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Preoperative functional MRI localization of language areas in Chinese patients with brain tumors

Validation with intraoperative electrocortical mapping

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Abstract
Ten Chinese patients with brain tumors involving language regions were selected. Preoperative functional MRI was performed to locate Broca's or Wernicke's area, and the cortex that was essential for language function was determined by electrocortical mapping. A site-by-site comparison between functional MRI and electrocortical mapping was performed with the aid of a neuronavigation device. Results showed that the sensitivity and specificity of preoperative functional MRI were 80.0% and 85.0% in Broca's area and 66.6% and 85.2% in Wernicke's area, respectively. These experimental findings indicate that functional MRI is an accurate, reliable technique with which to identify the location of Wernicke's area or Broca's area in patients with brain tumors.

Key Words
functional MRI; brain tumor; Chinese language; brain mapping; intraoperative electrocortical mapping; Wernicke's area; Broca's area; regeneration; neural regeneration

Research Highlights
(1) The sensitivity of functional MRI for preoperative location of language areas in the brain reaches 81% to 92%. Great individual variations and different language stimuli may activate different brain areas. Existing research focuses on a western population, and there is little evidence in Chinese patients. (2) This study aimed to understand the role of functional MRI in preoperative localization of language areas (Broca's area and Wernicke's area) in Chinese patients with brain tumors. Intraoperative electrocortical mapping results confirmed good sensitivity and specificity of functional MRI in terms of localization of language areas.

Abbreviations
BOLD, blood oxygen level-dependent; ECM, electrocortical mapping

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INTRODUCTION

Surgical removal of brain tumors, particularly gliomas adjacent to language areas, poses risks of postoperative neurological deficits. The traditional anatomical criteria alone are not always reliable for accurate localization of language areas. Functional MRI has shown great potential as a noninvasive tool for preoperative planning to demonstrate the relationship between functional eloquent brain regions and brain tumors[1].

Functional MRI for language mapping is a potential tool with which to improve preoperative planning of brain tumors, especially gliomas adjacent to an eloquent cortex. Although magnetoencephalography and positron emission tomography[2] are often used for presurgical planning, they are not as widely available as MRI. Detecting changes in T2-weighted images during the activation of functional brain areas is the theoretical basis of functional MRI. Blood oxygen level-dependent (BOLD) imaging has been widely used for preoperative brain mapping of the functional cortex, including language and motor areas, in patients with brain tumors[3]. Intraoperative electrocortical mapping (ECM) under awake craniotomy is still the “gold standard” of localization for language areas[4]. Functional MRI for language mapping compared with intraoperative ECM under awake craniotomy has been shown to have high sensitivity (81–92%), especially in patients with intra-axial brain tumors[5]. Functional language mapping is a particular challenge because there is great individual variability in the language cortex and there are still no international standards of language tasks. In addition, different language tasks may activate different areas of the language cortex in different patients[6]. Although many papers have been written on functional MRI application for presurgical localization of language areas in western patients with brain tumors, there is a paucity of studies in native Chinese speakers. Given the complexity of language function and the expected variability associated with the presence of glial brain tumors, we undertook the present study. The aim of this study was to assess the feasibility of preoperative functional MRI for localization and lateralization of language areas, including Broca’s and Wernicke’s areas, in Chinese patients with brain tumors and to determine the sensitivity and specificity of functional MRI for mapping language areas by comparison with intraoperative ECM.

RESULTS

Quantitative analysis of included subjects

The study included 10 patients with pathologically confirmed brain tumors involving regions in or near Wernicke’s or Broca’s areas. All patients underwent functional MRI and ECM, and all entered the result analysis.

Baseline data

All 10 patients (six males and four females, mean age of 46 years) with resectable brain tumors were prospectively evaluated (supplementary Figure 1 online). All patients were right-handed with the exception of Patient 1. All lesions were located close (0–24 mm) to the expected language areas, such as Wernicke’s area or Broca’s area, in the dominant hemisphere. The time between functional MRI and intraoperative ECM was within 1 week. The baseline data are listed in Table 1.

