Utility of presurgical navigated transcranial magnetic brain stimulation for the resection of tumors in eloquent motor areas

Clinical article

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Object. Navigated transcranial magnetic stimulation (nTMS) is a newly evolving technique. Despite its supposed purpose (for example, preoperative central region mapping), little is known about its accuracy compared with established modalities like direct cortical stimulation (DCS) and functional MR (fMR) imaging. Against this background, the authors performed the current study to compare the accuracy of nTMS with DCS and fMR imaging.

Methods. Fourteen patients with tumors in or close to the precentral gyrus were examined using nTMS for motor cortex mapping, as were 12 patients with lesions in the subcortical white matter motor tract. Moreover, preoperative fMR imaging and intraoperative mapping of the motor cortex were performed via DCS, and the outlining of the motor cortex was compared.

Results. In the 14 cases of lesions affecting the precentral gyrus, the primary motor cortex as outlined by nTMS correlated well with that delineated by intraoperative DCS mapping, with a deviation of 4.4 ± 3.4 mm between the two methods. In comparing nTMS with fMR imaging, the deviation between the two methods was much larger: 9.8 ± 8.5 mm for the upper extremity and 14.7 ± 12.4 mm for the lower extremity. In 13 of 14 cases, the surgeon admitted easier identification of the central region because of nTMS. The procedure had a subjectively positive influence on the operative results in 5 cases and was responsible for a changed resection strategy in 2 cases. One of 26 patients experienced nTMS as unpleasant; none found it painful.

Conclusions. Navigated TMS correlates well with DCS as a gold standard despite factors that are supposed to contribute to the inaccuracy of nTMS. Moreover, surgeons have found nTMS to be an additional and helpful modality during the resection of tumors affecting eloquent motor areas, as well as during preoperative planning.


KEY WORDS • preoperative mapping • rolandic region • tumor • transcranial magnetic stimulation • navigated brain stimulation • functional neurosurgery

The resection of tumors within or close to eloquent motor areas, particularly the precentral gyrus, always involves a compromise between the extent of resection and the preservation of motor function. Especially in gliomas, surgical tumor reduction significantly affects survival and thus must be as extensive as possible. On the other hand, motor function must be preserved to secure a good quality of life for the patient. To achieve both goals, neurosurgeons use multiple modalities to examine, visualize, and monitor anatomy and motor function presurgically as well as during a resection.

For preoperative delineation of the motor cortex in relation to tumor, some previously established modalities are at hand, such as fMR imaging, PET, electroencephalography, and magnetoencephalography. However, these methods use the distribution of metabolic (fMR imaging or PET) or electrical (electroencephalography or magnetoencephalography) activity to detect neuronal pathway activity. In theory, metabolic or electrical activity might correlate with neurophysiological pathways but does not have to. In the past 2 years, we witnessed the increasing use of another modality: nTMS. In 1985 Barker and colleagues used...
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developed nTMS, which is an electrophysiological technique that allows investigation of the human motor cortex and its tracts. The development of focally stimulating coils increased spatial resolution, and during the past 20 years, especially neurologists have used TMS for different kinds of examinations for or treatments of conditions such as tinnitus, depression, or chronic pain.1,6,20,29 Navigated TMS can reach cortical neurons by a briefly induced but strong magnetic field, causing α-motoneurons to be excited. The strength of the obtained CMAP relies on the number of these activated spinal motoneurons. Although many attempts were made in the past decade to develop a reliable method of navigating TMS, only one system truly succeeded methodically and was able to calculate the electric field precisely to accurately identify the cortical point of nTMS in relation to visualized cerebral cortex. This is possible because the system takes different head shapes into account, which is very important in allowing the investigator to position the coil exactly perpendicular to stimulated brain and therefore apply maximum energy at the marked location.11,12,15,16,31

However, as a new modality, nTMS is actually capable of giving us specific information where monosynaptic MEPs are elicited in the precentral gyrus, as shown in recently published studies.8,28 Thus, the present study was designed to prospectively evaluate the accuracy of nTMS in comparison with the gold standard of DCS and with an already established preoperative mapping method, that is, fMR imaging.

