); a second one performed during electrostimulation, and the third one (if necessary) without any stimulation again (this step only occurred when the previous stimulation had induced a disruption of calculation and it was to ensure the patient was able to perform the task again). In sum, there were at least 6 items per site for each operation, 3 with stimulation and 3 without. We used this small number of items per site for two reasons. First, we had an extremely limited amount of time during the actual surgical procedure (while the patient was awake) to cover the large number of sites. More importantly, we used three items with stimulation because several previous studies used the same number of trials with stimulation (e.g., Benzagmout, Gatignol, & Duffau, 2007; Ojemann, Miller, & Silbergeld, 1996). In fact, Benzagmout et al. (2007) concluded that "it is now accepted that three trials are sufficient to determine if a cortical site is or is not essential for language-generating speech disturbances" (p. 742).

There were three types of calculation errors during cortical stimulation: no answer (the patient was unable to give any response to a problem within 4 s), a wrong answer, and repetitive hesitations (for example, $7-3=2? \dots 4? \dots 5?$) (Roux et al., 2009). If two or more errors occurred in one site for each operation, this site was defined as a functional site.

The same items were presented for both stimulated and non-stimulated trials, but never consecutively. The patient was not informed when the brain was stimulated and when it was not. The same cortical site was never stimulated successively twice to avoid seizures.

3. Results

3.1. Pre- and post-operative evaluation

Before and after the surgery, the patient completed four cognitive tests, including a simple reaction test, single-digit subtraction, Stroop-like number comparison, and a verbal working memory (digit span) test. The results for these tests are summarized in Table 1.

Two-factor ANOVA (analysis of variance) was used with hand (left hand vs. right hand) and test order (pre-operation vs. post-operation) as between-subject independent variables. Results showed that on the simple reaction test, post-operation RT was

Table 1
Scores on the pre- and post-operative tests.

Test	Condition	Pre-operation	Post-operation
Simple reaction time	Left hand	316 ms ± 56 (0%)	558 ms ± 234 (0%)
	Right hand	312 ms ± 41 (0%)	502 ms ± 213 (0%)
Single-digit subtraction		2363 ms ± 690 (1.8%)	2607 ms ± 584 (5.4%)
Stroop-like number comparison	Congruent	862 ms ± 345 (3.3%)	991 ms ± 196 (0%)
	Incongruent	878 ms ± 293 (3.3%)	1072 ms ± 165 (3.6%)
	Neutral	835 ms ± 313 (0.0%)	1016 ms ± 153 (0.0%)
Verbal working memory	Forward	6 digits	6 digits
	Backward	4 digits	3 digits

Note: The numbers refer to mean reaction time and standard deviation. Numbers in parentheses refer to percentage of errors.

longer than pre-operation RT, $F(1,74)=34.51$, $p<.001$. No significant main effect of hand and no interaction of hand and test order were found. For single-digit subtraction, one-way ANOVA showed no significant difference in RT between before and after surgery, $F(1,104)=3.84$, $p>.05$. For Stroop-like number comparison, two-factor ANOVA with condition (congruent vs. incongruent vs. neutral) and test order (pre-operation vs. post-operation) as between-subject independent variables showed that RT was longer after surgery than before surgery, $F(1,168)=18.77$, $p<.001$. However, there were neither significant main effect of test conditions, $F(2,168)=0.71$, $p>.05$, nor interaction between the two factors, $F(2,168)=.28$, $p>.05$. Finally, for the verbal working memory, the patient's memory span did not change as a result of the surgery.

The RT results for the simple reaction test and the Stroop-like number comparison task indicated the surgery had made the patient slower to react. To investigate whether the slower RT for numerical processing abilities (i.e., the number Stroop task) could be explained by the slower simple RT, we ran an ANCOVA (analysis of covariance) with simple RT as the covariate. Results showed that, after controlling for simple RT, the RT for the Stroop task was no longer different between before and after the surgery, $F(1,168)=1.73$, $p>.05$. Moreover, the error rates of the four tasks were all low (only one exceeded 5%). Therefore, the patient did not seem to show any salient impairment after the glioma resection operation other than slower RT.