Table 1 Demographic information of patients

Patient No.	Sex	Age (year)	Diagnosis/tumor size (cm)	WHO glioma grade	Hemisphere
1	F	45	Cavernous angioma/2.0	–	Right frontal lobe
2	M	42	Astrocytoma/4.5	I	Left frontal lobe
3	F	35	Astrocytoma/5.0	II	Left frontal lobe
4	M	60	Oligoastrocytoma/6.0	II	Left temporal lobe; insula
5	F	43	Anaplastic astrocytoma/5.5	II	Left temporal lobe
6	M	46	Anaplastic astrocytoma/6.4	II	Left temporal lobe
7	M	50	Astrocytoma/6.5	II	Left frontal lobe
8	M	55	Oligoastrocytoma/5.6	II	Left temporal lobe; insula
9	M	65	Glioblastoma/4.3	IV	Left temporal lobe
10	F	47	Anaplastic astrocytoma/3.6	III	Left frontal lobe

M: Male; F: female.

Presurgical functional MRI localization of language areas (Figure 1)

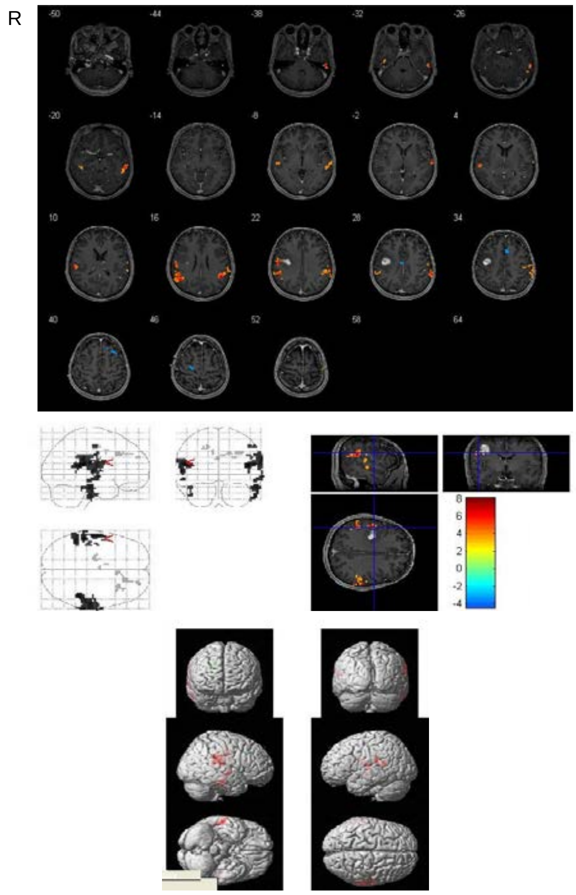

Figure 1 Motor language area was activated by preoperative reading tasks (Broca’s area; *P* < 0.001). R: Right.

Wernicke's area or Broca's area was mapped with functional MRI in all patients. A listening comprehension task revealed activation chiefly in the left temporal region and primary auditory cortex (bilateral activation). We found Broca's area in Chinese patients with brain tumors, especially gliomas, in the inferior frontal gyrus just anterior to the precentral gyrus (Brodmann area 44). The result of presurgical activation in this brain region is displayed in Figure 1.

Intraoperative ECM results

Intraoperative ECM under awake craniotomy is still the "gold standard" of localization of language areas. The results are listed in Figure 2 and supplementary Figure 2 online. Functional MRI was employed to determine the true-positive, true-negative, false-positive, and false-negative in localization of Wernicke's area and Broca's area (Table 2).

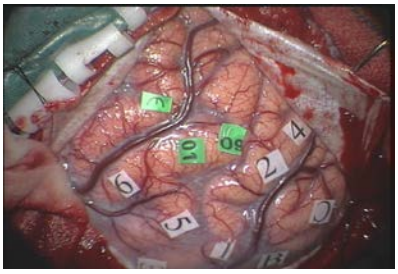

Figure 2 Intraoperative electrocortical mapping under awake craniotomy for localization of Broca's area.

