A Comparison of Language Mapping by Preoperative Navigated Transcranial Magnetic Stimulation and Direct Cortical Stimulation During Awake Surgery

Thomas Picht, MD*‡
Sandro M. Krieg, MD*§
Nico Sollmann§
Judith Rösler‡
Birat Niraula‡
Tuomas Neuvonen, MS¶
Petri Savolainen, MS¶
Pantelis Lioumis, PhD||
Jyrki P. Mäkelä, MD, PhD||
Vedran Deletis, MD, PhD#**
Bernhard Meyer, MD§
Peter Vajkoczy, MD*‡
Florian Ringel, MD*§

‡Department of Neurosurgery, Charité Universitätsmedizin, Berlin, Germany; §Department of Neurosurgery, Klinikum rechts der Isar, Technische Universität München, Germany; ¶Nexstim Ltd., Helsinki, Finland and Neuroscience Unit, Institute of Biomedicine/Physiology, University of Helsinki, Finland; ||BioMag Laboratory, HUS Medical Imaging, Hospital District of Helsinki and Uusimaa, Helsinki, Finland; #Department of Intraoperative Neurophysiology, St. Luke's-Roosevelt Hospital, New York, New York; **Laboratory for Human and Experimental Neurophysiology, School of Medicine, University of Split, Split, Croatia

*These authors contributed equally.

Correspondence:
Florian Ringel, MD,
Department of Neurosurgery,
Klinikum rechts der Isar Technische Universität,
MünchenIsmaninger Str. 22,
81675 Munich, Germany.
E-mail: Florian.Ringel@lrz.tum.de

Received, July 5, 2012.
Accepted, January 2, 2013.
Published Online, February 4, 2013.

BACKGROUND: Navigated transcranial magnetic stimulation (nTMS) is increasingly used in presurgical brain mapping. Preoperative nTMS results correlate well with direct cortical stimulation (DCS) data in the identification of the primary motor cortex. Repetitive nTMS can also be used for mapping of speech-sensitive cortical areas.

OBJECTIVE: The current cohort study compares the safety and effectiveness of preoperative nTMS with DCS mapping during awake surgery for the identification of language areas in patients with left-sided cerebral lesions.

METHODS: Twenty patients with tumors in or close to left-sided language eloquent regions were examined by repetitive nTMS before surgery. During awake surgery, language-eloquent cortex was identified by DCS. nTMS results were compared for accuracy and reliability with regard to DCS by projecting both results into the cortical parcellation system.

RESULTS: Presurgical nTMS maps showed an overall sensitivity of 90.2%, specificity of 23.8%, positive predictive value of 35.6%, and negative predictive value of 83.9% compared with DCS. For the anatomic Broca's area, the corresponding values were a sensitivity of 100%, specificity of 13.0%, positive predictive value of 56.5%, and negative predictive value of 100%, respectively.

CONCLUSION: Good overall correlation between repetitive nTMS and DCS was observed, particularly with regard to negatively mapped regions. Noninvasive inhibition mapping with nTMS is evolving as a valuable tool for preoperative mapping of language areas. Yet its low specificity in posterior language areas in the current study necessitates further research to refine the methodology.

KEY WORDS: Awake surgery, Language, Preoperative mapping, Transcranial magnetic stimulation, Tumor

Neurosurgery 72:808–819, 2013 DOI: 10.1227/NEU.0b013e3182889e01 www.neurosurgery-online.com

Patients with lesions of language-eloquent regions, particularly within the left-sided inferior frontal, supramarginal, and superior temporal gyri, are at risk of impairment of language function during resective surgery. Therefore, for optimal surgical results, awake craniotomy and intraoperative language mapping by bipolar direct cortical stimulation (DCS) is advocated.[1-3] A vast amount of information on the distribution and variability of cortical language representation has been gathered by DCS.[3-6]

ABBREVIATIONS: DCS, direct cortical stimulation; **fMRI,** functional magnetic resonance imaging; **nTMS,** navigated transcranial magnetic stimulation; **RMT,** resting motor threshold; **rTMS,** repetitive transcranial magnetic stimulation; **TMS,** transcranial magnetic stimulation

Intraoperative mapping is highly reliable. Nevertheless, preoperative language mapping can be of great value because elucidation of functional cortical organization preoperatively enables better patient selection and consultation based on objective risk-benefit balancing.[7] Furthermore, it may allow smaller, more targeted craniotomies and faster and safer intraoperative mapping. Moreover, it might enable safer surgery in patients who are not suitable for awake surgery. Functional magnetic resonance

imaging (fMRI) speech mapping has been compared with intraoperative DCS during awake surgery,[8-10] but its accuracy is insufficient for surgical decisions in patients with lesions in language-eloquent brain areas.[11]

Navigated transcranial magnetic stimulation (nTMS) is increasingly used for preoperative mapping of the primary motor cortex. Good correlation of preoperative nTMS and intraoperative DCS motor maps has been repeatedly reported.[12-15] In addition, repetitive transcranial magnetic stimulation (rTMS) has been used for disturbing speech and determination of language lateralization.[16-20] By using the combination of TMS and a navigation system, it is possible to specifically identify the cortical regions vulnerable to rTMS, which are presumably speech eloquent. When navigated rTMS is performed during an object-naming task, it is possible to map the cortex for language-eloquent regions.[21] However, so far, there has been only 1 case report published addressing the clinical accuracy and reliability of rTMS for language mapping.[22] Therefore, we prospectively compared the results of presurgical language mapping by rTMS with the present gold standard method, intraoperative DCS during awake surgery, in patients with left-sided lesions to assess these parameters.

PATIENTS AND METHODS

Ethics

The experimental protocol was approved by the local ethics committees in accordance with the Declaration of Helsinki. All patients provided written informed consent for all medical evaluation and treatment.

Study Design

This was a prospective, nonrandomized study.

Patients

The study was conducted on consecutive patients scheduled for surgery of tumors in the vicinity of the presumed essential language areas, typically the left perisylvian cortex. They were recruited from 2 hospitals (Department of Neurosurgery, Technische Universitaet Munich, and Department of Neurosurgery, Charité Universitaetsmedizin Berlin). There was no use of prophylactic anticonvulsants before awake surgery.

All patients were enrolled for preoperative noninvasive language mapping with nTMS and intraoperative DCS in awake surgery.

The inclusion criteria were the presence of a brain tumor in the vicinity of areas presumably controlling speech production, age older than 18 years, able to provide written informed consent. The exclusion criteria were frequent seizures (>1/week),general transcranial magnetic stimulation exclusion criteria (pacemaker, cochlear implant), aphasia too severe to complete the object-naming task.

Aphasia Grading

Preoperative aphasia grading of all patients, adapted to the Aachener Aphasia Test,[23] was done by the care team. A 4-level score (0 = no aphasia, 1 = mild aphasia, 2 = moderate aphasia, 3 = severe aphasia, A = motor accented, B = sensory accented) was used.