3.2. Intraoperative mapping

The patient performed three tasks (i.e., picture naming, subtraction and multiplication) while specific regions of his cortex were stimulated electronically and intraoperatively. The boundaries for the glioma were marked by letter tags on the brain surface (Fig. 2). The functional stimulation mapping was conducted on the 47 parietal cortical sites in the surgical field. Direct stimulation mapping was simple and well tolerated in the patient. There were no focal seizures occurring during the intraoperative stimulation.

As mention earlier, no responses, wrong answers, and hesitations were all classified as erroneous responses. If two or more errors occurred in one site for each task, this site was defined as a functional site. We found no sites whose stimulation led to failure in picture naming. We also did not find any functional sites for single-digit multiplication. However, of the 47 sites, we found three functional sites for single-digit subtraction (Fig. 2), two of which were located in the right inferior parietal lobule (Fig. 2, tags 1, 2) and the third in the right angular gyrus (Fig. 2, tag 4).

4. Discussion

The present study used the technique of intraoperative cortical electrical stimulation to investigate the role of the right parietal cortex in numerical processing. Picture naming and multiplication were not affected by the cortical electrical stimulation on all the targeted sites of the right parietal cortex as well as the right tem-

poral cortex. Stimulation at three right parietal sites (two sites in the right inferior parietal lobule and one in the right angular gyrus) impaired performance on simple subtraction problems. This is the first evidence from intraoperative cortical stimulation to show the dissociation of arithmetic operations in the right parietal cortex. This dissociation between subtraction and multiplication suggests that the right parietal cortex plays a more significant role in quantity processing (subtraction) than in verbal processing (multiplication) involved in numerical tasks.

The dissociation between subtraction and multiplication found in the current study is consistent with the dissociation of arithmetic operations found in the right parietal cortex in previous neuroimaging studies (Lee, 2000; Ischebeck et al., 2006; Kazui, Kitagaki, & Mori, 2000; Prado et al., in press; Zhou et al., 2007, 2009). For example, Zhou et al. (2007) found that addition problems typically elicited more activation in the right inferior and superior parietal cortex than multiplication. Prado et al. (in press) found that subtraction elicited greater activity than did multiplication in an area within the right IPS region that was defined by a numerosity comparison task. An event-related potentials study showed that, in comparison with multiplication, addition elicited smaller late positive potentials at the right posterior electrodes (Zhou et al., 2009). The smaller late positive potentials have been linked to greater visuospatial processing in previous ERP studies (e.g., Heil & Rolke, 2002; Milivojevic et al., 2003; Núñez-Peña et al., 2005; Yoshino et al., 2000). To our knowledge, the dissociation between subtraction and multiplication at the right parietal cortex has been reported only in one previous neuropsychological study (e.g., Dehaene & Cohen, 1997). Dehaene & Cohen (1997) reported that patient MAR, who had damages in the right inferior parietal lobule, showed an impairment in subtraction and number bisection (a type of quantitative numerical knowledge), while his knowledge of rote arithmetic facts (i.e., multiplication facts) was preserved.

In this study, subtraction was interrupted by direct stimulation at selected parietal sites. These areas are known to be involved in visual perception, visual mental imagery, visuospatial working memory, and spatial attention (e.g., Corbetta et al., 1998, 2000; Diwadkar et al., 2000; Göbel et al., 2001; LaBar et al., 1999; Linden et al., 2003; Nystrom et al., 2000; Postle et al., 2004; Thomas et al., 1999; Zurowski et al., 2002). These visuospatial brain regions seem to play a major role in numerical magnitude processing (Dehaene et al., 1999). As reviewed in the Introduction section, this was supported by several lines of research employing different methodologies such as split-brain patient research (Cohen & Dehaene, 1996), fMRI (Chochon et al., 1999), and rTMS (R. Cohen Kadosh, K. Cohen Kadosh, Schuhmann, et al., 2007), although not by others (e.g., Sandrini et al., 2004). Because subtraction involves magnitude manipulation along the mental number line (e.g., Pica et al., 2004), it is likely to be subserved by the right parietal cortex (especially as compared to multiplication, which relies more on verbal processing as discussed earlier).