Methods

This study was conducted in accordance with the ethical standards of the Technical University of Munich, the local ethics committee, and the Declaration of Helsinki. Informed consent was obtained from every patient.

Patient Population

Between May and October 2010, we performed presurgical mapping by using nTMS in 26 patients with tumors in or close to the precentral gyrus as well as in the subcortical white matter motor tract. The topographic association between tumor and corticospinal tract or rolandic cortex was preoperatively assessed via MR imaging, and eligible patients from among a group of 35 were recruited for this study. Patients were enrolled if tumor invasion of the rolandic region or corticospinal tract was suspected based on contrast-enhanced MR imaging. The lesion was located within or adjacent to the precentral gyrus in 14 cases, whereas it was in the subcortical white matter motor tract in 12 cases. Nine patients (34.6%) suffered from mild preoperative motor deficits. The mean age was 57.6 ± 15.5 years (range 18.7–78.8 years); 13 patients (50.0%) were female and 13 (50.0%) were male. Eighteen patients (69.2%) had a history of seizures; 15 (83.3%) of those 18 were on AEDs. Twenty-three patients (88.5%) were right-handed, 3 (11.5%) were left-handed, and none showed bilateral handedness. Twelve tumors (46.2%) were in the dominant hemisphere. Among the 26 cases, there were 13 glioblastomas (WHO Grade IV), 3 anaplastic astrocytomas (WHO Grade III), 2 diffuse astrocytomas (WHO Grade II), 1 dys-embryoplastic neuroepithelial tumor (WHO Grade I), and 7 metastases.

Preoperative MR Imaging

All patients underwent preoperative and postoperative MR imaging. Magnetic resonance imaging investigations were performed on a clinical 3-T MR unit (Achieva 3T, Philips Medical Systems) using an 8-channel phased-array head coil. For BOLD fMR imaging, each patient underwent 4 fMR image block-design paradigms: upper limb fine motor control (alternating-limb bilateral finger tapping) for both the right and left hands and lower limb motor control (alternating extension and flexion of the toes) for right and left limbs. The sequence parameters were as follows. For fMR imaging we used an echo planar sequence with an echo train length of 43, TR of 2500 msec, and TE of 35 msec within 2 minutes 53 seconds. Sixty-four dynamic sequences were acquired, each containing 32 contiguous 4-mm axial slices with an in-plane resolution of 2.75 × 2.75 mm. Parallel imaging (SENSE) was used to diminish susceptibility-related artifacts (SENSE factor 2). Data processing was performed using BrainLAB iPlan Net Cranial 3.0.1.

The fMR imaging data were transferred to an external workstation (Extended MR Workspace, Philips Medical Systems) and were postprocessed using the ViewBOLD package. After motion correction and spatial smoothing (2D Gaussian filter with 4-mm full width at half maximum, kernel 2 × 2 pixel), statistical parametric maps were generated using the general linear model. We chose a hemodynamic delay of 2 × TR, a single predictor, and a t-value threshold of 2.5. Only clusters with a positive correlation, which were bigger than 40 voxels in size, were considered to be activated areas. We checked the validity of the results by reviewing the time intensity diagrams of the activated voxels. Besides the fMR imaging, the scanning protocol consisted of a T2 FLAIR (TR 1200 msec, TE 140 msec, TI of 2500 msec, 30 slices with 1-mm gap, voxel size 0.9 × 0.9 × 4 mm², 3-minute acquisition time) and a 3D gradient echo sequence (TR 9 msec, TE 4 msec, 1-mm² isovoxel covering the whole head, 6 minutes 58 seconds acquisition time) after intravenous administration of 0.1 mmol/kg body weight of gadopentetate dimeglumin (Magnevist, Marostrast GmbH) for anatomical coregistration. The 3D data set was then transferred to the nTMS system (eXimia 3.2, Nexstim) using the DICOM standard.

