Impairment of preoperative language mapping by lesion location: a functional magnetic resonance imaging, navigated transcranial magnetic stimulation, and direct cortical stimulation study

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OBJECT  Language mapping by repetitive navigated transcranial magnetic stimulation (rTMS) is increasingly used and has already replaced functional MRI (fMRI) in some institutions for preoperative mapping of neurosurgical patients. Yet some factors affect the concordance of both methods with direct cortical stimulation (DCS), most likely by lesions affecting cortical oxygenation levels. Therefore, the impairment of the accuracy of rTMS and fMRI was analyzed and compared with DCS during awake surgery in patients with intraparenchymal lesions.

METHODS  Language mapping was performed by DCS, rTMS, and fMRI using an object-naming task in 27 patients with left-sided perisylvian lesions, and the induced language errors of each method were assigned to the cortical parcellation system. Subsequently, the receiver operating characteristics were calculated for rTMS and fMRI and compared with DCS as ground truth for regions with (w/) and without (w/o) the lesion in the mapped regions.

RESULTS  The w/ subgroup revealed a sensitivity of 100% (w/o 100%), a specificity of 8% (w/o 5%), a positive predictive value of 34% (w/o: 53%), and a negative predictive value (NPV) of 100% (w/o: 100%) for the comparison of rTMS versus DCS. Findings for the comparison of fMRI versus DCS within the w/ subgroup revealed a sensitivity of 32% (w/o: 62%), a specificity of 88% (w/o: 60%), a positive predictive value of 56% (w/o: 62%), and a NPV of 73% (w/o: 60%).

CONCLUSIONS  Although strengths and weaknesses exist for both rTMS and fMRI, the results show that rTMS is less affected by a brain lesion than fMRI, especially when performing mapping of language-negative cortical regions based on sensitivity and NPV.

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KEY WORDS  language; tumor; transcranial magnetic stimulation; functional magnetic resonance imaging; awake surgery; diagnostic and operative techniques

S ince transcranial magnetic stimulation (TMS) was introduced for stimulating the human motor cortex by Barker et al. in 1985, the method has become more sophisticated and was extensively refined.1 Pascual-Leone and colleagues introduced the term “virtual lesion” and were already in 1991 able to induce speech arrests and counting errors by the use of rapid-rate TMS.35,36 In the late 1990s and early 2000s, a combination of TMS with optically tracked stereotactic navigation systems was established, whereby it was possible to visualize the stimulation sites via the 3D reconstructed MRI data of the patient’s brain.31,37 Thus, the door to the operating theater was opened since the recorded and analyzed stimulation sites could be used for presurgical planning and data could be
transferred via neuronavigation. In the meantime, repetitive navigated TMS (rTMS) became increasingly used for preoperative language mapping in patients with left-sided perisylvian brain lesions. The results of rTMS language mapping in our study were correlated to direct cortical stimulation (DCS) during awake surgery, which is currently the most precise method for the localization of individual language-eloquent brain regions. Especially with regard to the mapping of language-negative cortical regions, rTMS produced promising results compared with DCS in subsequent studies, as reflected by its excellent sensitivity and negative predictive value (NPV). These results are reliable, particularly with regard to current protocols for DCS language mapping, as some authors also rely on negative language mapping by DCS during awake surgery. Considering these results, rTMS has already replaced functional MRI (fMRI) for preoperative language mapping in some institutions. Moreover, in 2010, Giussani et al. reviewed comparisons of fMRI and DCS during awake surgery and concluded that fMRI appears to be inappropriate for preoperative language mapping of cortical language function.

However, fMRI was considered to be the standard for noninvasive language mapping for a long time. However, since fMRI is supposed to be mainly affected by impaired oxygenation levels in the proximity of intracerebral lesions, the present study was designed to investigate the impact of adjacent brain lesions on the correlation of rTMS and fMRI language mapping with intraoperative DCS during awake surgery. In this context, the present study is the first to examine the results obtained by rTMS and fMRI language mapping in a single cohort of patients.

Methods

Ethics Approval

The experimental setup of this study was approved by the local ethics committee of our university in accordance with the Declaration of Helsinki. Before undergoing rTMS examination, all patients provided written informed consent to this study.

Study Design

The study was designed to be prospective and nonrandomized.