The current study also found a functional site for subtraction at the right angular gyrus. This finding is consistent with previ-

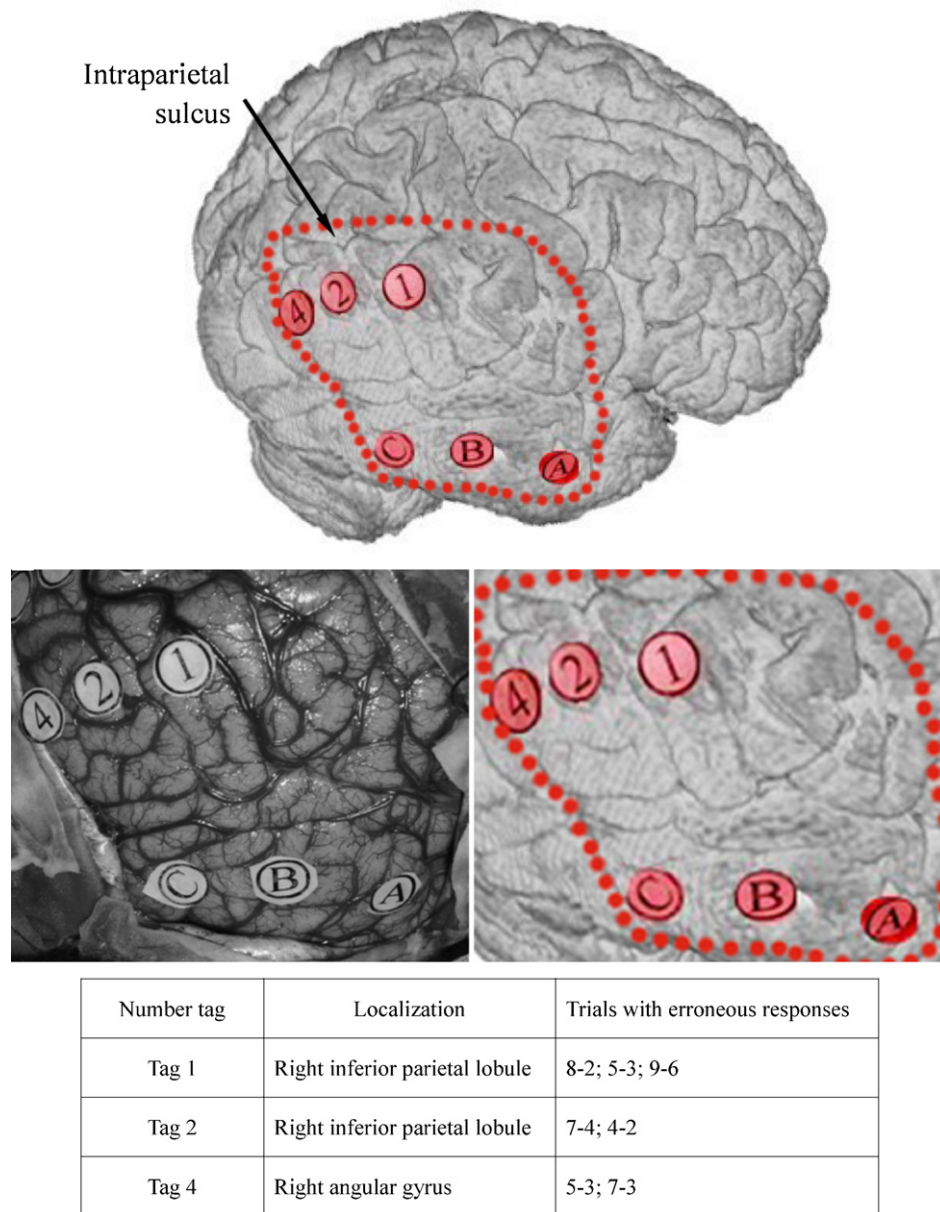


Fig. 2. The surgical field (top panel and left bottom panel) on the brain and the intraoperative image of the brain (right bottom panel) before glioma resection. The letters "A", "B" and "C" marked the tumor boundaries. The number tags show the functional sites for simple subtraction identified using electrical stimulations. The 3-dimension brain image was reconstructed according to the gray matter using MRICroGL (Chris Rorden, <http://www.cabiatl.com/mricro/mricrogl>), based on the results of SPM5 processing of the patient's 3-dimension structural data. The cortical location with tag numbers and trials with incorrect responses (subtraction problems only) are listed in the table below (the total number of trials was 571). There was no functional site for picture naming and simple multiplication.

ous results that the right angular gyrus was involved in numerical processing (e.g., Cattaneo et al., 2009; Göbel et al., 2001; Keller and Menon, 2009; Menon et al., 2000). For example, Menon et al. (2000) found a greater activation for three-operand arithmetic problems relative to two-operand arithmetic problems at the right angular gyrus as well as the left angular gyrus. Göbel et al. (2001) applied focal repetitive TMS to investigate the hemispheric organization of a language-independent spatial representation of number magnitude. In their study, repetitive TMS over either the left or the right angular gyrus disrupted performances in both visuospatial search tasks and the organization of the mental number line.

One potential confounding factor of our results (i.e., the dissociation of neural correlates for subtraction and multiplication in the right parietal cortex) needs to be discussed. It concerns possible differences in problem difficulty between subtraction and multiplication. If multiplication problems had been easier than subtraction

