Cortical Areas Involved in Numerical Processing: An Intraoperative Electrostimulation Study

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Key Words

Awake craniotomy · Gliomas · Surgical treatment · Electrical stimulations

Abstract

Background: Numerical processing is important in our everyday lives. However, very few attempts have been made to map the numerical processing function areas during lesion surgery. **Objective:** To identify and protect the cortical areas involved in numerical processing, the authors used the intraoperative brain mapping approach to study numerical processing areas in patients with parietal lobe tumors. **Methods:** During resection in patients with parietal lobe tumors, local anesthesia was administered and numerical processing mapping was performed. Our mapping procedures were conducted before glioma removal and included somatosensory, language and numerical processing tasks. We focused on the numerical processing task. **Results:** Different brain sites within the parietal lobe were detected to be specifically related to multiplication or subtraction processing. They displayed precise spatial distribution and overlapped with each other. No brain sites were found to be specifically related to numerical processing in the right hemisphere. **Conclusions:** To improve the quality of resection while minimizing the neurological deficits, functional boundaries of

numerical processing areas should be considered during the removal of a parietal low-grade glioma. Moreover, only the left intraparietal sulcus is necessary for numerical processing, whereas the right intraparietal sulcus does not appear to be critically involved in numerical processing.

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Introduction

Numerical processing is one of the most important and basic functions of the human brain in our daily lives. Its impairment can cause social and professional disturbances [1]. Nowadays, neuroimaging and neuropsychological studies indicate that the parietal lobe, especially the intraparietal sulcus (IPS), plays an important role in processing and representing numerical magnitude [2–4].

The regular application of the direct stimulation method, that is to identify the eloquent areas when the patient is awake, has recently been confirmed to improve the postoperative function [5–8]. However, very few attempts were specifically made to map the numerical processing function areas during lesion surgery [9, 10]. To identify and protect cortical areas involved in the numerical processing function, we used the intraoperative brain mapping approach to study numerical processing in pa-

tients with brain tumors. The lesions were located close to brain regions that may be involved in mathematical functions.

The present study focuses on the numerical processing functions of the brain, especially the subtraction and multiplication tasks. At the same time, the recent progress made in direct electrostimulation methods is taken into account. The cortical organization of areas involved in subtraction and multiplication tasks can be detected and analyzed using the surgical data from intraoperative brain mapping.

Methods

Case Recruitment

Between May 2008 and January 2009, brain mapping for the numerical processing task was offered to 5 patients (3 men and 2 women) with various low-grade gliomas (LGGs). All cases were identified as right-handed when assessed by a Chinese version of the Edinburgh Handedness Inventory [11–13]. When a lesion was close to the inferior parietal lobe, a numerical processing task was added to the standard brain mapping. This region was presumed to be involved in numerical processing [1, 9, 10].

All patients and their families signed written informed consent forms to undergo direct brain mapping.

Preoperative and Postoperative Evaluation

The preoperative neurological clinical test results were normal for all patients. The language ability was tested by a speech therapist using a Chinese version of the West Aphasia Battery [11–13]. The Mini-Mental State Examination was used as a preoperative neuropsychological test. The Karnofsky Performance Scale score was evaluated for all patients. All patients underwent preoperative numerical processing examinations by a neurophysiologist team to rule out any specific deficits. Numerical processing, including number comparison (which of 2 numbers presented in Arabic digits is larger), single-digit multiplication and simple subtraction, was performed using a computer system with a liquid crystal display screen [9, 10]. The duration of each stimulation was 4 s.

Preoperative Training

Within 3 days prior to the surgery, patients were informed in detail about the monitoring procedure of the intraoperative stimulation. Patients were familiarized with the stimulus material and trained to perform the naming and calculating tasks. The task was based on the individual capabilities of each patient. If a patient could not name certain objects, these pictures were removed from the stimulus pool.

Intraoperative Cortical Stimulation

Language, motor and sensorimotor functions were mapped first [5–8]. Then, in order to investigate the function of IPS in arithmetic processing, subtraction and multiplication tasks (4–6 mA) were carried out [9, 10]. One subtraction and 1 multiplication block were presented for all sites exposed to the bone flap. Num-

bers were printed on sterilized paper and placed on the cortical surface. Moreover, a photograph was obtained immediately after the stimulation in order to identify sites of positive stimulations later on.

The subtraction task included 36 subtraction equations (2-digit integer minus 1-digit integer) from $11 - 2 = 9$ to $18 - 9 = 9$. The answer for each equation was a single-digit number. Each complete equation consisted of 4 digits. Stimuli were presented at the center of the screen, but the '=' sign and the answers were not presented (such as, $11 - 2$ or $18 - 9$), and the participants had to orally report the answer within 4 s. We also used single-digit multiplication with at least 1 operand >6 (e.g. 4×7 , 3×5 , 2×8).

Each stimulation site was tested with 2 stimuli. For the first stimulus, we did not use electrostimulation (to check if the patient was able to solve the problem without any stimulation, especially when the previous stimulation had induced a disruption of numerical processing), but for the second stimulus electrostimulation was applied.