Preoperative Language Mapping

Experimental Setup

Cortical language mapping was performed with nTMS eXimia NBS version 3.2.2 and Nexstim NBS 4.3. with a NEXSPEECH module (Nexstim Oy, Helsinki, Finland). Three-dimensional (3-D) T1-weighted magnetic resonance imaging (MRI) of each patient was performed as an anatomic reference, coregistered to the subject's brain to localize the activated brain area during nTMS. The nTMS system uses a stereotactic camera for tracking coil position with respect to a patient's head. Head position was tracked by reflectors fastened to the head with an elastic strap. During nTMS, the stimulating coil induces an electric field, which is visualized over the brain's 3-D reconstruction, and the intracranial points of stimulation are saved for later examination.[24] Before speech mapping, the resting motor threshold (RMT) was defined by motor mapping of the cortical representation of the contralateral hand area (abductor pollicis brevis muscle). The individual patient's RMT reflecting motor cortex excitability was used to select the appropriate intensity for subsequent rapid-rate transmagnetic stimulation (TMS). The speech cortical representation was activated by an object-naming task. The stimuli were 122 black-and-white drawings of common objects, displayed at an interpicture interval of 2.5 seconds. The interpicture interval was adjusted in the range of 2 to 4 seconds according to individual abilities to keep the task challenging but still within the range of reliable performance. The frequency and intensity of the rTMS were personalized based on the following protocol:

1. RMT on the tumor hemisphere was determined.
2. A train of 10 to 20 TMS bursts was administered to the ventral precentral gyrus and opercular inferior frontal gyrus: (a) 5 Hz, 5 pulses, 100% RMT; (b) 7 Hz, 7 pulses, 100% RMT (center at Munich additionally used 7 Hz, 5 pulses); (c) 10 Hz, 7 pulses, 100% RMT.
3. The frequency most effectively disturbing speech processing was identified (patient's and examiner's impression; video analysis if in doubt).
4. The most comfortable frequency was chosen if there was no clear difference in the effect on speech.
5. If no evident responses were obtained, the intensity was increased to 110% to 120% RMT and step 1 was repeated.
6. The intensity was decreased to 80% to 90% RMT or as much as needed if pain was reported to avoid any discomfort interfering with the consecutive response evaluation.[16]

The electric fields produced by the selected TMS parameters ranged between 45 and 80 V/m at the cortical surface. To make the potential speech arrest clearer, the train of TMS pulses started 300 ms after the picture presentation onset, in line with the timing of naming-related activity reported in magnetoencephalography studies.[25]

The object-naming baseline performance and all stimulation trials were videorecorded for later analysis.[21]

Speech Mapping Procedure

The images to be named were displayed on a screen in front of the patient. Each image represented a common object. The subject was instructed to name the objects in his or her mother tongue as quickly and precisely as possible. Before TMS speech mapping, the picture-naming task was performed without stimulation to acquaint the patient with the procedure and images (baseline recording). All misnamed objects were discarded from the stimulus sequence and the number of baseline errors was documented. A second baseline recording with the remaining image stack was carried out, and any additional erroneously named images were

again discarded to ensure that the patient named each item correctly. Subsequently, the actual diagnostic naming task was presented time-locked to a train of nTMS pulses. The stimulation coil was randomly moved, in between the visual display of 2 images, in roughly 10-mm steps over the perisylvian cortex. The coil was placed perpendicular to the sulcus posterior to the stimulated point to achieve maximum field induction.[21] Altogether, 80 to 120 sites of the frontal, temporal, and parietal cortex were stimulated 3 times each. The same sites were not targeted consecutively. Areas of particular importance for resection, eg, tumor or lesion and their proximity, were examined in detail. Fourteen of 20 patients underwent stimulation of both hemispheres. The hemispheres were stimulated alternately to avoid potential learning effects and progressive exhaustion, which might interfere with the subsequent outcome. After the examination, the subject was asked to rate any pain associated with the examination according to the visual analogue scale from 0 (no pain) to 10 (maximum pain).

Data Analysis

Two experienced examiners analyzed the data independently. The video of the baseline performance was analyzed first. Thereafter, each video recorded during TMS was screened, and any disturbance of speech processing during the object-naming performance was compared with the corresponding baseline response. The observed errors were categorized following a rule presented in Corina et al[5]:

No-response errors: stimulation lead to a complete lack of naming response.

Performance errors: form-based distortions that are slurred, stuttered, or imprecisely articulated. This category contains both dysarthric and apraxic speech production errors.

Neologisms: form-based errors that are possible but nonexistent words. For example, the target word "horse" is replaced with the word "herp."

Semantic paraphasias: errors in which the patient substitutes a semantically related or associated word for the target word. For example, the target word "cow" is replaced by the word "horse."

Phonologic paraphasias: characterized by unintended phonemic modification of the target word. The spoken word resembles the target word, but is phonetically different. For example, the target word "pants" is replaced with "plants."

Circumlocution errors: errors in which the subject talks about or "around" the target instead of naming it. For example, the target word "chair" is replaced with "sit down," explaining the use of the target word.

The errors were searched for from the videos of the patient performing the object-naming task. The cortical stimulation sites were hidden from the 2 examiners. Errors related to direct stimulation of muscles or associated with pain were discarded from the analysis.

In case of disagreement, a third examiner made the decisive verdict on a response. The individual RMT and rTMS frequency, the baseline error rate, and the number of potentially painful stimuli were also documented. In addition, the analysis of TMS data was cross-checked between the centers to ensure comparability.

Intraoperative Language Mapping

Setup

To ensure maximum comfort during the operation, the patient was placed in the semilateral position and supported with individually fitted foamed plastic cushions. The head was fixed with a 3-point crania-fixation device (Mayfield clamp), and the reflector for navigation was attached to it. During the operation, an operating room neuronavigation system (BrainLAB Vectorvision Cranial or BrainLAB Curve, Brainlab AG, Feldkirchen, Germany) was used at both sites in positioning the surgical tools and cortical stimulation electrodes with respect to the brain anatomy. The patient's head was coregistered with the same 3-D MRI used during nTMS session.

Anesthesiological and Surgical Procedures

During the operation, the following parameters were monitored continuously: respiratory rate, exhaled carbon dioxide, oxygen saturation, electrocardiography, blood pressure (direct or oscillometry), and temperature. A mixture of bupivacaine and epinephrine was used for regional and infiltration anesthesia of the galea and dura. An adequate level of analgesia and sedation was maintained by continuous infusion of remifentanil and propofol. The depth of analgesia and sedation was monitored using the Ramsay sedation scale with a target score of 5 to 6 (weak or no response to pain stimuli). Additional bolus doses were administered immediately before incision of the scalp and dura to adjust analgesia and sedation to the pain level of the surgical stimuli. Analgesia and sedation were discontinued about 10 minutes before neuropsychological testing. Baseline analgesic infusion was continued. The goal during this phase was a Ramsay sedation score of 2 (patient awake, calm, cooperative). After completion of cortical mapping, the operation was continued with the patient under either conscious sedation with the option of resuming language testing after reduction of the depth of analgesia and sedation or after intubation or general anesthesia (for additional details, see Picht et al[26]).

Speech Mapping Procedure

The sites of cortical stimulation were placed 5 to 10 mm apart. The raster was tighter close to the planned corticotomy. Electrical stimulation (0-20 mA, 40/60 Hz, 4-second duration) for cortical language mapping was done using bipolar stimulation forceps (electrode distance of 5 mm, Viasys Healthcare, Madison, WI [Berlin site], Inomed Medizintechnik GmbH, Emmendingen, Germany [Munich site]) and blinded to the TMS mapping results. To detect epileptic seizures and monitor possible inhibition of adjacent cortical areas, a surface electroencephalogram (band pass 10 Hz-1.5 kHz) was recorded with a cortical grid electrode. An object-naming task was used during cortical mapping since a as its disturbance is a common feature shared by all forms of aphasia.[27] The same object images were used for preopertive rTMS as well as for intra-operative language mapping by DCS. However, in intraoperative mapping, the line drawing was presented with the matrix sentence "This is a. . .." The patient's task was to say this sentence and complete it by the name of the object presented during the 4-second cortical stimulation. All sites were stimulated at least 3 times unless epileptic afterdischarges were evoked. A site was considered language positive if the same effect was induced in at least 2 of 3 stimulations.[28] All positive sites were marked with tags with letters indicating the event evoked (speech disturbance/arrest, aphasic disturbance/arrest, epilepsy). On completion of cortical mapping, the positive sites were transferred to the navigation system with the navigation pointer. If the procedure was continued with the subject awake, language testing was conducted during subcortical resection as needed.

Comparison of Preoperative nTMS and Intraoperative DCS Language Mapping

Anatomic Localization

The location of stimulation in the nTMS system was determined with a real-time physics modeling system that calculates the intracranial

location of stimulation induced by the coil and displays this information on high-resolution 3-D MRI. When the coil position is tracked, the effects of the stimulation train can be pinpointed to an anatomic location. For intraoperative direct cortical stimulation, the localization of stimulation effects was based on the assumption that the stimulation is strongest in the tissue in contact with the electrode. The stimulating electrode was localized by attaching the probe to the operating room neuronavigation system.