problems, it is plausible that the stimulation would have had a less detrimental effect on the former than the latter. The current study did not collect RT data before surgery on multiplication (only on subtraction) to allow for direct comparisons of the problem difficulty for this particular patient. However, previous studies have consistently shown that multiplication is more difficult, not easier, than subtraction. For example, our earlier study of Chinese adults found that the mean RTs were 700 ms for multiplication and 640 ms for subtraction (Zhou et al., 2006). Similarly, Lemer et al. (2003) found that adults in their study made more errors (5.0%) and took longer (about 1200 ms) when solving multiplication problems than when solving subtraction problems (2.2%; about 1050 ms).

Finally, it is worth mentioning that the dissociation of neural correlates of subtraction and multiplication found in the current study could be a direct result of early learning experience during childhood. Procedural strategies and rote verbal memory are the

two main strategies used in single-digit arithmetic. School children usually use the procedural strategy to do simple addition and subtraction, but use the rote memory strategy to memorize multiplication facts (e.g., Dehaene & Cohen, 1997; Roussel et al., 2002; Zhou et al., 2006, 2007; Zhou & Dong, 2003). These differences in strategies may contribute to distinct mental representations (e.g., Siegler & Shipley, 1995; Siegler & Shrager, 1984). The differential acquisition strategies can lead to dissociated representations of arithmetic facts of different mathematical operations.

In summary, the current intraoperative cortical electrical stimulation study showed an important role of the right parietal cortex in numerical processing. We found that subtraction, but not multiplication, was impaired when the parietal cortex was stimulated. Given the close relation between quantity processing and subtraction, we conclude that the right parietal cortex plays a more significant role in quantity processing (more relevant to subtraction) than in verbal numerical processing (more relevant to multiplication).