Multiplication and subtraction questions were alternated 3 times. If an error occurred, at least 1 stimulus presentation was performed without stimulation to ensure that the patient was able to perform the task correctly [9]. The patients were never informed when the brain was stimulated. The same cortical site was never stimulated successively twice to avoid seizures.

Surgical Strategy

The surgical approach for the lesion was determined by T₁- and T₂-weighted MRI data, supported by information from intraoperative ultrasonography. Tumor removal was conducted using these functional landmarks as boundaries of the resection. The cortical incision procedure was customized according to the results of the cortical mapping procedure [11].

Postoperative Course

The extent of tumor residue was evaluated by postoperative imaging 3 h after the surgical procedure (CT scans and MRI), according to the classification method reported by Xie et al. [12]. Conventional MRI and functional MRI were performed in all cases 3 months after surgery. Formal neurological examinations were preoperatively performed once (1–3 days before the operation) and postoperatively twice (within 21 days and 6–12 months after surgery). Numerical processing was also assessed using a computer system.

Results

Among the 5 patients who underwent numerical processing cortical stimulation, 4 were treated in the left hemisphere and 1 in the right hemisphere.

Intraoperative Stimulation

Direct stimulation mapping was simple and well tolerable in all patients. Focal seizures during the intraoperative stimulation mapping procedure occurred in 1 case. The focal seizures were controlled by irrigating the cortex with cold saline solution. Twenty-two number-specific

Fig. 1. **a** Intraoperative cortical mapping before resection of patient 2. Tumor edge = A–C; motor areas = 1–4; counting = 11, 12; naming = 21, 23, 25; reading = 31, 32, 45; multiplication = 41, 42, 44, 46, 47; subtraction = 41, 44, 47, 50; multiplication/subtraction = 41, 44, 47. **b** Cortical mapping after resection of patient 2.

Table 1. The clinical, radiological and pathological summary of patients

Patient No.	Age/sex	L/R	Site	Pathology	M	MS	S	Naming
1	27/F	L	parietal	astrocytoma	no	no	4	1
2	33/F	L	temporal	astrocytoma	2	3	1	6
3	23/M	L	parietal	astrocytoma	3	1	2	5
4	17/M	L	frontal	astrocytoma	3	1	2	8
5	25/M	R	temporal	astrocytoma	0	0	0	0
Total					8	5	9	20

S = Subtraction; M = multiplication; MS = multiplication + subtraction; no = no multiplication task.

sites, without naming or reading interference, were found in the left hemisphere (fig. 1). No number-specific interference sites were found in the right hemisphere.

Localization of Numerical Processing Sites

Eight sites were multiplication-specific sites (no subtraction interference). Nine sites were subtraction-specific sites (no multiplication interference). Five sites were multiplication and subtraction interference sites. These results are summarized in table 1. The maximal current ranged from 4 to 6 mA.

Overall, numerical processing interferences were found in 3 particular regions: angular gyrus (5 interferences: 1 multiplication, 3 subtraction and 1 multiplication/subtraction); the horizontal segment of the IPS (12 interferences: 2 multiplication, 6 subtraction and 4 multiplication/subtraction), and supramarginal gyrus (5 interferences: 5 multiplication). These results are summarized in table 2. Subcortical numerical processing stimulations were used for 1 patient, and numerical processing interferences were not found.

Fig. 2. **a** CT 1 night after the operation. **b** MRI 1 day after the operation.

Table 2. Localization of numerical processing sites in 4 patients treated in the left hemisphere

Patient No.	Angular gyrus	HIPS	Supramarginal gyrus
1	1S	3S	
2	1S	1M; 3MS	1M
3	1MS	1M; 2S	2M
4	1S; 1M	1S; 1MS	2M
Total	5 (1M; 3S; 1MS)	12 (2M; 6S; 4MS)	5 (5M)

HIPS = Horizontal segment of the IPS; S = subtraction; M = multiplication; MS = multiplication + subtraction.

Extent of Resection

The immediate postoperative MRI procedures showed complete tumor removals in all patients. Postoperative CT/MRI revealed gross-total resections in 4 out of 5 patients. There were no deaths. For 1 patient, the surgical site was very close to the numerical processing sites (<1 cm). For the other patients, numerical processing interference sites were far from the surgical site (>1 cm) or were spared from surgery (fig. 2).

Postoperative Course

One patient showed symptoms of right inferior quadrantanopia. Numerical processing tasks were performed in all patients. Four patients did not have any postoperative numerical processing difficulties. One patient had numerical processing difficulties 1 month after surgery, but did not have any language difficulties. The margin of the tumor removal of this patient was very close (<1 cm) to the numerical processing areas. This patient was tested

again after 6 months of his operation. Mild numerical processing difficulties persisted. The patient was able to read and write Arabic numbers, answer single-digit multiplication questions more easily and faster than 6 months before, and solve these questions without any mistakes. He could do mental arithmetic subtraction normally, even serial subtractions, such as $100 - 7 - 7$.