An approach for evaluating effects of intraoperative language mapping on an anatomic level has been presented.[5] In this method, chosen for the current analysis, the cortex is parcellated into 37 individual anatomic regions for evaluation of the anatomic site of the stimulation. The cortical gyri belonging to these anatomic cortical parcellation system (CPS) subregions were identified from 3-D MRI, and the regions were drawn on a 3-D image.[29] The nTMS data and intraoperative DCS mapping data were both projected on the parcellated cortex. This approach allows a comparison of the localization data between individual patients and over the entire studied population.

The locations of these regions are displayed on an anatomic brain template (Figure 1).[5] Figure 2 shows as an example the MRI of patient M11 with anatomic areas defined according to the area division. The DCS positive stimulation points are highlighted in orange.

In patients with large tumors causing significant anatomic distortions and obscuring the cortical gyri, the definition of anatomic areas from the MRI was challenging. However, the same definition of areas was used in the anatomic labeling of both nTMS mapping and DCS results, so the possible ambiguities of areal border definition in some patients would have no effect on the comparison of the 2 datasets.

Stimulation Assessment

The intraoperative results were first assigned to anatomic regions to obtain a "ground truth" for each area. Here "ground truth" means either a "positive" language area where DCS induced naming errors (ie, area stimulated contained essential language functions) or negative language area where DCS did not induce naming errors (ie, area stimulated did not contain essential language functions).

During the preoperative language mapping with nTMS, each area was stimulated several times. Because the nTMS gave more freedom to the operator in terms of mapping time and extent of studied regions, the cortex was stimulated much more extensively with nTMS than with DCS. To determine whether an individual brain region gave rise to speech deficits during nTMS, the following definitions for region positivity and negativity were used: (1) positive brain region, a region was considered to give rise to speech deficits if any of the trains delivered to the region elicited naming errors regardless of the error type; (2) negative brain region, a brain region was considered not to give rise to speech deficits if the region had been stimulated with at least 1 stimulation train and no speech deficits of any error type were generated. Following these rules and regarding the intraoperative DCS result as the "ground truth" for each anatomic region; the nTMS results were labeled as true positive, true negative, false positive, or false negative. Thereafter, the sensitivity and specificity values were calculated (Table 1). This comparison could be made for each region studied with intraoperative DCS. No ground truth data were available for assessment outside the region studied by DCS.

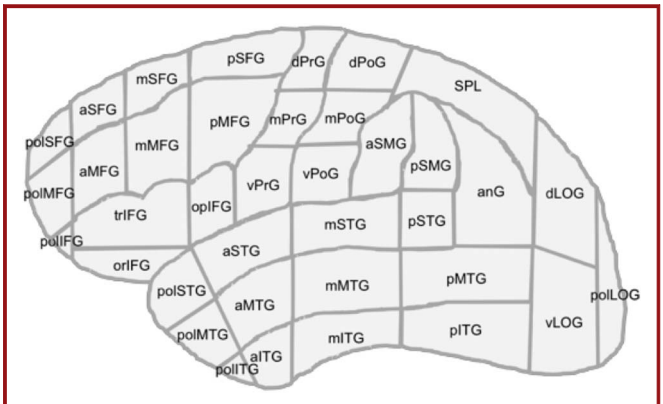

FIGURE 1. *Anatomic areas, as described in Corina et al.*[5]

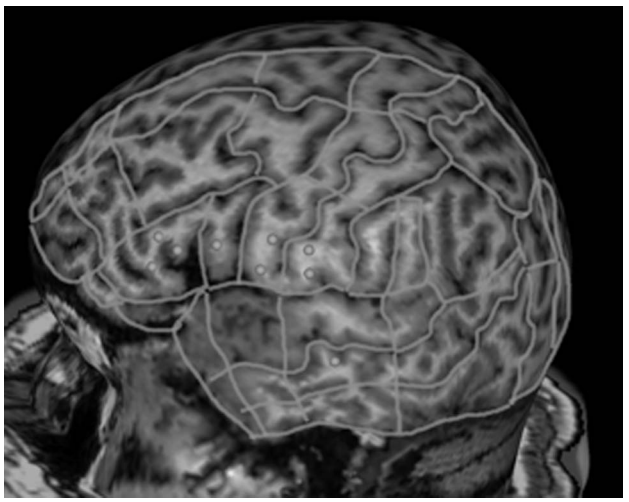

FIGURE 2. *Anatomic areas in patient M11.*

RESULTS

Patients

Between April and December 2011, 20 patients were enrolled; 9 men and 11 women. The mean age was 48 ± 12 years. Six of them were mapped and operated on at Charité Berlin and 14 at TU Munich. All lesions were located within the left hemisphere. Eight

TABLE 1. Classification of nTMS Language Mapping Results Compared With Intraoperative Language Mapping With Direct Cortical Stimulation[a]

Classification	Criteria
True positive	NBS positive AND intraoperative DCS positive
True negative	NBS negative AND intraoperative DCS negative
False positive	NBS positive AND intraoperative DCS negative
False negative	NBS negative AND intraoperative DCS positive
No data	No NBS data OR no intraoperative DCS data

[a]nTMS, navigated transcranial magnetic stimulation; DCS, direct cortical stimulation; NBS, navigated brain stimulation.

were frontal and 9 temporal gliomas. Ten patients had a glioblastoma WHO grade IV, 6 had anaplastic astrocytoma WHO grade III, 1 had a diffuse astrocytoma WHO grade II, 1 a pilocytic astrocytoma WHO grade I, and 2 had cavernomas. Two patients were left-handed but had aphasia due to a left-sided tumor (Table 2).

Speech disturbances due to focal seizures were the initial symptom in 7, generalized seizures in 6, and aphasia in 8 patients. The aphasic symptoms were predominantly sensory in 4 and motor in 4 patients.

Preoperative nTMS Mapping

Preoperative nTMS speech mapping was done in all 20 patients over the whole left hemisphere. The stimulation was generally well tolerated by all patients. The mean (range) visual analog scale score for maximum painful stimuli was 2.7 (range, 0-8). One patient requested reduction of the stimulation intensity due to discomfort related to transient temporal muscle activation. We did not observe any adverse events. No difference in the data evaluation method between the sites was observed.

Baseline errors during preoperative object naming ranged from 0.7% to 76.3% of shown objects. The left hemisphere was stimulated at 166 to 683 sites (median, 452.5 sites). Each nTMS train consisted of 5 to 10 pulses given at rates between 5 and 10 Hz (Table 3). Trains with 5- or 7-Hz frequencies were best tolerated and used most often. During stimulation, 3 to 177 naming errors (median, 61.5 naming errors) were observed (Table 4).

The occurrence of different naming error types per each region was recorded for each patient (Table 4). Moreover, we calculated the total errors for each patient induced by the stimulation trains (Table 3).