Acknowledgments

This study was supported by two grants from the Natural Science Foundation of China (project nos. 60931003 and 30870759), the program New Century Excellent Talents at Universities (NCET-07-0101), the Program for Changjiang Scholars and Innovative Research Teams at Universities (IRT0710), and the National Key Project of Science and Technology Supporting Programs of China (no. 2007BAI05B08).

References

- Andres, M., Seron, X., & Olivier, E. (2005). Hemispheric lateralization of number comparison. *Cognitive Brain Research*, *25*, 283–290.
- Ansari, D., Fugelsang, J. A., Dhital, B., & Venkatraman, V. (2006). Dissociating response conflict from numerical magnitude processing in the brain: An event-related fMRI study. *NeuroImage*, *32*, 799–805.
- Ashkenazi, S., Henik, A., Ifergane, G., & Shelef, I. (2008). Basic numerical processing in left intraparietal sulcus (IPS) acalculia. *Cortex*, *44*, 439–448.
- Baldo, J. V., & Dronkers, N. F. (2007). Neural correlates of arithmetic and language comprehension: A common substrate? *Neuropsychologia*, *45*, 229–235.
- Benzagmout, M., Gatignol, P., & Duffau, H. (2007). Resection of World Health Organization grade II gliomas involving Broca's area: Methodological and functional considerations. *Neurosurgery*, *61*, 741–753.
- Cantlon, J. F., Brannon, E. M., Carter, E. J., & Pelphrey, K. A. (2006). Functional imaging of numerical processing in adults and 4-y-old children. *PLoS Biology*, *4*, e125.
- Cattaneo, Z., Silvanto, J., Pascual-Leone, A., & Battelli, L. (2009). The role of the angular gyrus in the modulation of visuospatial attention by the mental number line. *NeuroImage*, *44*, 563–568.
- Chochon, F., Cohen, L., van de Moortele, P. F., & Dehaene, S. (1999). Differential contributions of the left and right inferior parietal lobules to number processing. *Journal of Cognitive Neuroscience*, *11*, 617–630.
- Cohen, L., & Dehaene, S. (1996). Cerebral networks for number processing: Evidence from a case of posterior callosal lesion. *NeuroCase*, *2*, 155–174.
- Cohen Kadosh, R., Cohen Kadosh, K., Kaas, A., Henik, A., & Goebel, R. (2007). Notation-dependent and -independent representations of numbers in the parietal lobes. *Neuron*, *53*, 307–314.
- Cohen Kadosh, R., Cohen Kadosh, K., Schuhmann, T., Kaas, A., Goebel, R., Henik, A., et al. (2007). Virtual dyscalculia induced by parietal-lobe TMS impairs automatic magnitude processing. *Current Biology*, *17*, 1–5.
- Cohen Kadosh, R., Henik, A., Rubinsten, O., Mohr, H., Dori, H., Van de Ven, V., et al. (2005). Are numbers special? The comparison systems of the human brain investigated by fMRI. *Neuropsychologia*, *43*, 1238–1248.
- Colvin, M. K., Funnell, M. G., & Gazzaniga, M. S. (2005). Numerical processing in the two hemispheres: Studies of a split-brain patient. *Brain and Cognition*, *57*, 43–52.
- Corbetta, M., Akbudak, E., Conturo, T. E., Snyder, A. Z., Ollinger, J. M., Drury, H. A., et al. (1998). A common network of functional areas for attention and eye movements. *Neuron*, *21*, 761–773.
