News Release

Title：

Navigated repetitive transcranial magnetic stimulation as preoperative assessment in patients with brain tumors

Key Points

- **We aimed to investigate clinical parameters that affected the results of navigated repetitive transcranial magnetic stimulation (nrTMS) language mapping by comparing the results of preoperative nrTMS language mapping with those of direct cortical stimulation (DCS) mapping.**
- **In the 50 patients with left-side gliomas, nrTMS language mapping showed 81.6% sensitivity, 59.6% specificity, 78.5% positive predictive value, and 64.1% negative predictive value when compared with the respective DCS values for detecting language sites in all regions.**
- **Based on the receiver operating curve statistics, subgroup analysis showed that the non-involvement of language-related regions afforded significantly better the area under the curve (AUC) values (AUC = 0.81, 95% confidence interval (CI): 0.74–0.88) than the involvement of language-related regions (AUC = 0.58, 95% CI: 0.50–0.67; p <0.0001).**
- **Our findings suggest that nrTMS language mapping could be a reliable method, particularly in obtaining responses for cases without tumor-involvement of classical perisylvian language areas.**

Summary

This work is mainly from the team of Kazuya Motomura (Associate professor, Department of Neurosurgery), Atsushi Natsume (Associate professor, Department of Neurosurgery) in Nagoya University Graduate School of Medicine (Dean: Kenji Kadomatsu) and Hiroki Takeuchi (Department of Neurosurgery) in Higashinagoya National Hospital and Ippei Nojima (Associate professor, Department of Physical Therapy) in Shinshu University School of Medicine (Dean: Jun Nakayama).

We aimed to investigate clinical parameters that affected the results of navigated repetitive transcranial magnetic stimulation (nrTMS) language mapping by comparing the results of preoperative nrTMS language mapping with those of direct cortical stimulation (DCS) mapping. In the prospective, non-randomized study, patients had to meet all of the following inclusion criteria: the presence of left- or right-side brain tumors in the vicinity of or inside the areas anatomically associated with language functions; awake brain surgery scheduled; and age >18 years. Sixty one patients were enrolled, and this study included 42 low-grade gliomas and 19 high-grade gliomas (39 men, 22 women; mean age, 41.1 years, range 18–72 years). The tumor was located in the left and right hemisphere in 50 (82.0%) and 11 (18.0%) patients, respectively. In the 50 patients with left-side gliomas, nrTMS language mapping showed 81.6% sensitivity, 59.6% specificity, 78.5% positive predictive value, and 64.1% negative predictive value when compared with the respective DCS values for detecting language sites in all regions. We then investigated how some parameters, including age, tumor type, tumor volume, and the involvement of anatomical language-related regions, affected

different subpopulations. Based on the receiver operating curve statistics, subgroup analysis showed that the non-involvement of language-related regions afforded significantly better the area under the curve (AUC) values (AUC = 0.81, 95% confidence interval (CI): 0.74–0.88) than the involvement of language-related regions (AUC = 0.58, 95% CI: 0.50–0.67; p <0.0001). Our findings suggest that nrTMS language mapping could be a reliable method, particularly in obtaining responses for cases without tumor-involvement of classical perisylvian language areas.

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Research Background

While intraoperative language mapping is highly reliable, preoperative language evaluation can be of great value because the investigation of cortical language functions preoperatively makes brain tumor surgery safe, practical, and effective. Furthermore, the risk of postoperative language deficits significantly increases when brain tumor surgery involves the language dominant hemisphere; it is therefore crucial to determine language dominance for surgical planning. Language task-based functional magnetic resonance imaging (fMRI) allows preoperative non-invasive identification of language areas. This technique has been widely used in preoperative risk assessment and planning to reduce the rate of post-surgical functional impairments. Because a fMRI activation also represents excitatory activation, which is the result of having been recruited by an upstream or downstream area, there is a fundamental problem with fMRI to predict speech localization for presurgical planning. Although one surgical study has shown fMRI for neurosurgical planning was a useful, comparing with intraoperative DCS during awake surgery, most studies have not clarified the reliability of language fMRI in preoperative neurosurgical planning for patients with tumors in language-eloquent brain regions.