Navigated Brain Stimulation

The nTMS system used in this study includes a magnetic stimulator with a biphasic figure-8 TMS coil with a radius of 50 mm. The navigation device orients individual 3D MR imaging data to the patient’s head through infrared tracking (Polaris Spectra) using spheres coated with a retroreflective surface. The system can estimate the induced electric field strength with regard to the patient’s head shape. This electric field strength is then visualized on the cortex surface, which is reconstructed by the MR imaging data set.11,31

While applying TMS, electrical activity was continuously monitored using EMG (eXimia 3.2), with 4 channels
for the upper extremity and 2 channels for the lower extremity. For EMG recording, we used disposable pre-gelled Ag/AgCl electrodes (Neuroline 720, Ambu). For mapping, we used electrodes over the skin of the APB, abductor digit minimi, flexor carpi radialis, and biceps brachii muscles, as well as the tibialis anterior and gastrocnemius muscles. The reference electrode was placed at the ipsilateral elbow above the tendon of the biceps brachii muscle. The sampling rate was 3 kHz for all channels; resolution was 0.3 mV. The noise of the device was lower than 5 mV for peak-to-peak measurements. The TMS device triggers the EMG system.

The day before surgery, we performed primary motor cortex mapping by using biphasic nTMS in all 26 patients. First, the rMT was determined for the hemisphere ipsilateral to the tumor. The motor threshold is the lowest stimulation intensity capable of eliciting a response in the relaxed APB muscle in 5 of 10 stimulations. Therefore, we first determined the most excitable region in the hand knob that elicited the strongest CMAP in the APB muscle, which is termed the “hot spot.” Repeated stimuli were then applied above this most sensitive region, and the stimulation intensity was increased until a peak-to-peak CMAP response above 50 mV was recorded in 5 of 10 stimulations. While determining the rMT, premotorization was diminished to a maximum extent, resulting in maximum EMG activity levels of 15 mV (peak to peak). After determining the rMT, mapping of the primary motor cortex was performed with a stimulator output of 110% of the rMT. Mapping began at the hot spot and proceeded over the entire precentral gyrus, the tumor, and adjacent gyri until a CMAP was no longer detected. For mapping of the lower extremity, stimulation intensity was increased until a CMAP was recorded up to 130% of stimulator output. During mapping, the electrical field was directed strictly perpendicular to the stimulated gyrus. In the upper as well as the lower extremity, a CMAP above 50 mV was considered significant if latency was within the commonly known latency range of monosynaptic MEPs for each muscle. After finishing the mapping, every stimulation point was post hoc assessed for its appropriateness while the assessor remained blinded to the acquired data. For the detection of CMAPs, 27-gauge disposable subdermal bipolar needle electrodes (AD-Tech Medical Instrument Corp. and Inomed Medizintechnik) were placed over the same muscles of the contralateral side of the tumor with a distance of approximately 10 mm between the electrodes, using the same muscles as in nTMS. Processing of the acquired data was achieved using the Epoch XP neuromonitoring system (Axon Systems, Inc.) or the ISIS IOM neuromonitoring system (Inomed Medizintechnik).

Subsequent to durotomy and determination of the motor threshold, mapping of the rolandic region was performed in 14 patients via navigated DCS by using a monopolar anodal probe (Inomed Medizintechnik) to recognize and save the stimulated region in the neuronavigation system. A subdermal electrode positioned above the nasion at Fpz according to the 10-20 International System was used as the cathodic pole. Direct cortical stimulation was performed with intensities between 5 and 14 mA, square-wave pulses with a duration of 0.2–0.3 msec, a frequency of 350 Hz, and as a train of 5 pulses, as described previously. After DCS mapping was finished, a strip electrode (AD Tech Medical Instrument Corp. or Inomed Medizintechnik) was positioned over the primary motor cortex for continuous MEP monitoring, as described previously.

Surgical Questionnaire

After surgery, each surgeon received a questionnaire regarding his or her experience with nTMS data during surgery. He or she was asked whether nTMS data improved, impaired, or did not influence identification of the central gyrus, his or her confidence in the anatomy, the operative result, or the operative strategy. A positive influence on the operative result meant that according to the personal impression of the surgeon the combination of extent of resection and patient outcome would have been worse without nTMS.
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Postoperative Evaluation

For every patient, neurological status was assessed at the 1st postoperative day, at discharge, and during postoperative follow-up. Moreover, each patient underwent MR imaging the day after surgery to evaluate the extent of resection as well as diffusion-weighted imaging to detect ischemic events.