Patients

Twenty-seven consecutive patients (18 male and 9 female) with left-sided perisylvian brain lesions met the following inclusion criteria: presence of a left-sided perisylvian brain lesion, planned awake craniotomy, and age of at least 18 years. We did not include patients younger than 18 years or those with severe aphasia. The latter criterion was controlled by an aphasia grading scheme adapted from the Aachen aphasia test. Further exclusion criteria included those for general TMS, such as the presence of a pacemaker or cochlear implant.

All patients were scheduled for awake craniotomy in our neurosurgical department, and all underwent preoperative language mapping by rTMS and fMRI using an object-naming task the day before surgery. All lesions were located in the left hemispheric perisylvian brain regions, and 25 patients (93%) were right handed (Table 1).

Navigational MRI Scan

As described in previous publications, the same 3D data set was used for preoperative rTMS language mapping and intraoperative neuronavigation. The navigational MRI scans of all patients were performed on a 3-Tesla MR scanner (Achieva 3T, Philips Medical System) combined with an 8-channel phased array head coil. Our standard protocol consisted of a T2-weighted FLAIR (TR/TE 12,000/140 ms, inversion time 2500 msec, 30 slices with 1-mm gap, voxel size 0.9 × 0.9 × 4 mm, 3-minute acquisition time), a 3D gradient echo sequence (TR/TE 9/4 msec, 1-mm³ isovoxel covering the whole head, 6-minute, 58-second acquisition time), and an intravenous contrast administration of 0.1 mmol/kg body weight gadopentetate dimeglumine (Magnevist, Guerbet) for anatomical coregistration.

Preoperative fMRI Language Mapping

Each of the included patients received a blood oxygen–level dependent (BOLD) fMRI using an object-naming task. The echo planar sequence was performed with a train length of 43 msec (TR/TE 2500/35 msec). Each of the acquired 64 dynamic sets (2 minutes, 53 seconds) consisted of 32 contiguous axial 4-mm slices (in-plane resolution of 2.75 mm × 2.75 mm). We used parallel imaging (SENSE) to decrease susceptibility-related artifacts (SENSE factor 2).

As also previously described, the fMRI data were transferred to an external workstation (Extended MR Workspace, Philips Medical Systems) and postprocessed using the IViewBOLD package. This was done by an independent investigator blinded to the rTMS results. Using the general linear model, statistical parametric maps were generated after motion correction and spatial smoothing (2D gaussian filter with 4-mm full width at half maximum, kernel 2 × 2 pixel). The hemodynamic delay was 2 × repetition time, and a single predictor and a t-value threshold of 2.5 were used. Furthermore, only clusters with positive correlation and bigger than 40 voxels were accepted as activated areas. Finally, the time-intensity diagrams of the activated voxels were reviewed. Thus, we checked the validity of the results.

Preoperative rTMS Language Mapping

Experimental Setup

We performed rTMS language mapping using the eXimia NBS system version 3.2.2 and Nexstim NBS 4.3 with a NEXSPEECH module (Nexstim Oy) according to the conventionally accepted protocol for rTMS language mapping. In short, after coregistration of the 3D T1-weighted MRI scan and the patient’s head, we conducted motor mapping of the cortical representation of the contralateral abductor pollicis brevis muscle. Once determined, the individual patient’s resting motor threshold (RMT) was used as a basic value for the rTMS language mapping procedure. Next, the patient performed the baseline object-naming task (131 colored pictures of...
common objects) twice without stimulation to adapt the picture data set to the patient’s individual vocabulary. The misnamed pictures were discarded. To define the individual patient’s mapping frequency and intensity, 3 different setups of rTMS bursts (5 Hz, 5 pulses; 7 Hz, 5 pulses; 7 Hz, 7 pulses) were applied to vPrG and opIFG, each with an intensity of 100% RMT. The most effective setup in evoking language errors was then used for the language mapping of the whole hemisphere. If there was no distinct effect on naming, the intensity was increased to 110%–120% RMT, whereas it was decreased to 80%–90% RMT if significant pain was reported. In the latter case, we could avoid the interference of pain or discomfort with the consecutive-response evaluation; hence, we even lowered the stimulation intensity if 100% RMT was painful. This was necessary in 2 patients (7%).