- Corbetta, M., Kincade, J. M., Ollinger, J. M., McAvoy, M. P., & Shulman, G. L. (2000). Voluntary orienting is dissociated from target detection in human posterior parietal cortex. *Nature Neuroscience*, *3*, 292–297.
- 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 Neuropsychology*, *20*, 487–506.
- Dehaene, S., Spelke, E., Stanescu, R., Pinel, P., & Tsivkin, S. (1999). Sources of mathematical thinking: Behavioral and brain-imaging evidence. *Science*, *284*, 970–974.
- Delazer, M., & Benke, T. (1997). Arithmetic facts without meaning. *Cortex*, *33*, 697–710.
- Denes, G., & Signorini, M. (2001). Door but not four and 4 a category specific transcoding deficit in a pure acalculic patient. *Cortex*, *37*, 267–277.
- Diwadkar, V. A., Carpenter, P. A., & Just, M. A. (2000). Collaborative activity between parietal and dorso-lateral prefrontal cortex in dynamic spatial working memory revealed by fMRI. *NeuroImage*, *12*, 85–99.
- Duffau, H. (2007). Contribution of cortical and subcortical electrostimulation in brain glioma surgery: Methodological and functional considerations. *Neurophysiologie Clinique/Clinical Neurophysiology*, *37*, 373–382.
- Duffau, H., Capelle, L., Sichez, N., Denvil, D., Lopes, M., Sichez, J. P., et al. (2002). Intraoperative mapping of the subcortical language pathways using direct stimulations. *Brain*, *125*, 199–214.
- Eger, E., Sterzer, P., Russ, M. O., Giraud, A.-L., & Kleinschmidt, A. (2003). A supramodal number representation in human intraparietal cortex. *Neuro*, *37*, 719–725.
- Fias, W., Lammertyn, J., Reynvoet, B., Dupont, P., & Orban, G. A. (2003). Parietal representation of symbolic and nonsymbolic magnitude. *Journal of Cognitive Neuroscience*, *15*, 47–56.
- Funnell, M. G., Colvin, M. K., & Gazzaniga, M. S. (2007). The calculating hemispheres: Studies of a split-brain patient. *Neuropsychologia*, *45*, 2378–2386.
- Gazzaniga, M. S., & Smylie, C. E. (1984). Dissociation of language and cognition: A psychological profile of two disconnected right hemispheres. *Brain*, *107*, 145–153.
- Gerstmann, J. (1940). Syndrome of finger agnosia, disorientation for right and left, agraphia, and acalculia. *Archives of Neurology and Psychiatry*, *44*, 398–408.
- Göbel, S., Walsh, V., & Rushworth, M. F. (2001). The mental number line and the human angular gyrus. *NeuroImage*, *14*, 1278–1289.
- Heil, M., & Rolke, B. (2002). Toward a chronopsychophysiology of mental rotation. *Psychophysiology*, *39*, 414–422.
- Ischebeck, A., Zamarian, L., Siedentopf, C., Koppelstätter, F., Benke, T., Felber, S., et al. (2006). How specifically do we learn? Imaging the learning of multiplication and subtraction. *NeuroImage*, *30*, 1365–1375.
- Kaufmann, L., Koppelstätter, F., Delazer, M., Siedentopf, C., Rhomberg, P., Golaszewski, S., et al. (2005). Neural correlates of distance and congruity effects in a numerical Stroop task: An event-related fMRI study. *NeuroImage*, *25*, 888–898.
- Kazui, H., Kitagaki, H., & Mori, E. (2000). Cortical activation during retrieval of arithmetical facts and actual calculation: A functional magnetic resonance imaging study. *Psychiatry and Clinical Neurosciences*, *54*, 479–485.