Intraoperative DCS Mapping

In all patients, intraoperative language mapping was successful. The individual stimulation intensity varied according to the

TABLE 2. Patient Characteristics Including Aphasia Preoperatively, Directly After Surgery, and at 3-Month Follow-up vs Preoperatively

Patient	Handedness	Sex	Language	Entity	Location	Symptoms	Baseline Errors, %	Aphasia Preoperatively	Aphasia Postoperatively vs Preoperatively	Aphasia at 3-Month Follow-up vs Preoperatively
B1	Right	M	Monolingual	Astrocytoma grade III	Frontal	Speech arrest	8	No	Aggravated	Aggravated
B2	Right	F	Bilingual	Glioblastoma	Frontal	Seizure	8	Yes	Decreased	Decreased
B3	Right	F	Monolingual	Astrocytoma grade III	Temporal	Speech arrest	0.7	No	Unchanged	Unchanged
B4	Right	M	Monolingual	Astrocytoma grade III	Temporal	Seizure	7	No	Unchanged	Unchanged
B5	Right	F	Monolingual	Glioblastoma	Frontal	Aphasia	7	No	Unchanged	Unchanged
B6	Right	F	Monolingual	Astrocytoma grade I	Temporal	Speech arrest	12	No	Unchanged	Unchanged
M1	Right	M	Monolingual	Cavernoma	Frontal	Seizure	11	No	Unchanged	Unchanged
M2	Right	F	Monolingual	Astrocytoma grade III	Angular gyrus	Seizure	23	No	Aggravated	Unchanged
M3	Right	M	Monolingual	Glioblastoma	Frontal	Seizure	38	No	Unchanged	Unchanged
M4	Right	F	Monolingual	Astrocytoma grade III	Temporal	Speech arrest	32	No	Aggravated	Aggravated
M5	Right	M	Monolingual	Astrocytoma grade III	Temporal	Speech arrest	13	No	Unchanged	Unchanged
M6	Left	M	Bilingual	Glioblastoma	Frontal	Speech arrest	27	Yes	Unchanged	Unchanged
M7	Right	M	Monolingual	Glioblastoma	Angular gyrus	Aphasia	45	Yes	Unchanged	Unchanged
M8	Left	F	Monolingual	Glioblastoma	Angular gyrus	Aphasia	73	Yes	Aggravated	Decreased
M9	Right	F	Monolingual	Glioblastoma	Frontal	Seizure	38	Yes	Aggravated	Unchanged
M10	Right	M	Monolingual	Glioblastoma	Temporal	Aphasia	32	Yes	Unchanged	Decreased
M11	Right	M	Monolingual	Cavernoma	Frontal	Seizure	21	No	Decreased	Unchanged
M12	Right	F	Monolingual	Astrocytoma grade II	Temporal	Aphasia	31	Yes	Aggravated	Unchanged
M13	Right	F	Monolingual	Glioblastoma	Temporal	Aphasia	76	Yes	Unchanged	Unchanged
M14	Right	F	Monolingual	Glioblastoma	Temporal	Speech arrest	58	No	Aggravated	Aggravated

TABLE 3. Stimulation Parameters Used in the Study[a]

		Stimulation 1			Stimulation 2			Stimulation 3		
	MT %	Hz[b]	No. of Pulses in Train	Int %	Hz	No. of Pulses in Train	Int %	Hz	No. of Pulses in Train	Int %
B1	36	10	5	36						
B2	31	5	5	31	5	5	37			
B3	44	5	7	44						
B4	25	5	5	26	7	7	23	10	7	23
B5	48	5	5	25						
B6	24	10	7	26						
M1	35	5	5	35	10	7	35	77	7	35
M2	47	5	5	48						
M3	33	5	5	34						
M4	38	5	5	38	7	5	38			
M5	28	5	5	28	7	5	28	7	7	28
M6	53	5	5	53	5	5	46	7	5	46
M7	31	5	5	31						
M8	58	5	5	51	5	5	47	5	5	39
M9	27	5	5	25	7	7	25			
M10	39	5	5	47	7	5	43	5	5	43
M11	36	7	7	44	7	5	44	5	5	44
M12	43	5	5	52	7	5	47	5	5	43
M13	30	5	5	30						
M14	31	5	5	31						

[a]MT%, resting motor threshold (stimulator output); Int %, stimulation intensity (percentage of maximum stimulator output).
[b]Hz, stimulation train frequency.

afterdischarge recordings. One patient (B2) had a completely negative DCS language mapping. The number of naming errors in other patients varied between 1 and 8. Two patients (B3 and B4) had a stimulation-induced seizure during DCS. The seizures were immediately observed with electroencephalographic monitoring and terminated with cold Ringer solution. There were no cases in which DCS positive sites were resected.

General Correlation of nTMS With Intraoperative DCS Mapping

Both methods were capable of eliciting naming errors. The detection of these errors relies on subjective assessment of the patient performance. Intraoperative DCS mapping data were available for 1 to 19 areas (median, 9 areas) according to the CPS, whereas nTMS data were available for 9 to 27 regions (median 15 regions) (Table 5). In total, DCS data were available for 189 regions and nTMS data for 326 regions. In a total of 160 regions, data for both methods were available. The overall occurrence of the 4 categories (true positive, true negative, false positive, or false negative) is presented in Table 6.

The results of the comparison were collected on a CPS brain template and the number of different classifications (true positive, true negative, false positive, or false negative) was recorded for each anatomic region for each patient (Figures 3 through 6). Patient B5 was excluded from this analysis (see Exclusion of Data section).

True-Positive Responses

We observed true-positive responses, ie, DCS and nTMS positive, in 46 brain regions in 18 patients. True-positive responses occurred across all studied cortical regions but more frequently in regions considered to belong to the classic Broca's area (triangular inferior frontal gyrus, opercular inferior frontal gyrus, ventral precentral gyrus). In these 3 regions, a total of 26 true-positive responses were obtained in 15 patients (Figure 3).

True-Negative Responses

True-negative responses (DCS and nTMS did not elicit any speech disturbance) were recorded in 26 cortical regions in 12 patients and were evenly distributed over the studied regions. In the regions considered to belong to the classic Broca area, we observed only 3 true-negative responses in 2 patients (Figure 4).

False-Positive Responses

False-positive responses (nTMS impaired speech without any positive DCS confirmation) were obtained in 83 brain regions in 18 patients and were evenly distributed over the studied cortical regions. Within the classic Broca's area, 20 false-positive responses were obtained in 18 patients (Figure 5).

Within false-positive nTMS spots, there were 10 patients with TMS-positive sites within or above tumor tissue, which were resected. Locations were posterior supramarginal gyrus, opercular inferior frontal gyrus, middle middle frontal gyrus, posterior middle frontal gyrus, posterior superior temporal gyrus, ventral precentral gyrus, ventral postcentral gyrus, anterior middle temporal gyrus, anterior superior temporal gyrus, and anterior inferior temporal gyrus. Only 1 of these patients showed temporary impairment of language function.

False-Negative Responses

False-negative responses of nTMS mapping (DCS positive and nTMS negative) were rare. A total of 5 false-negative responses were observed from 5 brain regions in 3 patients. None of the false-negative responses occurred in the regions belonging to the classic Broca's area. Instead, all false-negative responses were found in posterior brain regions (supramarginal, angular, posterior superior temporal gyri) (Figure 6).

Receiver-Operating Characteristics

We also calculated receiver-operating characteristics: sensitivity, specificity, and positive/negative predictive values. These receiver-operating characteristics are provided for all regions and separately for the classic Broca's area (Table 7).

When the DCS responses were taken as the gold standard, nTMS results had an overall sensitivity of 90.2%, specificity of 23.8%, positive predictive value of 35.6%, and negative predictive value of 83.9%. Within the classic Broca's area, sensitivity was 100%, specificity 13.0%, positive predictive value, 56.5%, and negative predictive value 100% (Table 6).

Exclusion of Data: Patient B5

During nTMS mapping in patient B5, stimulation intensity had to be decreased to 52% of the RMT due to discomfort (Table 2).