Statistical Analysis

Differences between groups were tested using the Friedman test for nonparametric 1-way ANOVA followed by the Dunn test as a post hoc test. Differences between groups (modalities) were tested using the Wilcoxon signed-rank test for comparisons of related samples. All results are presented as the means ± standard deviation in the graphs, whereas range is mentioned in the text (SigmaStat 3.5, Jandel Scientific). A value of p < 0.05 was considered significant.

Results

Preoperative nTMS Mapping

Preoperative mapping of the primary motor cortex was possible in all 26 patients. In all patients, the mean rMT was $35.7\%\pm9.2\%$ (range 25%–65%) of maximum stimulator output. For patients on AEDs (15 patients), the rMT was $33.7\%\pm7.1\%$ (range 25%–55%), whereas it was $38.0\%\pm11.1\%$ (range 27%–65%) for those not taking AEDs (not significant; Fig. 1). Levetiracetam was used as an AED in all but 1 case in which lamotrigine was used. For complete mapping of the motor cortex, between 121 and 253 stimulation points were needed. In 51.9% of cases, mapping of both the lower and the upper extremity was possible. Out of 26 patients, 1 experienced nTMS mapping as unpleasant, although no patient actually stated that the procedure was painful.

Correlation Between nTMS and Intraoperative DCS Mapping Data

In the 14 patients with lesions within or adjacent to the precentral gyrus, preoperative motor cortex mapping was compared with intraoperative DCS mapping via a navigated DCS electrode. Postoperatively, borders between positive and negative stimulation points for both modalities were compared on axial slices by using recalibrated screenshots and BrainLAB iPlan Net Cranial 3.0.1. The measured difference between the two modalities represents the difference between the same edges of the functional motor area as defined by the two different modalities. Intraoperative DCS mapping of the primary motor cortex differed from the nTMS data by a mean of $4.4\pm3.4$ mm (range 1.9–9.2 mm). No monodirectional systematic deviation was observed.

Correlation Between nTMS and Preoperative fMR Imaging Data

In 24 of 26 cases, fMR imaging was performed before tumor resection and analyzed by a neuroradiologist blinded to the nTMS results. In 1 case, the patient did not tolerate fMR imaging because of claustrophobia; in another case, the general condition of the patient was too poor. Both fMR imaging and nTMS data were imported to the neuronavigation system (BrainLAB iPlan Net Cranial 3.0.1), and borders delineating the primary motor cortex according to BOLD data and the margin between the positive and negative stimulation points of nTMS were measured on axial slices by using recalibrated screenshots and iPlan Net Cranial 3.0.1. Again, the measured difference between nTMS and fMR imaging data is the difference between the same edges of the functional motor area as defined by both modalities. As compared with nTMS data, determination of the primary motor cortex using BOLD data differed strongly between the upper and lower extremities. For the upper extremity, the deviation between nTMS and fMR imaging was $9.8\pm8.5$ mm (range 5.3–39.7 mm; Fig. 2). For the lower extremity, this difference was $14.7\pm12.4$ mm (range 8.4–33.5 mm). Again, no monodirectional systematic deviation was observed.

Fig. 1. Bar graph showing rMT in relation to AED use. No significant difference was observed.

Fig. 2. Deviation of nTMS compared with DCS and fMR imaging. Bar graph showing that nTMS data correlate quite well with DCS data ($4.4\pm3.4$ mm), whereas delineation of the primary motor cortex via fMR imaging differs significantly from nTMS, depending on whether the extremity is upper ($9.8\pm8.5$ mm) or lower ($14.7\pm12.4$ mm; p < 0.05).
**Influence of nTMS Data on the Neurosurgeon**

With regard to the tumor cases in the precentral gyrus, the surgeons reported that identification of the central region was easier using the nTMS data in 13 of the 14 cases. The nTMS data increased his or her confidence in the anatomy in 7 cases, showed a positive influence on the operative result in 5 cases, and even changed the operative strategy in 2 cases (Fig. 3). During the 14 resections of tumors affecting the precentral gyrus, additional modalities were used. Continuous MEP monitoring was used in 14 cases, diffusion tensor imaging fiber tracking was applied in 8 cases, fluorescence guidance with 5-aminolevulinic acid was applied in 2 cases, and intraoperative ultrasonography was used in 1 case.