Table 2 Paradigm and results of correlation of functional MRI with electrocortical mapping (*n*)

Patient No.	Paradigm	TP tags	TN tags	FP tags	FN tags
1	VGEN	3	2	1	1
2	VGEN	5	2	1	1
3	VGEN	6	5	0	2
4	LC	4	6	1	1
5	LC	5	5	1	3
6	LC	4	5	1	2
7	VGEN	3	5	0	1
8	LC	3	7	1	2
9	LC	0	0	0	0
10	VGEN	3	3	1	0

VGEN: Word generation; LC: listening comprehension; TP: true-positive; TN: true-negative; FP: false-positive; FN: false-negative.

Sensitivity and specificity of presurgical functional MRI localization of language areas

Overall, 90 cortical sites were tested with ECM. The functional MRI sensitivity and specificity were 80.0% and 85.0% in Broca's area and 66.6% and 85.2% in Wernicke's area, respectively (Table 3). In Patient 9, although ECM did not induce any speech arrest or faltering, the patient did not develop any speech deficits during or after surgery. Therefore, it was concluded that no eloquent area of language was present in the exposed cortex.

Table 3 Results of task sensitivity and specificity of functional MRI with electrocortical mapping

Statistical and tag data	Broca area	Wernicke area
Statistic		
Sensitivity (%)	80.0 (20, 5)	66.6 (16, 8)
Specificity (%)	85.0 (17, 3)	85.2 (23, 4)
No. of tags		
TP	20	16
TN	17	23
FP	3	4
FN	5	8
Total	45	51

Sensitivity was calculated as TP/(TP+FN); Specificity was calculated was TN/(TN+FP). Numbers in parentheses are 95% confidence intervals. TP: True-positive; TN: true-negative; FP: false-positive; FN: false-negative.

Tumor resection and adverse reactions

Reversible postoperative deficits occurred in three patients and resolved within 72 hours. Postoperative deficits of variable intensity were still present in four patients 3 months after surgery. We avoided a minimum distance of 10 mm from the area of language activity. With these constraints, we achieved gross total resection in 60% of the 10 surgical cases and partial resection in the remaining 40%. The tumor was completely removed at 3 months after surgery (supplementary Figure 3 online). None of our patients had persistent language deficits.

DISCUSSION

Surgical removal of brain tumors near an eloquent cortex such as the motor and language areas requires an understanding of the relationship between the lesion and the eloquent tissue to avoid postoperative neurological deficits. Unlike the primary motor cortex, the language cortex in the human brain shows high individual variability[7]. Language areas may also shift from their original positions because of the growth of brain tumors[8]. Furthermore, normal sulcal anatomy is often not recognizable because of the effects of expansion and pressure produced by the underlying tumor. The use of preoperative functional brain mapping with functional MRI provides important information for the neurosurgeon in terms of the hemispheric dominance of patients, the risk of the surgical procedure, and the craniotomy approach. The classic model of language involving Broca's area (left inferior frontal gyrus) and Wernicke's area (posterior left superior temporal gyrus) has recently been replaced with a more complex model describing a more expansive language network. The application of functional MRI and the determination of language lateralization can identify which patients would benefit from awake surgery and intraoperative (ECM and iOIS) mapping[9].

Listening comprehension of sentences includes different aspects of language processing, such as syntax, semantics, phonology, and short-term memory[10]. Studies of clinical and functional activation have confirmed that the following areas are involved in language comprehension: Wernicke's area, lexical and semantic representations in large cortical areas of the left (and even the right) hemisphere, and Broca's area for aspects of syntactic comprehension[3]. Some authors have proposed that Wernicke's area is part of a semantic system, such as a lexicon for written and spoken words[11]. In several activation studies, the angular gyrus was activated by a listening comprehension task. The verb generation task has been widely used, mainly in patients with the ability to perform complex tasks. It shows better lateralization of language. In our study, we found that 90% of our patients were left-dominant and 10% were right-dominant. One left-handed patient had clear language dominance in the right hemisphere.