Navigated repetitive transcranial magnetic stimulation (nrTMS) has been increasingly used for preoperative language mapping in patients with tumors in left-side perisylvian brain regions. These studies compared preoperative nrTMS and intraoperative DCS language mapping. nrTMS in combination with picture-naming tasks has enabled the mapping of the cerebral cortex for language-eloquent regions. However, the accuracy of preoperative language nrTMS mapping varies across cortical language regions, protocol types, and some clinical parameters.

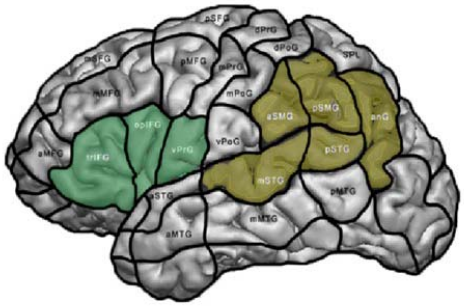
In the present study, we performed preoperative language mapping using nrTMS and awake brain surgery using DCS in patients with tumors in left- and right-side brain regions that are associated with language functions. We aimed to identify the clinical parameters that affect the results of nrTMS language mapping by prospectively comparing the results of preoperative nrTMS language mapping with DCS mapping. Furthermore, we analyzed the nrTMS language mapping data of those patients with right-sided gliomas that were not located within or adjacent to anatomically defined language-eloquent brain regions.

Research Results

Awake brain surgery was successfully performed with intraoperative functional mapping using DCS in all

50 patients with left gliomas. In these patients, we compared the results of nrTMS and DCS language mapping in 278 regions according to Corina's cortical parcellation system (CPS). Responses of intraoperative DCS mapping were positive for 1–8 areas (median, 3 areas), whereas responses of nrTMS were positive for 0–8 regions (median, 4 regions). The overall accuracy values (sensitivity, specificity, positive and negative predictive values) for all regions in the 50 patients with left-side gliomas are shown in Figure 1. Sensitivity was 81.6%, specificity was 59.6%, the positive predictive value was 78.5%, and the negative predictive value was 64.1%, for detecting language sites across all regions. Sensitivity (89.5%) and the positive predictive value (82.8%) were higher in the anterior compared with the posterior language-related CPS regions, while specificity (73.5%) and the negative predictive value (71.4%) were higher in the posterior compared with the anterior language-related CPS regions.

Parameters	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
All brain regions	81.6	59.6	78.5	64.1
Anterior language-related regions	89.5	28.1	82.8	40.9
Posterior language-related regions	63.6	73.5	66	71.4



: Anterior language-related region

: Posterior language-related region

Figure 1. Sensitivity, specificity and positive/negative predictive values for all brain regions, anterior and posterior language-related regions in left-side and right-side brain tumor patients

Next, we sought to determine how subpopulations were affected differently by different parameters, including age, tumor type, tumor volume, and the involvement of anatomical language-related regions. A subgroup analysis showed that involvement of language-related regions compared to non-involvement of language-related regions was associated with lower sensitivity (70% vs. 90.9%, respectively), specificity (46.9% vs. 72.0%, respectively), a lower positive predictive value (68.3% vs. 86.5%, respectively), and a lower negative predictive value (48.9% vs. 80.0%, respectively) (Fig. 2). We obtained similar results for accuracy across groups for age (≥40 or <40 years), tumor type (high- or low-grade), and tumor volume (≥40 or <40 cm^3).