**Patient Outcome**

On the 1st postoperative day, 11 patients (42.3%) showed aggravated paresis, and none of the 26 patients had improvement. On the day of discharge, however, 5 patients with supplementary motor area syndrome recovered, whereas 6 patients (23.1%) still suffered from surgery-related paresis. Two patients (7.7%) had improved as a result of surgery. Regarding the 6 patients with resection-related motor deficits, MEP amplitude loss > 50% occurred as a result of resection within the fibers of the corticospinal tract in 4 cases. Postoperative MR imaging showed increased edema in another 2 cases with stable intraoperative MEP amplitudes. Two patients without postoperative deficits were lost to long-term follow-up. Of the 6 patients with postoperatively aggravated deficits at discharge, 3 (12.5%) showed persisting motor deficits on long-term follow-up; all 3 of these patients showed MEP amplitude loss > 50% during resection within the fibers of the corticospinal tract. The mean follow-up period was 20.4 ± 14.4 weeks (range 0.7–46.7 weeks). Compared with their preoperative motor status, 18 patients (75.0%) remained unchanged and 3 patients (12.5%) improved during long-term follow-up.

**Postoperative MR Images**

Two patients worsened immediately after the tumor resection, and instant imaging showed secondary hemorrhage in one and epidural hematoma in the other, and thus reoperation and extensive hemostasis were performed in both cases. On the day after tumor resection, MR imaging showed no further secondary events and both patients were discharged with no new motor deficits. Postoperative diffusion-weighted imaging sequences showed circumscribed ischemia in 4 patients and increased edema in 1 patient; none of these patients showed any kind of new postoperative motor deficit. Thus, among 11 patients with a new postoperative motor deficit, all cases were attributable to the resection of brain tissue as mentioned above.

**Illustrative Case**

A 67-year-old male with colon cancer that had been initially diagnosed and completely resected in 2005 presented with slightly disturbed fine motor skills of the left hand. Magnetic resonance imaging showed a single metastasis 1.5 cm in diameter within the right hand knob. Functional MR imaging showed the primary motor cortex of the left hand was dorsolateral to the lesion (Fig. 4A). However, nTMS mapping of the primary motor cortex showed the primary motor cortex of the left hand was ventromedial to the lesion (Fig. 4B). These results influenced the operative approach significantly, and DCS confirmed nTMS mapping of the left hand with a deviation of 6.7 ± 4.0 mm. Postoperatively, the patient showed increased disturbance of motor function limited to the left hand, which resolved during the inpatient stay.

**Discussion**

**Functional MR Imaging Versus nTMS Mapping**

Today, the only widely used and applicable method of preoperative functional brain mapping is fMR imaging. But, as repeatedly shown, fMR imaging is insufficient for reliable delineation of functional areas. Moreover, we have confirmed the discrepancy between metabolic and electrophysiological (that is, true functional) mapping (Fig. 2). Especially in cases of tumors with pathological vasculature compromising the central region, mapping the primary motor cortex by metabolic measures has been shown to be an unreliable method. Furthermore, metabolically activated brain parenchyma is not essential for motor function. But because fMR imaging is the only established and widely available noninvasive method for preoperative characterization, we used the highest achievable standard of fMR imaging for comparison with nTMS. Moreover, fMR imaging evaluation was performed by those blinded to neurological status, anatomical MR imaging, and nTMS mapping. Note that another disadvantage of fMR imaging is its frequent effect of claustrophobia and its dependence on patient cooperation.