Development of a robust and feasible clinical Functional MRI language task is still an unresolved issue. There are no international standards of language tasks for language brain mapping. Currently, silent word generation, picture naming, semantic decision, rhyme detection, word stem completion, and silent reading tasks are most frequently used in language brain mapping. The use of spoken output in language localization studies is desirable. During the language task in our study, if the tumor was present within Broca's area, for the language task, patients were asked to perform reciting to activate Broca's area in the stimulated period.

The limitations of functional MRI for presurgical planning in neurosurgery have been well documented[12]. The following sources limit the accuracy of fMRI imaging for localization of functional areas of the brain or correlation with ECM: excessive motion, failure of task performance, and EPI signal voids. We used an optimized plaster cast helmet for head fixation in accordance with a report by Vikingstad *et al* [13]. The overall failure rate because of head motion was 11%[13]. Previous studies have reported failure rates of 10% to 31% in healthy volunteers[14] and 0% to 30% in patients with brain tumors. The spatial accuracy of the BOLD signal depends on the proximity of the larger draining veins and the activated neurons. The growth of glioblastomas is reportedly an important source of a reduced BOLD signal.

Different patterns of activation occur depending on the language task and statistical analysis used[4]. To provide more information about the language cortex, the sensitivity and specificity of functional language brain mapping with functional MRI must be improved. However, intraoperative ECM remains the "gold standard" in cortical language localization and could be applied in patients in whom surgical resection is uncertain and who are able to undergo intraoperative ECM under awake craniotomy[15]. The technique does have significant limitations; for example, during awake surgery, the patient must perform language tasks and undergo cortical stimulation. The technique is labor-intensive and may produce after-discharges, which require additional time to elapse before retesting. In addition, ECM uses bipolar electrodes (spacing near 1 cm), limiting the resolution of the technique.

Nevertheless, many researchers have compared preoperative functional MRI imaging and the Wada test in terms of language hemisphere dominance. Many researchers now consider that functional MRI is a reliable technology with which to determine language lateralization[16]. In contrast to the Wada test, functional MRI is a noninvasive technique that may replace the Wada test in the future.

In our study, a total of 90 cortical sites were tested with ECM. Functional MRI sensitivity and specificity were 80.0% and 85.0% in Broca's area and 66.6% and 85.2% in Wernicke's area, respectively. Sensitivity was lower and specificity was higher in glioblastoma than in WHO grade II or III glioma. There are two possible explanations for the higher rate of FN tags in glioblastoma. Glioblastoma is an undifferentiated tumor with a rich abnormal vasculature caused by angiogenesis. Neurovascular uncoupling has been described in higher-grade tumors, and it could lead to loss of the BOLD response[17]. Patient outcome in terms of permanent sequelae was 10% in this series of 10 patients. Other studies have shown a low rate of postoperative deficits in patients who underwent presurgical fMRI[18].

A novel intraoperative strategy for language mapping using intraoperative ECM of the cortex was established by the research group of Ojemann *et al* [19] as well as other researchers as early as the 1970s and 1980s. Since then, intraoperative ECM for language brain mapping and awake surgery have evolved into the "gold standard" for patients undergoing removal of lesions in and around the frontotemporal language areas of the dominant hemisphere[20]. The neuronavigation system can be helpful in verifying the sensitivity and specificity of presurgical functional MRI compared with intraoperative ECM, and it can reduce the experimental error[16].

There are few studies in which sensitivity and specificity of presurgical fMRI of language areas were measured using ECM as the reference standard[21]. We found two studies involving site-by-site correlation with a large number of tags. Roberts *et al* [15] evaluated 140 sites in 11 patients with 5 language tasks and found a sensitivity of 81% and a specificity of 53%. Intraoperative ECM has repeatedly demonstrated that stopping tumor resection 0.5 to 2 cm from the eloquent cortex greatly reduces the risk of postoperative neurological deficits[15, 22].