TABLE 4. Summary of Naming Errors Induced by Navigated Transcranial Magnetic Stimulation Trains: Reported Number of Trials (Transcranial Magnetic Stimulation Trains), Total Number of Errors, Error Type, and Ratio of Each Given Error Type of All Induced Errors

	No Response		Semantic		Performance		Phonological		Neologism		Circumlocution		Totals		
Patient	Errors	Ratio	Errors	Ratio	Errors	Ratio	Errors	Ratio	Errors	Ratio	Errors	Ratio	Errors	Trials	Error Rate
B1	1	0.07	10	0.67	2	0.13	0	0.00	2	0.13	0	0.00	15	304	0.05
B2	1	0.33	0	0.00	2	0.67	0	0.00	0	0.00	0	0.00	3	166	0.02
B3	0	0.00	0	0.00	19	1.00	0	0.00	0	0.00	0	0.00	19	186	0.10
B4	10	0.16	23	0.38	27	0.44	0	0.00	1	0.02	0	0.00	61	394	0.15
B5	0	0.00	0	0.00	3	1.00	0	0.00	0	0.00	0	0.00	3	336	0.01
B6	5	0.23	8	0.36	7	0.32	1	0.05	0	0.00	1	0.05	22	506	0.04
M1	4	0.14	0	0.00	23	0.82	0	0.00	1	0.04	0	0.00	28	217	0.13
M2	55	0.50	0	0.00	53	0.49	0	0.00	1	0.01	0	0.00	109	319	0.34
M3	94	0.61	1	0.01	55	0.35	0	0.00	5	0.03	0	0.00	155	683	0.23
M4	11	0.31	1	0.03	21	0.60	0	0.00	2	0.06	0	0.00	35	606	0.06
M5	13	0.21	2	0.03	33	0.53	2	0.03	12	0.19	0	0.00	62	679	0.09
M6	92	0.84	0	0.00	16	0.15	0	0.00	2	0.02	0	0.00	110	424	0.26
M7	17	0.27	13	0.20	27	0.42	2	0.03	5	0.08	0	0.00	64	651	0.10
M8	49	0.28	0	0.00	121	0.68		0.00	7	0.04		0.00	177	547	0.32
M9	8	0.09	1	0.01	68	0.76	7	0.08	5	0.06	0	0.00	89	666	0.13
M10	14	0.22	2	0.03	46	0.71	1	0.02	0	0.00	2	0.03	65	572	0.11
M11	16	0.23	7	0.10	44	0.62	4	0.06	0	0.00	0	0.00	71	607	0.12
M12	1	0.03	1	0.03	26	0.90	1	0.03	0	0.00	0	0.00	29	389	0.07
M13	36	0.78	0	0.00	10	0.22	0	0.00	0	0.00	0	0.00	46	218	0.21
M14	64	0.74	4	0.05	16	0.19	0	0.00	1	0.01	1	0.01	86	481	0.18
Minimum	0	0.00	0	0.00	2	0.13	0	0.00	0	0.00	0	0.00	3	166	0.01
Maximum	94	0.84	23	0.67	121	1.00	7	0.08	12	0.19	2	0.05	177	683	0.34
Median	12	0.23	1	0.02	24.5	0.57	0	0.00	1	0.01	0	0.00	61.5	452.5	0.12

TABLE 5. Navigated Transcranial Magnetic Stimulation Results Compared With Gold Standard Results[a]

					Classic Broca			Regions Stimulated	
Patient	TP	TN	FP	FN	OpIFG	TrIFG	vPrG	DCS	NBS
B1	1	0	2	0	FP	ND	TP	4	11
B2	0	3	0	0	TN	ND	TN	6	9
B3	2	2	2	0	TP	FP	FP	6	15
B4	1	2	2	0	TP	TN	FP	6	21
B5 (*)	0	0	0	1	ND	ND	ND	1	17
B6	4	2	3	1	FP	FP	TP	10	22
M1	3	1	1	0	TP	TP	TP	7	15
M2	1	0	4	0	FP	FP	TP	8	11
M3	4	0	9	0	TP	FP	TP	14	19
M4	2	4	5	1	TP	TP	FP	12	17
M5	2	1	4	0	TP	FP	FP	9	14
M6	5	0	6	0	FP	FP	TP	12	13
M7	1	4	2	3	FP	ND	TP	15	14
M8	1	0	4	0	FP	FP	TP	7	13
M9	3	2	7	0	TP	ND	TP	15	14
M10	3	2	14	0	FP	TP	TP	19	25
M11	6	2	3	0	TP	TP	TP	11	27
M12	3	0	4	0	FP	TP	FP	8	20
M13	1	1	5	0	ND	ND	ND	10	10
M14	3	0	6	0	FP	ND	FP	9	19

[a]TP, true positive; TN, true negative; FP, false positive; FN, false negative; OpIFG, opercular inferior frontal gyrus; TrIFG, pars triangularis; vPrG, ventral precentral gyrus. DCS, direct cortical stimulation; NBS, navigation brain stimulation; ND, no data. The number of regions with TP, TN, FP, and FN results in patients is shown. A separate classification is provided for regions belonging to regions classically associated with Broca's area: OpIFG, TrIFG, and vPrG.

TABLE 6. Occurrence of Different Classifications[a]

	All Regions			Classic Broca's Area		
	Charité Berlin (B1-B6)	TU Munich (M1-M14)	All (N = 19)	Charité Berlin (B1-B6)	TU Munich (M1-M14)	All (N = 19)
True positives	8	38	46	6	20	26
True negatives	9	17	26	3	0	3
False positives	9	74	83	4	16	20
False negatives	1	4	5	0	0	0

[a]Occurrence of different classifications in the classic Broca's area: opercular inferior frontal gyrus, pars triangularis, and ventral precentral gyrus.

In all other patients, the stimulation intensity ranged between 90% and 120% RMT. With the resulting electric field strength being below 45 V/m in patient B5, we excluded this patient from analysis because this low stimulation intensity is probably ineffective in inducing naming errors. This decision is supported by the very low number of errors observed in patient B5 (Table 3).

Patient Outcome

In 7 of 20 patients, aphasia was aggravated within the first 7 postoperative days. Three patients had aggravated and 3 had diminished aphasia at the 3-month follow-up (Table 2). Gross total resection was achieved in 18 cases. Only subtotal resection was possible in 2 cases because the tumor infiltrated areas having eloquent language function.

DISCUSSION

Permanent language deficits with their deleterious impact on quality of life are the main concern when planning the treatment of tumors in the dominant perisylvian areas. The main challenge of this planning is the unpredictability of the location of essential language sites as evaluated from anatomic landmarks. The current study analyzed for the first time the potential of a novel noninvasive approach to induce and document language disturbances with navigated repetitive TMS. Compared with the gold standard of intraoperative DCS, we observed an excellent sensitivity, particularly within the classic motor speech areas (1.0). The specificity with DCS as the ground truth was low (0.24).

DCS, either in an awake craniotomy or through an implanted subdural electrode grid, is the gold standard for unraveling the anatomic relationship of tumor and essential language areas. These methods were already used in the first half of the past century and were later refined by others.[2,3,6,30,31] In these studies, it has become evident that the classic language sites (areas of Broca and Wernicke) are merely parts of a complex and highly individualized language network. The cortical entry sites to this network have also been described as language mosaics because predominantly a pattern of solitary spots rather than of clusters is observed.[3] It is not clear which of these so-called essential language sites are really indispensable for function. In general, the language sites identified by DCS are preserved during the surgical procedure. Nevertheless, individual reports also state that if more than 1 cortical language site has been identified by DCS, 1 of them can be removed without permanent neurological sequelae.[30,32] Also, planning the resection strategy based on the language-negative cortical map has been proposed for fMRI[33] as well as for intraoperative DCS-based language mapping.[6] The relationship between resection margins and functional outcome has been described in various reports.[3,6,28,34-38] Recently, efforts to identify true, generally essential hot spots—"minimal common brain"—have been undertaken.[35]

Preoperative Noninvasive Language Mapping

Due to the imminent risk of causing language deficits, neurosurgeons traditionally hesitate to propose surgery when the lesion is located in the perisylvian areas, particularly if the inferior frontal