**Direct Cortical Stimulation Versus nTMS**

Both DCS and nTMS are techniques that elicit neuronal activation. Today, DCS is the gold standard for functional mapping; however, it is limited to intraoperative use. Navigated TMS also uses neuronal stimulation...
and excitation of CMAPs to characterize the primary motor cortex, but it is used most favorably in a presurgical way. Taking the standard deviation into account, we found that the spatial deviation between DCS and nTMS data ranges within the calculated accuracy of the nTMS system that was used (eXimia 3.2), which is 5.73 mm. Such precision was already documented in previous reports on nTMS accuracy, indicating that a spatial resolution of 5 mm is obtainable. Nonetheless, this is the first study to focus on the precision of the Nexstim eXimia 3.2 nTMS system as compared with DCS.

Furthermore, we recognized that, especially for lower-extremity mapping, nTMS was possible more frequently than DCS, most likely because of the comparatively large stimulated cortical volume, which was calculated to be 1–2 cm³ for the figure-8 coil used. Yet, this estimated volume originates from nonnavigated TMS using a considerably higher stimulation intensity. Although many studies have shown DCS to be an exact and reliable method, until now there have been no precise investigations of the extent of stimulated brain volume via anodal DCS.

Despite the good agreement between nTMS and DCS (Fig. 2), we must be aware that our results strongly rely on many parameters, such as the definition of rMT, the voltage at which CMAP is considered significant, registration errors, navigation errors for both systems, and brain shift after durotomy. Regardless of these confounders, we demonstrated that when using the parameters mentioned here, surprisingly good accuracy is achievable, which is in part superior to the accuracy documented in previous reports. However, because of the above-mentioned navigation errors, it seems unlikely that nTMS is capable of completely replacing intraoperative neuromonitoring. And yet, when the rolandic region is compromised by tumor growth, it is highly valuable to have another modality at hand that confirms the results of DCS mapping.

General Results of nTMS

Compared with fMR imaging, nTMS is less affected by patient cooperation or claustrophobia. As shown in Fig. 4, nTMS showed monosynaptic representations of the motor cortex located frontal to the precentral gyrus such as the supplementary motor area. This result accords well with both intraoperative and previous findings of neuroanatomists and neurophysiologists.

With nTMS mapping, we were able to recognize how to prepare the patient for the moment after anesthesia, given that we preoperatively knew how close the primary motor region for proximal or distal extremities or even the face was. Thus, we can assess operative risks more precisely and prepare the patient for postoperative motor deficits even if they are transient due to edema.

From another point of view, we showed that nTMS data increased the surgeon's confidence in 7 of 12 cases (Fig. 3). This finding may suggest that the intraoperative availability of nTMS data in the neuronavigation system can accelerate the learning curve of neurosurgeons during their first operations within the central region. Although our group does not base operative indications on nTMS data, this study showed that we already changed the operative approach in 2 cases, which indicates an impact of nTMS data on our decisions. Further, newly evolving possibilities in nTMS involve deciding whether DCS is mandatory and whether it enhances intraoperative neuromonitoring by guiding the DCS probe, thus significantly accelerating DCS mapping.

Conclusions

Data in this study demonstrate that nTMS is possible in almost every case without strain to the patient and that its results highly correlate with intraoperative DCS. In contrast, fMR imaging differed significantly. Navigated TMS may not only influence surgeon confidence during resection, but also improve planning, psychological preparation of the patient, or even evaluation of lesion resectability in general. However, more studies with more patients must be conducted to investigate the influence of nTMS mapping on patient outcomes, the extent of resection, survival, and the learning curve of inexperienced neurosurgeons. Patient outcome is the most crucial parameter for evaluating the utility of new techniques. Yet, given this study's small number of patients, our data must be regarded as proof of the feasibility of this technique and is not able to statistically show influence on patient outcome.
Disclosure

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Author contributions to the study and manuscript preparation include the following. Conceptual design: Ringel, Krieg. Acquisition of data: Krieg, Shiban, Buchmann. Analysis and interpretation of data: Ringel, Krieg. Drafting the review: Ringel, Krieg. Critically revising the article: all authors. Submitted manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Ringel. Statistical analysis: Krieg. Study supervision: Krieg, Meyer.

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References


31. Ruohonen J, Ilmoniemi RJ: Modeling of the stimulating field
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