Roux *et al* [23] correlated 426 ECM tags in 14 patients with two combined tasks (word generation and naming). The sensitivity and specificity were 59% and 97%, respectively, with a *P* value of < 0.005. The sensitivity in the study by Roux *et al* was lower than that in our study. Factors in these experiments included patient population, tumor type, location, craniotomy size, functional MRI paradigms, methods used to compare functional MRI images and intraoperative ECM, and so on. Lurito *et al* [24] focused on functional MRI mapping of receptive language in three patients with gliomas in the temporal and parietal lobes. They correlated 10 ECM tags and found that all with the exception of 1 located within the boundary of the tumor in the left parietal lobe had been mapped by functional MRI. They concluded that their functional MRI tasks were good, but not perfect.

Sensitivity and specificity were highest in patients with cavernous angiomas in our study. Pouratian *et al* [25] reported similar results in three patients with cavernous angioma. This result is consistent with our findings.

There were limitations to our study. Image post-processing error, language tasks, and pathological types will lead to experimental error. Errors occurring during coregistration of anatomic and functional MRI images result in errors occurring during neuronavigational registration. These errors may sum up to a few millimeters.

In conclusion, functional MRI is a sensitive and specific method for localization of the eloquent cortex of language and has good prospect in functional brain mapping of language in Chinese patients with brain tumors.

SUBJECTS AND METHODS

Design

A block design for functional MRI observation

Time and setting

Experiments were performed in the Department of Neurosurgery, General Hospital of Ningxia Medical University from January 1, 2008, to December 31, 2011.

Subjects

A total of 10 consecutive awake craniotomy procedures for the removal of intra-axial tumors near and/or within language areas were performed. Patients were selected because their lesions abutted the frontal or temporoparietal language areas, such as Wernicke's area or Broca's area, in the dominant hemisphere. All lesions were located close (0–24 mm) to the expected language areas, such as Wernicke's area or Broca's area. All patients were tested for handedness by the Edinburgh inventory[13]. All patients had gliomas with the exception of one (Patient 1), who had a cavernous angioma. The tumor diagnosis was confirmed histologically. The locations of the tumors were assessed from standard MRI scans. We estimated tumor size by measuring the largest diameter of the tumor on a preoperative, contrast-enhanced, T1-weighted sequence image. All patients were able to perform the preoperative functional MRI task and undergo intraoperative ECM under awake craniotomy. All patients gave written informed consent, and the experimental protocol was in accordance with the declaration of Helsinki.

Methods

MRI scanning

All images were acquired using the 3.0 T Excite HD superconducting MRI system (GE Medical Systems, Milwaukee, WI, USA) at the General Hospital of Ningxia Medical University, China. Head motion was minimized using pillows and cushions placed around the head. Functional MRI was performed during a word generation task or paragraph comprehension task in Chinese using T2* BOLD echo planar imaging capabilities (repetition time = 3 000 ms, echo time = 35 ms, filp angle = 90°, field of view = 240 mm × 240 mm, matrix size = 64 × 64, and slice thickness = 4 mm). Thirty-two axial slices were acquired to cover the whole brain at 108 time points.

Functional MRI paradigms and analysis

We determined the number of paradigms by the individual variability of the patients. All patients were briefly trained 1 hour before the image scanning. The neurologists verified the patients' ability to perform the task correctly before and after the image scanning. If the tumor was within Broca's area, patients were asked to perform reciting to activate Broca's area in the stimulated period of the language task. If the tumor was within Wernicke's area, we used the Chinese paragraph comprehension task, acoustic stimulation to activate Wernicke's area; in this task, subjects listened to a story comprising 25 to 30 Chinese words (supplementary Table 1 online). During rest periods, patients were asked to mentally count from 0 to 10 iteratively. A block design with 30-second alternating periods was used. The trace time was 324 seconds (including a 24-second pre-stimulus period excluded from analysis to allow for stabilization of the BOLD signal) (Figure 3).

Image processing and statistical analyses were performed using SPM5 (Wellcome Department of Imaging

Neuroscience, University College London, London, England; http://www.fil.ion.ucl.ac.uk/spm).

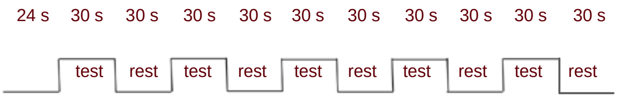

Figure 3 Tasks for testing. s: Second.