- Keller, K., & Menon, V. (2009). Gender differences in the functional and structural neuroanatomy of mathematical cognition. *NeuroImage*, *47*, 342–352.
- Knops, A., Nuerk, H. C., Sparing, R., Foltys, H., & Willmes, K. (2006). On the functional role of human parietal cortex in number processing: How gender mediates the impact of a 'virtual lesion' induced by rTMS. *Neuropsychologia*, *44*, 2270–2283.
- LaBar, K. S., Gitelman, D. R., Parrish, T. B., & Mesulam, M. (1999). Neuroanatomic overlap of working memory and spatial attention networks: A functional MRI comparison within subjects. *NeuroImage*, *10*, 695–704.
- Lee, K.-M. (2000). Cortical areas differentially involved in multiplication and subtraction: A functional magnetic resonance imaging study and correlation with a case of selective acalculia. *Annals of Neurology*, *48*, 657–661.
- Lemer, C., Dehaene, S., Spelke, E., & Cohen, L. (2003). Approximate quantities and exact number words: Dissociable systems. *Neuropsychologia*, *41*, 1942–1958.
- Linden, D. E. J., Bittner, R. A., Muckli, L., Waltz, J. A., Kriegeskorte, N., Goebel, R., et al. (2003). Cortical capacity constraints for visual working memory: Dissociation of fMRI load effects in a fronto-parietal network. *NeuroImage*, *20*, 1518–1530.
- Mayer, E., Martory, M. D., Pegna, A. J., Landis, T., Delavelle, J., & Annoni, J. M. (1999). A pure case of Gerstmann syndrome with a subangular lesion. *Brain*, *122*, 1107–1120.
- Menon, V., Rivera, S. M., White, C. D., Glover, G. H., & Reiss, A. L. (2000). Dissociating prefrontal and parietal cortex activation during arithmetic processing. *NeuroImage*, *12*, 357–365.
- Milivojevic, B., Johnson, B. W., Hamm, J. P., & Corballis, M. C. (2003). Non-identical neural mechanisms for two types of mental transformation: Event-related potentials during mental rotation and mental paper folding. *Neuropsychologia*, *41*, 1345–1356.
- Núñez-Peña, M. I., Honrubia-Serrano, M. L., & Escera, C. (2005). Problem size effect in additions and subtractions: An event-related potential study. *Neuroscience Letters*, *373*, 21–25.
- Nystrom, L. E., Braver, T. S., Sabb, F. W., Delgado, M. R., Noll, D. C., & Cohen, J. D. (2000). Working memory for letters, shapes, and locations: fMRI evidence against stimulus-based regional organization in human prefrontal cortex. *NeuroImage*, *11*, 424–446.
- Ojemann, J. G., Miller, J. W., & Silbergeld, D. L. (1996). Preserved function in brain invaded by tumor. *Neurosurgery*, *39*, 253–259.
- Pica, P., Lemer, C., Izard, V., & Dehaene, S. (2004). Exact and approximate arithmetic in an Amazonian indigenous group. *Science*, *306*, 499–503.
- Postle, B. R., Awh, E., Jonides, J., Smith, E. E., & D'Esposito, M. (2004). The where and how of attention-based rehearsal in spatial working memory. *Cognitive Brain Research*, *20*, 194–205.
- Prado et al., Prado, J., Mutreja, R., Zhang, H., Mehta, R., Desroches, A. S., Minas, J. E., et al. (in press). Distinct representations of subtraction and multiplication in the neural systems for numerosity and language. *Human Brain Mapping*, doi:10.1002/hbm.21159.