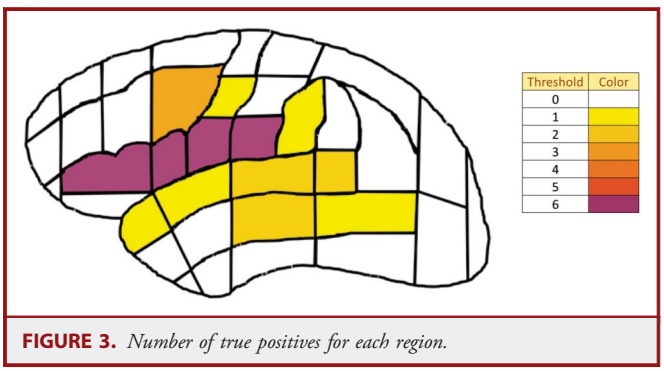

FIGURE 3. *Number of true positives for each region.*

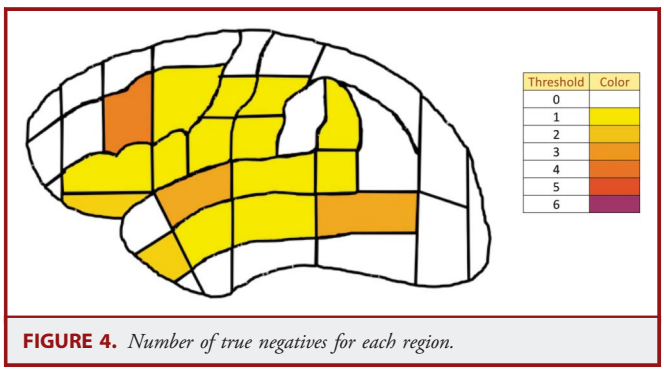

FIGURE 4. *Number of true negatives for each region.*

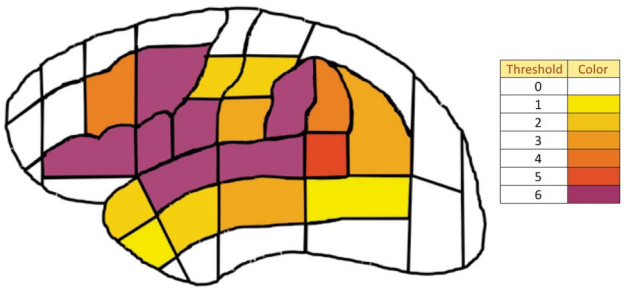

FIGURE 5. *Number of false positives for each region.*

or superior temporal gyrus are affected. Ideally, these patients are referred to specialized centers with vast experience in invasive cognitive mapping procedures. This may not always be feasible due to the lack of information and organizational restrictions or to patient-specific reasons such as unwillingness to undergo awake brain surgery or comorbidities rendering the awake approach too dangerous. Even if an awake procedure is planned, the value of counseling the patient as well as planning the surgical strategy based on objective preoperative functional information must not be underestimated. This was recently demonstrated in patients with tumors within essential motor areas.[15,39]

Until now, fMRI has been the only noninvasive method with broad availability for preoperative speech assessment. It has been widely used to study language function in both normal subjects and in brain tumor patients.[40-42] Several studies have shown a good correlation between fMRI and the Wada test for defining the hemispheric dominance,[43,44] but comparison of fMRI activity with DCS language sites has produced disappointing results.[8,10] These discrepancies probably reflect the marked methodological differences in the 2 methods.[33] DCS and TMS are lesion-based approaches and therefore allow targeted analysis of circumscribed cortical areas essential for function, whereas fMRI relies on statistical analysis of changes in regional blood oxygenation. Analysis of the same fMRI raw data by different examiners leads to different results even when the same original dataset is used. The reliance on predefined and used statistical thresholds is the main limitation of all cluster overlap methods.[7] Moreover, intracerebral lesions such as gliomas induce edema and change oxygenation in the brain, which hampers the accuracy of fMRI.[8,11] The tumor-induced proliferation of vessels increases the cerebral blood volume and provokes oxygen extraction. Furthermore, especially high-grade gliomas invade the normal brain parenchyma, which results in a decreased cell-to-cell contact rate of astrocytes and capillary cells. This affects the release of neurotransmitters, which also leads to increased cerebral blood flow and a decreased oxygen extraction fraction.[11,45-47] In both cases, a reduction of the BOLD signal is unavoidable.[11,22] Therefore, fMRI is insufficient for precise delineation of functional brain areas when they are impaired by intracerebral lesions, as shown previously.[9,10] fMRI can also be compromised by the patient's lack of cooperation or claustrophobia, whereas nTMS is better tolerated, as shown for preoperative motor mapping.[15] The strength of fMRI resides in visualization of networks. In line with experiences of functional localization of motor areas, we believe that TMS/DCS and fMRI are complementary methods and should be used accordingly.[12,15]

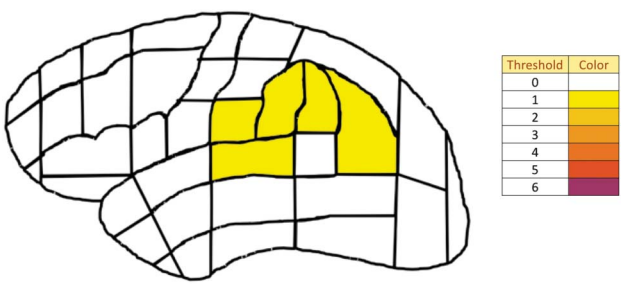

FIGURE 6. *Number of false negatives for each region.*

TMS has been used in basic research of language for many years, but only recently technical improvements have introduced the technique to the presurgical workflow. Here the combination with neuronavigation and electric field modeling has significantly improved the clinical value of the technique.[24] This is reflected in the increasing number of papers on nTMS in neurosurgery.[13-15,24,48,49] With regard to language mapping, TMS is the only painless noninvasive method that emulates the DCS principles, namely, repetitive depolarization of axons involved in language processing.[16] The potential of TMS to interfere with language tasks has been proved in several studies.[16,50,51] Yet these studies have been conducted without the use of neuronavigation, and the effects have not been compared with DCS. Recently a first anecdotal description of the clinical application of the new nTMS language mapping method was published.[22]

TMS and DCS: Neurophysiological Differences

It is assumed that DCS-induced electrical current disrupts signal processing at the cortex and thus transiently alters the patient's performance in language tasks. A few millimeters movement of the bipolar stimulation electrode changes the stimulation effect. This suggests that the stimulation effect occurs mainly between the electrode poles. In stimulation with intensity below the after-discharge threshold, controlled for by electrocorticography, current spread is limited and DCS is considered to have an error margin of 10 mm in speech mapping.[4,6,52-54]

For TMS, repetitive high-frequency trains maintain a current within the cortex, which is the prerequisite to induce a virtual lesion and allows analysis of a higher cognitive function such as language. Yet, the profile of the induced current in terms of current density and direction by TMS differs from that induced by DCS. Because it is known from motor mapping, DCS activates motor cortical axons directly, whereas TMS activates motor neurons

TABLE 7. Sensitivity, Specificity, and Positive/Negative Predictive Values Over All Brain Regions in All Patients[a]

	All Regions			Classic Broca's Area		
	Charité Berlin (B1-B6)	TU Munich (M1-M14)	All (N = 19)	Charité Berlin (B1-B6)	TU Munich (M1-M14)	All (N = 19)
Sensitivity	0.89	0.90	0.90	1.0	1.0	1.0
Specificity	0.5	0.19	0.24	0.43	0	0.13
Positive predictive value	0.47	0.34	0.36	0.6	0.56	0.57
Negative predictive value	0.9	0.81	0.84	1.0	N/A	1.0

[a]N/A, not available. Sensitivity, specificity, and positive/negative predictive values in the classic Broca's area: opercular inferior frontal gyrus, pars triangularis, and ventral precentral gyrus.

mainly through indirect intracortical pathways.[55] The unspecific activation and/or inhibition of intracortical pathways might render sites TMS positive that do not carry essential language function. This could explain why in those 10 patients, who underwent resection of TMS-positive spots, there were no long-term sequelae. These differences need to be considered when interpreting stimulation results and possible discrepancies between the 2 methods. To overcome this potential limitation of the current method, further investigation of optimal intensities, frequencies, and duration of the TMS trains for language mapping is required. Also, the potential immediate impact of repetitive TMS on the cortical excitability (immediate short-term plasticity) requires further study. We chose to use the range of parameters applied in previous studies and were able to induce language errors in all patients. Tests of higher frequency trains and bursts might provide further insight into the mechanisms inducing speech disturbances. However, induction of pain and muscle tetanization may limit the use of high frequencies, at least when delivered in long trains.[50] We had to lower the nTMS intensity because of discomfort in 1 patient; otherwise, no relevant pain or discomfort was elicited.