Realignment, slice timing adjustment, spatial normalization to the standard brain space, and smoothing with an isotropic Gaussian kernel of 8-mm full width at half maximum using the standard SPM method were carried out. To avoid signal loss, a high-pass filter with a frequency of second, which is half the frequency of the paradigm used, and a low-pass filter were applied to the time series. The uncorrected *P* value threshold of 0.001 (minimum of 5-voxel clustering) was used to estimate *t*-test maps. Coregistration of the *t*-test maps with the anatomic image was performed for anatomic localization of the functional foci. We calculated the activation voxel to assess the dominant hemisphere. The cerebellum lateralization index (LI) was calculated with xjview8 (http://www.alivelearn.net/xjview8/about/). LI was calculated using the formula (left - right)/(left + right). If LI ≥ 0.10, the patient had a left-dominant hemisphere; if LI ≤ 0.10, the patient had a right-dominant hemisphere.

Intraoperative ECM

The intraoperative ECM was performed under awake craniotomy. The patients were awakened under the care of the anesthesiologist after craniotomy. Image guidance (StealthStation; Medtronic Surgical Navigation Technologies, Minneapolis, MN, USA) was used in all patients for the surgical approach. During the awake phase, navigation-guided stimulation (alternating current of 60 Hz, 1–16 mA peak) with an electric probe of a cortical stimulator (inomed Medizintechnik GmbH, Teningen near Freiburg, Germany) was performed. Amplitude was progressively increased by 1 mA. Biphasic square-wave pulses of 2 ms at 60 Hz, with 2-second maximal duration of a sequence of pulses, were used for stimulation of the language function. Language mapping was performed using the largest current in the range between 4 and 10 mA. We stimulated the entire exposed cortex, including the preplanned area of resection. We tested about 10 sites on the cortex in every patient. When the object-naming test was carried out, subjects were presented with line drawings. Objects were obtained from the Boston Naming Test (a standardized test of object-naming with well established norms)[26]. We relied on thumb movement to determine whether a patient named an object correctly (*e.g.*, thumb up for word, down for nonword). Object presentation rates were determined based on the patient's ability and were approximately 0.5 to 1.0 Hz. If arrest of speech, random answering, or perseveration to stimulation occurred, the sites were considered positive.

The sites in every patient were confirmed at least twice. Results were classified intraoperatively by a trained neurologist with experience in evaluation of speech disorders. The neurologist observed the patient's response during the awake phase and informed the surgeon of any errors at the same time. A numbered tag made of a 1-cm-radius sphere identified each positive stimulated area of cortex. Before the neurosurgeon began the tumor removal, location of each ECM tag was present only on the exposed cortical surface. Therefore, the cortex away from the craniotomy site was not tested and validated with intraoperative ECM.

Assessment of language function

Neurological examination was performed by a neurosurgeon with 20 years of experience for 7 preoperative days and 3 postoperative months. The language evaluation criteria included verbal fluency, denomination, and comprehension of simple objects and categories.

Statistical analysis

A numbered tag made of a 1-cm-radius sphere identified each positive stimulated area of cortex. The positive stimulated area of cortex and functional MRI image were considered to match when the functional MRI image focus was within the volume defined by the sphere (the distance between the two was 1 cm or less). We computed the numbers of true-positive, true-negative, false-positive, and false-negative tags for each patient postoperatively. Every language area of the cortex was stimulated independently. The same assumption was made for statistical analysis in similar previously published studies.

Sensitivity and specificity were also computed in four main locations (left inferior frontal gyrus or Broca's area, and superior temporal gyri or Wernicke's area). Exact 95% confidence intervals that were based on binomial distribution were calculated with SPSS 13.0 software (SPSS, Chicago, IL, USA).

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Conflicts of interest: None declared.

Ethical approval: This study was approved and reviewed by

the Institutional Review Board at the General Hospital of Ningxia Medical University in China.

Supplementary information: Supplementary data associated with this article can be found, in the online version, by visiting www.nrronline.org.

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