- Rickard, T. C., Romero, S. G., Basso, G., Wharton, C., Flitman, S., & Grafman, J. (2000). The calculating brain: An fMRI study. *Neuropsychologia*, *38*, 325–335.
- Roussel, J., Fayol, M., & Barrouillet, P. (2002). Procedural vs. direct retrieval strategies in arithmetic: A comparison between additive and multiplicative problem solving. *European Journal of Cognitive Psychology*, *14*, 61–104.
- Roux, F. E., Boukhatef, L., Draper, L., Sacko, O., & Demonet, J. F. (2009). Cortical calculation localization using electrostimulation. *Journal of Neurosurgery*, *110*, 1291–1299.
- Sandrini, M., Rossini, P. M., & Miniussi, C. (2004). The differential involvement of inferior parietal lobule in number comparison: A rTMS study. *Neuropsychologia*, *42*, 1902–1909.
- Seymour, S. E., Reuter-Lorenz, P. A., & Gazzaniga, M. S. (1994). The disconnection syndrome: Basic findings reaffirmed. *Brain*, *117*, 105–115.
- Siegler, R. S., & Shipley, E. (1995). Variation, selection, and cognitive change. In G. Halford, & T. Simon (Eds.), *Developing cognitive competence: New approaches to process modeling Hillsdale* (pp. 31–76). NJ: Lawrence Erlbaum Associates, Inc.
- Siegler, R. S., & Shrager, J. (1984). Strategy choices in addition and subtraction: How do children know what to do? In C. Sophian (Ed.), *Origins of cognitive skills* (pp. 229–293). Hillsdale, NJ: Lawrence Erlbaum Associates Inc.
- Takayama, Y., Sugishita, M., Akiguchi, I., & Kimura, J. (1994). Isolated acalculia due to left parietal lesion. *Archives of Neurology*, *51*, 286–291.
- Thomas, K. M., King, S. W., Franzen, P. L., Welsh, T. F., Berkowitz, A. L., Noll, D. C., et al. (1999). A developmental functional MRI study of spatial working memory. *NeuroImage*, *10*, 327–338.
- Van Harskamp, N. J., Rudge, P., & Cipolotti, L. (2002). Are multiplication facts implemented by the left supramarginal and angular gyri? *Neuropsychologia*, *40*, 1786–1793.
- Venkatraman, V., Ansari, D., & Chee, M. W. L. (2005). Neural correlates of symbolic and non-symbolic arithmetic. *Neuropsychologia*, *43*, 744–753.
- Vuilleumier, P., Ortigue, S., & Brugger, P. (2004). The number space and neglect. *Cortex*, *40*, 399–410.
- Warrington, E. K. (1982). The fractionation of arithmetical skills: A single case study. *The Quarterly Journal of Experimental Psychology*, *A*, *34*, 31–51.
- Whalen, J., McCloskey, M., Lesser, R. P., & Gordon, B. (1997). Localizing arithmetic processes in the brain: Evidence from a transient deficit during cortical stimulation. *Journal of Cognitive Neuroscience*, *9*, 409–417.
- Yoshino, A., Inoue, M., & Suzuki, A. (2000). A topographic electrophysiologic study of mental rotation. *Cognitive Brain Research*, *9*, 121–124.
- Zago, L., Petit, L., Turbelin, M. R., Andersson, F., Vigneau, M., & Tzourio-Mazoyer, N. (2008). How verbal and spatial manipulation networks contribute to calculation: An fMRI study. *Neuropsychologia*, *46*, 2014–2403.
- Zhou, X., Chen, C., Dong, Q., Zhang, H., Zhou, R., Zhao, H., et al. (2006). Event-related potentials of single-digit addition, subtraction, and multiplication. *Neuropsychologia*, *44*, 2500–2507.
- Zhou, X., Chen, C., Qiao, S., Chen, C., Chen, L., Lu, N., et al. (2009). Event-related potentials for simple arithmetic in Arabic digits and Chinese number words: A study of the mental representation of arithmetic facts through notation and operation effects. *Brain Research*, *1302*, 212–224.
- Zhou, X., Chen, C., Zang, Y., Dong, Q., Chen, C., Qiao, S., et al. (2007). Dissociated brain organization for single-digit addition and multiplication. *NeuroImage*, *35*, 871–880.
- Zhou, X., & Dong, Q. (2003). The representation of addition and multiplication. *Acta Psychologica Sinica*, *35*, 345–351 (in Chinese)
- Zorzi, M., Priftis, K., & Umiltà, C. (2002). Neglect disrupts the mental number line. *Nature*, *417*, 138.
- Zurowski, B., Gostomzyk, J., Gron, G., Weller, R., Schirmer, H., Neumeier, B., et al. (2002). Dissociating a common working memory network from different neural substrates of phonological and spatial stimulus processing. *NeuroImage*, *15*, 45–57.