Another explanation for the discrepancy between DCS and nTMS results in our study is the difference of the applied language task. Intraoperatively we administered the traditional object naming task with the leader phrase "this is. . .," as described by Ojemann et al,[3] whereas for the nTMS mapping, only the object was presented. The reason for this is the shorter stimulation train (1 second) chosen for TMS mapping compared with DCS (4 seconds) and the synchronization of the nTMS stimulation starting 300 ms after the image presentation. This difference may explain our observation of the high sensitivity of nTMS to detect classic motor speech areas but the significant weakness in posterior language areas. The current methodology's shortcoming of insufficiently interfering with language perception and initial processing may be overcome by implementation of alternative language tasks that challenge more the semantic processing. In addition, different stimulus onset and duration timings based on data on language processing[25] have to be tested to increase sensitivity as well in the posterior regions.

Finally, the occurrence of false- positive nTMS results may reflect higher sensitivity of the examiner for errors in the offline video analysis for nTMS compared with the online intraoperative response detection in which only very clear observations are regarded as useful. On the other hand, the (by our definition) "false"-positive sites may also indicate the presence of language sites not intraoperatively defined and, in this case, may also be regarded as potentially dangerous areas for resection. The CPR areas, although relatively small, still exceed the size of the 10-mm error margin of the DCS, and thus some false-positive results may be due to less dense spatial sampling by the DCS.

TMS Tolerance and Outcome

No adverse events related to nTMS speech mapping were reported. This result adds to the body of evidence in the existing literature that the short rTMS trains can be used in normal subjects and patients without adverse events.[16,18] It also demonstrates that the noninvasive nTMS speech mapping procedure is safe in the indicated patient population. Because intraoperative speech mapping with DCS produced seizures in 2 patients, the safety profile of TMS mapping was better than that of DCS in the current limited series. Also, TMS studies can be performed under laboratory conditions, and the navigation allows exact reproduction of previous stimuli.[24] This results in a more comprehensive examination than intraoperatively possible due to the restrictions associated with awake craniotomy. This is also reflected in the significantly higher number of areas examined preoperatively than intraoperatively in this series.

The percentage of aggravated aphasia 3 months postoperatively is relatively high at 15% (3/20). It must be taken into account that the sample size of the current series is small and that all 3 aphasic aggravations were observed in patients with malignant gliomas. However, it must be stressed that radical resection of malignant gliomas in eloquent locations should not be pursued at the cost of neurological functioning, given the natural course of the disease.

CONCLUSION

Noninvasive language mapping with navigated TMS could be completed in 100% of patients. It was well tolerated and no adverse events occurred. In addition, the training effect of noninvasive TMS language mapping on the patient's performance and compliance during intraoperative speech mapping should not be underestimated.

TMS speech mapping was highly reliable in obtaining negative response maps within motor speech–related areas of the cortex. These negative responses can be used to identify regions where DCS responses are unlikely to be obtained and support the surgical team to custom tailor the craniotomy size and location as well as the resection trajectory. Given the low specificity of the current method in posterior language areas, its clinical utility in these areas is limited at the moment, and positive TMS responses need to be verified by intraoperative DCS.

Disclosures

This research was supported in part by a grant from the Berlin Cancer Society to Thomas Picht. Pantelis Lioumis was supported by grants from SalWe Research program for Mind and Body (TEKES-the Finnish Funding Agency for Technology and Innovation grant 1104/10) and from Helsinki University Central Hospital (EVO-funding). Tuomas Neuvonen and Petri Savolainen are employed by Nexstim. Ethics Committee Registration Number is 2793/10. The authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article.