Discussion

Mathematics is one of the most important and basic functions of the human brain in our daily lives [1]. Nowadays, neuroimaging and neuropsychological studies indicate that the parietal lobe, especially IPS, plays an important role in processing and representing numerical magnitude [2–4].

In previous studies, the activities of functional areas were evaluated based on blood oxygenation level-dependent functional MRI signals. Although neuroimaging and neuropsychological studies have established a frame of the role of IPS, they are not able to locate the functional areas directly and precisely. In addition, it is hard to define the exact location of brain lesions in patients with numerical processing deficits. Intraoperative electrocortical stimulation produces an electrical stream at a small part of the cortex and temporarily disturbs functioning of these areas [5, 7, 8]. Hence the functional evidence of the stimulated areas can be revealed directly, specifically and accurately. Nonetheless, only a few direct electrostimulation studies have been published so far that examine the neural basis of numerical processing [1, 9, 10]. Whalen et al. [10] were the first to use electrocortical stimulation to investigate the relationship between arithmetic problems and IPS. The results showed that stimula-

tion at the left parietal impaired abilities to solve simple multiplication problems. Duffau et al. [9] found that the left angular gyrus was the key area for subtraction and multiplication. Roux et al. [1] found interference with 2-digit plus 2-digit addition and symptoms of Gerstmann syndrome when stimulating the angular gyrus.

In this study, our results confirmed that the essential cortices for numerical processing in multiplication and subtraction could be identified and spared from surgery. The application of brain stimulation methods allowed an accurate mapping of the region in the parietal cortices. The effects of intraoperative mapping were verified by the postoperative clinical course, that is, all the crucial numerical processing sites could be preserved. Therefore, in order to improve the quality of resection and to minimize the neurological deficits, functional boundaries of numerical processing areas should be implemented during the removal of a parietal LGG.

The Role of Bilateral IPS in Mathematics

Several brain-imaging experiments have shown significant activation of the bilateral or unilateral IPS when subjects compare the magnitude of 2 numbers, enumerate dots, or solve simple and complex numerical processing problems (addition, multiplication, subtraction and division) [14–16]. In addition, IPS activation seems to be the neural instantiation of a domain-specific system for representing and processing numerical magnitude. And it is independent of the language and the number format (Arabic or in words) [17–19].

Single-case studies show that brain-damaged patients with focal parietal lesions can exhibit striking deficits in numerical processing despite well-preserved language and semantic abilities [20, 21]. The double dissociations suggest that the bilateral inferior parietal network is dedicated to the mental manipulation of numerical quantities. Recently, 2 voxel-based lesion-symptom mapping studies demonstrated that arithmetic was associated with a small number of foci and the most significant of them are located in the left inferior parietal lobule, whereas comprehension was highly associated with left middle and superior temporal gyri [22, 23]. However, the role of the right IPS in mathematics processes is still under debate. It remains an open question whether the right IPS plays the same critical role as the left IPS in numerical processing.

Our electrical stimulation results showed that 22 numerical processing-specific sites were found in the left hemisphere, and no numerical processing-specific interference sites were found in the right hemisphere. More

recently, numerical processing mapping was used in several different studies [1, 9, 10]. Cortical areas on the dominant parietal lobe involved in numerical processing can be detected by using different tasks. But there were no reports on whether non-dominant parietal lobe is involved in numerical processing functions. Our results thus support the conclusion that the IPS is involved in numerical processing, as demonstrated in previous neuroimaging studies which showed bilateral IPS activations [15–17]. Moreover, our investigation specifies that only the left IPS is necessary for multiplication and subtraction processing, whereas the right IPS does not appear to be critically involved in this process. Our results are well in accordance with the recent functional imaging and transcranial magnetic stimulation studies of the involvement of the left hemisphere in number processing [23, 24]. This is very interesting. To our knowledge, it could be the first time to find that numerical processing is originated predominantly in the left/dominant cerebral hemisphere through brain stimulation methods. That is, just like language, calculation function is found in the left hemisphere or in the dominant hemisphere. If this hypothesis is true, more attention should focus on the dominant hemisphere either in fMRI studies or in numerical processing mapping.

However, only 5 patients (4 dominant and 1 non-dominant) were studied in our research. Studies with larger samples of patients are needed to confirm this finding. The absence of deficits after brain stimulation over the right IPS does not mean that this region is not involved in numerical processing, but indicates that it is not crucial for numerical processing in the range selected for this study. Complex tasks are assumed to be processed sequentially across multiple stages including arithmetic fact retrieval, working memory and short-term memory processing. Whether complex numerical processing tasks might involve bilateral parietal lobes or not, as compared with simple tasks, is worth further investigation.

Conclusion

To improve the quality of resection while minimizing the neurological deficits, functional boundaries of numerical processing areas should be used during the removal of a parietal LGG. Moreover, only the left IPS is necessary for numerical processing, whereas the right IPS does not appear to be critically involved in this process. That is, just like language, numerical processing function has been found in the left hemisphere or in the dominant

hemisphere. We conclude that studying the different involvement of both hemispheres and their different numerical processing styles may help to understand functions and impairments of numerical processing in the future.

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