Furthermore, we calculated receiver operating characteristic (ROC) curve statistics for the sensitivity, specificity, positive predictive values, and negative predictive values (Fig. 2). Notably, our results show that the non-involvement of language-related regions led to significantly better AUC values (AUC = 0.81, 95% CI: 0.74–0.88) than the involvement of language-related regions (AUC = 0.58, 95% CI: 0.50–0.67; p

<0.0001; Fig. 2).

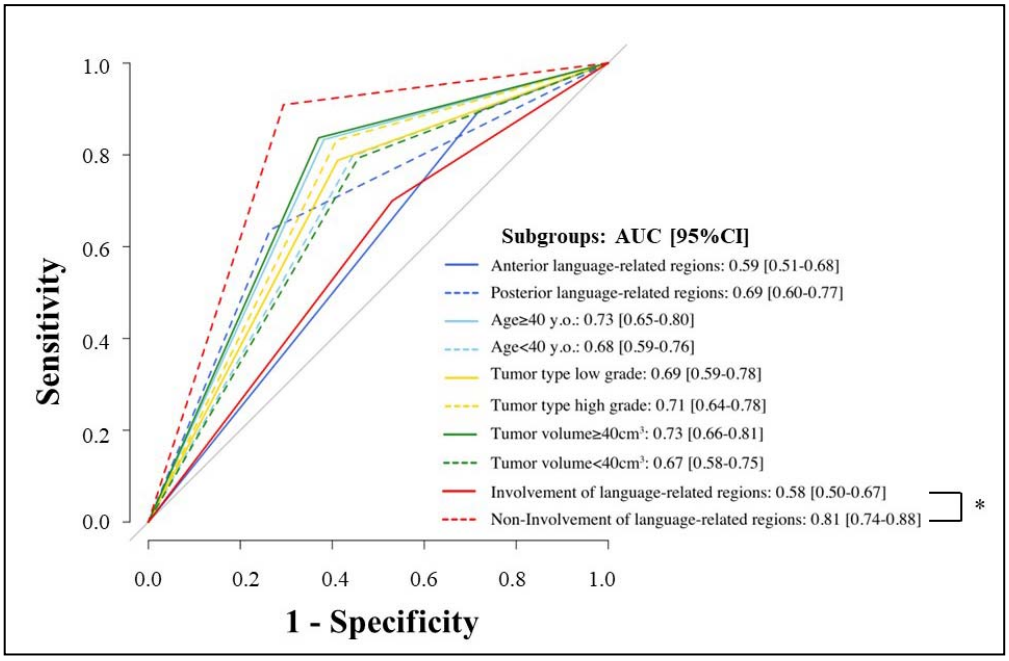


Figure 2. Receiver operating characteristics (ROC) curve of navigated repetitive transcranial magnetic stimulation (nrTMS) vs. direct cortical stimulation (DCS) in each subgroup.

The statistical significance of observed AUC differences between the scores was assessed using DeLong's test; * p <0.0001.

Research Summary and Future Perspective

To investigate the clinical parameters that affect the results of nrTMS language mapping, we prospectively compared the results of preoperative nrTMS and DCS language mapping. Tumor involvement of anatomical language-related regions significantly affected the results of the nrTMS mapping. Furthermore, nrTMS language mapping enabled the determination of hemispheric language dominance in a preoperative assessment of patients with gliomas. Our findings suggest that nrTMS language mapping could be a reliable method, particularly in obtaining responses for cases without tumor-involvement of classical perisylvian language areas. Further studies are required to validate nrTMS language mapping as a preoperative mapping tool of cortical language function.

Publication

Kazuya Motomura, Hiroki Takeuchi, Ippei Nojima, Kosuke Aoki, Lushun Chalise, Kentaro Iijima, Toshihiko Wakabayashi and Atsushi Natsume. Anterior insular cortex stimulation and its effects on emotion recognition. Scientific Reports, published online on May 3, 2020.
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Japanese ver.
https://www.med.nagoya-u.ac.jp/medical_J/research/pdf/Sci_Rep_200603.pdf