REFERENCES

1. Sacko O, Lauwers-Cances V, Brauge D, Sesay M, Brenner A, Roux FE. Awake craniotomy vs surgery under general anesthesia for resection of supratentorial lesions. *Neurosurgery*. 2011;68(5):1192-1198; discussion 1198-1199.
2. Ojemann GA, Whitaker HA. Language localization and variability. *Brain Lang.* 1978;6(2):239-260.
3. Ojemann G, Ojemann J, Lettich E, Berger M. Cortical language localization in left, dominant hemisphere. An electrical stimulation mapping investigation in 117 patients. *J Neurosurg.* 1989;71(3):316-326.
4. Haglund MM, Berger MS, Shamseldin M, Lettich E, Ojemann GA. Cortical localization of temporal lobe language sites in patients with gliomas. *Neurosurgery*. 1994;34(4):567-576.
5. Corina DP, Loudermilk BC, Detwiler L, Martin RF, Brinkley JF, Ojemann G. Analysis of naming errors during cortical stimulation mapping: implications for models of language representation. *Brain Lang.* 2010;115(2):101-112.
6. Sanai N, Mirzadeh Z, Berger MS. Functional outcome after language mapping for glioma resection. *N Engl J Med.* 2008;358(1):18-27.
7. Bennett CM, Miller MB. How reliable are the results from functional magnetic resonance imaging? *Ann N Y Acad Sci.* 2010;1191:133-155.
8. Roux FE, Boulanouar K, Lotterie JA, Mejdoubi M, LeSage JP, Berry I. Language functional magnetic resonance imaging in preoperative assessment of language areas: correlation with direct cortical stimulation. *Neurosurgery*. 2003;52(6):1335-1345; discussion 1345-1347.
9. Yetkin FZ, Mueller WM, Morris GL, et al. Functional MR activation correlated with intraoperative cortical mapping. *AJNR Am J Neuroradiol.* 1997;18(7):1311-1315.
10. FitzGerald DB, Cosgrove GR, Ronner S, et al. Location of language in the cortex: a comparison between functional MR imaging and electrocortical stimulation. *AJNR Am J Neuroradiol.* 1997;18(8):1529-1539.
11. Giussani C, Roux FE, Ojemann J, Sganzerla EP, Pirillo D, Papagno C. Is preoperative functional magnetic resonance imaging reliable for language areas mapping in brain tumor surgery? Review of language functional magnetic resonance imaging and direct cortical stimulation correlation studies. *Neurosurgery*. 2010;66(1):113-120.
12. Picht T, Mularski S, Kuehn B, Vajkoczy P, Kombos T, Suess O. Navigated transcranial magnetic stimulation for preoperative functional diagnostics in brain tumor surgery. *Neurosurgery*. 2009;65(6 suppl):93-98.
13. Picht T, Schmidt S, Brandt S, et al. Preoperative functional mapping for rolandic brain tumor surgery: comparison of navigated transcranial magnetic stimulation to direct cortical stimulation. *Neurosurgery*. 2011;69(3):581-588; discussion 588.
14. Forster MT, Hattingen E, Senft C, Gasser T, Seifert V, Szelényi A. Navigated transcranial magnetic stimulation and functional magnetic resonance imaging: advanced adjuncts in preoperative planning for central region tumors. *Neurosurgery*. 2011;68(5):1317-1324.
15. Krieg SM, Shiban E, Buchmann N, et al. Utility of presurgical navigated transcranial magnetic brain stimulation for the resection of tumors in eloquent motor areas. *J Neurosurg.* 2012;116(5):994-1001.
16. Epstein CM, Lah JJ, Meador K, Weissman JD, Gaitan LE, Dihenia B. Optimum stimulus parameters for lateralized suppression of speech with magnetic brain stimulation. *Neurology*. 1996;47(6):1590-1593.
17. Epstein CM. Transcranial magnetic stimulation: language function. *J Clin Neurophysiol.* 1998;15(4):325-332.
18. Pascual-Leone A, Gates JR, Dhuna A. Induction of speech arrest and counting errors with rapid-rate transcranial magnetic stimulation. *Neurology*. 1991;41(5):697-702.
19. Sparing R, Mottaghy FM, Hungs M, et al. Repetitive transcranial magnetic stimulation effects on language function depend on the stimulation parameters. *J Clin Neurophysiol.* 2001;18(4):326-330.
20. Wassermann EM, Blaxton TA, Hoffman EA, et al. Repetitive transcranial magnetic stimulation of the dominant hemisphere can disrupt visual naming in temporal lobe epilepsy patients. *Neuropsychologia*. 1999;37(5):537-544.
21. Lioumis P, Zhdanov A, Makela N, et al. A novel approach for documenting naming errors induced by navigated transcranial magnetic stimulation. *J Neurosci Methods.* 2012;204(2):349-354.
22. Sollmann N, Picht T, Mäkelä JP, et al. Navigated TMS refutes negative left sided fMRI activation for language in a patient with a left fronto-opercular GBM: a case report. *J Neurosurg.* 2013;118(1):175-179.
23. Huber W, Weniger D, Poeck K, Willmes K. The Aachen Aphasia Test Rationale and construct validity (author's transl) [in German]. *Nervenarzt.* 1980;51(8):475-482.
24. Ruohonen J, Karhu J. Navigated transcranial magnetic stimulation. *Neurophysiol Clin.* 2010;40(1):7-17.
25. Salmelin R, Helenius P, Service E. Neurophysiology of fluent and impaired reading: a magnetoencephalographic approach. *J Clin Neurophysiol.* 2000;17(2):163-174.
26. Picht T, Kombos T, Gramm HJ, Brock M, Suess O. Multimodal protocol for awake craniotomy in language cortex tumour surgery. *Acta Neurochir (Wien).* 2006;148(2):127-137; discussion 137-138.
27. Kohn SE, Goodglass H. Picture-naming in aphasia. *Brain Lang.* 1985;24(2):266-283.
28. Sanai N, Berger MS. Mapping the horizon: techniques to optimize tumor resection before and during surgery. *Clin Neurosurg.* 2008;55:14-19.
29. Corina DP, Gibson EK, Martin R, Poliakov A, Brinkley J, Ojemann GA. Dissociation of action and object naming: evidence from cortical stimulation mapping. *Hum Brain Mapp.* 2005;24(1):1-10.
30. Robles SG, Gatignol P, Lehericy S, Duffau H. Long-term brain plasticity allowing a multistage surgical approach to World Health Organization Grade II gliomas in eloquent areas. *J Neurosurg.* 2008;109(4):615-624.
31. Penfield W, Boldrey E. Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation. *Brain*. 1937;60(4):389-443.
32. Duffau H. New concepts in surgery of WHO grade II gliomas: functional brain mapping, connectionism and plasticity—a review. *J Neurooncol.* 2006;79(1):77-115.
33. Rutten GJ, Ramsey NF. The role of functional magnetic resonance imaging in brain surgery. *Neurosurg Focus.* 2010;28(2):E4.
34. Duffau H, Lopes M, Arthuis F, et al. Contribution of intraoperative electrical stimulations in surgery of low grade gliomas: a comparative study between two series without (1985-96) and with (1996-2003) functional mapping in the same institution. *J Neurol Neurosurg Psychiatry.* 2005;76(6):845-851.
35. Ius T, Angelini E, Thiebaut de Schotten M, Mandonnet E, Duffau H. Evidence for potentials and limitations of brain plasticity using an atlas of functional resectability of WHO grade II gliomas: towards a "minimal common brain". *Neuroimage*. 2011;56(3):992-1000.
36. Yordanova YN, Moritz-Gasser S, Duffau H. Awake surgery for WHO Grade II gliomas within "noneloquent" areas in the left dominant hemisphere: toward a "supratotal" resection. Clinical article. *J Neurosurg.* 2011;115(2):232-239.
37. Sanai N, Berger MS. Intraoperative stimulation techniques for functional pathway preservation and glioma resection. *Neurosurg Focus.* 2010;28(2):E1.
38. Schaffler L, Luders HO, Beck GJ. Quantitative comparison of language deficits produced by extraoperative electrical stimulation of Broca's, Wernicke's, and basal temporal language areas. *Epilepsia*. 1996;37(5):463-475.
39. Picht T, Schulz J, Hanna M, Schmidt S, Suess O, Vajkoczy P. Assessment of the influence of navigated transcranial magnetic stimulation on surgical planning for tumors in or near the motor cortex. *Neurosurgery*. 2012;70(5):1248-56.

40. Brannen JH, Badie B, Moritz CH, Quigley M, Meyerand ME, Haughton VM. Reliability of functional MR imaging with word-generation tasks for mapping Broca's area. *AJNR Am J Neuroradiol.* 2001;22(9):1711-1718.
41. Holodny AI, Schulder M, Ybasco A, Liu WC. Translocation of Broca's area to the contralateral hemisphere as the result of the growth of a left inferior frontal glioma. *J Comput Assist Tomogr.* 2002;26(6):941-943.
42. Petrella JR, Shah LM, Harris KM, et al. Preoperative functional MR imaging localization of language and motor areas: effect on therapeutic decision making in patients with potentially resectable brain tumors. *Radiology.* 2006;240(3): 793-802.
43. Fernandez G, de Greiff A, von Oertzen J, et al. Language mapping in less than 15 minutes: real-time functional MRI during routine clinical investigation. *Neuroimage.* 2001;14(3):585-594.
44. Pelletier I, Sauerwein HC, Lepore F, Saint-Amour D, Lassonde M. Non-invasive alternatives to the Wada test in the presurgical evaluation of language and memory functions in epilepsy patients. *Epileptic Disord.* 2007;9(2):111-126.
45. Ojemann JG, Buckner RL, Akbudak E, et al. Functional MRI studies of word-stem completion: reliability across laboratories and comparison to blood flow imaging with PET. *Hum Brain Mapp.* 1998;6(4):203-215.
46. Ojemann JG, Neil JM, MacLeod AM, et al. Increased functional vascular response in the region of a glioma. *J Cereb Blood Flow Metab.* 1998;18(2):148-153.
47. Ulmer JL, Krouwer HG, Mueller WM, Ugurel MS, Kocak M, Mark LP. Pseudo-reorganization of language cortical function at fMR imaging: a consequence of tumor-induced neurovascular uncoupling. *AJNR Am J Neuroradiol.* 2003;24(2): 213-217.
48. Hannula H, Ylioja S, Pertovaara A, et al. Somatotopic blocking of sensation with navigated transcranial magnetic stimulation of the primary somatosensory cortex. *Hum Brain Mapp.* 2005;26(2):100-109.
49. Säisänen L, Julkunen P, Niskanen E, et al. Motor potentials evoked by navigated transcranial magnetic stimulation in healthy subjects. *J Clin Neurophysiol.* 2008;25(6): 367-372.
50. Devlin JT, Watkins KE. Stimulating language: insights from TMS. *Brain.* 2007; 130(pt 3):610-622.
51. Vigliocco G, Vinson DP, Druks J, Barber H, Cappa SF. Nouns and verbs in the brain: a review of behavioural, electrophysiological, neuropsychological and imaging studies. *Neurosci Biobehav Rev.* 2011;35(3):407-426.
52. Tharin S, Golby A. Functional brain mapping and its applications to neurosurgery. *Neurosurgery.* 2007;60(4 suppl 2):185-201; discussion 201-202.
53. Szelenyi A, Bello L, Duffau H, et al. Intraoperative electrical stimulation in awake craniotomy: methodological aspects of current practice. *Neurosurg Focus.* 2010;28(2):E7.
54. Mandonnet E, Jbabdi S, Taillandier L, et al. Preoperative estimation of residual volume for WHO grade II glioma resected with intraoperative functional mapping. *Neuro-Oncol.* 2007;9(1):63-69.
55. Kombos T, Picht T, Derdilopoulos A, Suess O. Impact of intraoperative neurophysiological monitoring on surgery of high-grade gliomas. *J Clin Neurophysiol.* 2009;26(6):422-425.