**TMS Language Mapping Procedure**

According to the setup of the baseline recording and the determination of the individual mapping frequency, the rTMS language mapping procedure was performed with the following parameters: the picture-to-trigger interval (PTI; time between presentation of stimulus and onset of rTMS burst) was 300 msec for 22 patients (81%) and 0 msec for 5 patients (19%). Both PTIs proved to be effective in former studies. The display time (time of picture presentation on screen) was 700 msec, and the interpicture interval (time between 2 pictures) was 2500 msec. During the interpicture interval, the stimulation coil was moved to the next stimulation site. The remaining pictures of the baseline recording were presented time locked to the rTMS pulses while the stimulation coil was moved over the whole hemisphere. This was done randomly, and

**TABLE 1. Lesion location***

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (yrs), Sex</th>
<th>Lesion Type</th>
<th>Main Lesion Location†</th>
<th>Infiltrated CPS Regions†</th>
<th>Preop Aphasia Grade‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>25, M</td>
<td>C</td>
<td>trIFG</td>
<td>NI</td>
<td>0</td>
</tr>
<tr>
<td>A2</td>
<td>62, M</td>
<td>GBM</td>
<td>opIFG</td>
<td>trIFG, aSTG, pMFG</td>
<td>0</td>
</tr>
<tr>
<td>A3</td>
<td>43, M</td>
<td>GBM</td>
<td>opIFG</td>
<td>vPrG, bMFG</td>
<td>1A</td>
</tr>
<tr>
<td>A4</td>
<td>51, F</td>
<td>GBM</td>
<td>vPrG</td>
<td>opIFG, pMFG, aSTG, vPoG</td>
<td>1A</td>
</tr>
<tr>
<td>A5</td>
<td>34, M</td>
<td>C</td>
<td>mMFG</td>
<td>NI</td>
<td>0</td>
</tr>
<tr>
<td>A6</td>
<td>53, M</td>
<td>GBM</td>
<td>opIFG</td>
<td>vPrG, pMFG</td>
<td>1A</td>
</tr>
<tr>
<td>A7</td>
<td>47, M</td>
<td>GBM</td>
<td>opIFG</td>
<td>trIFG, vPrG, pMFG</td>
<td>0</td>
</tr>
<tr>
<td>A8</td>
<td>43, M</td>
<td>DA</td>
<td>vPoG, bMFG</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>A9</td>
<td>48, M</td>
<td>GBM</td>
<td>opIFG</td>
<td>trIFG, vPrG, pMFG</td>
<td>0</td>
</tr>
<tr>
<td>A10</td>
<td>49, M</td>
<td>DA</td>
<td>vPoG, aSTG, trIFG</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>A11</td>
<td>51, F</td>
<td>GBM</td>
<td>vPoG, bMFG</td>
<td>2A</td>
<td></td>
</tr>
<tr>
<td>A12</td>
<td>24, M</td>
<td>DA</td>
<td>pMFG, vPrG, mMFG</td>
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<td></td>
</tr>
<tr>
<td>P1</td>
<td>28, F</td>
<td>AA</td>
<td>anG</td>
<td>pSMG, pSTG, pMTG</td>
<td>0</td>
</tr>
<tr>
<td>P2</td>
<td>56, F</td>
<td>AA</td>
<td>mMTG</td>
<td>mSTG, aSTG</td>
<td>0</td>
</tr>
<tr>
<td>P3</td>
<td>53, M</td>
<td>AA</td>
<td>pMTG</td>
<td>pSTG, anG</td>
<td>0</td>
</tr>
<tr>
<td>P4</td>
<td>51, M</td>
<td>GBM</td>
<td>anG</td>
<td>pSMG, pSTG, pMTG</td>
<td>2B</td>
</tr>
<tr>
<td>P5</td>
<td>50, M</td>
<td>GBM</td>
<td>anG</td>
<td>aSMG, pSMG</td>
<td>2A</td>
</tr>
<tr>
<td>P6</td>
<td>40, M</td>
<td>GBM</td>
<td>pSTG</td>
<td>mSTG, pMTG</td>
<td>2B</td>
</tr>
<tr>
<td>P7</td>
<td>63, F</td>
<td>DA</td>
<td>pSTG</td>
<td>mSTG, pMTG</td>
<td>1B</td>
</tr>
<tr>
<td>P8</td>
<td>47, F</td>
<td>GBM</td>
<td>pMTG</td>
<td>pSTG, anG</td>
<td>2B</td>
</tr>
<tr>
<td>P9</td>
<td>56, F</td>
<td>GBM</td>
<td>pMTG</td>
<td>pSTG, anG</td>
<td>0</td>
</tr>
<tr>
<td>P10</td>
<td>47, M</td>
<td>AA</td>
<td>aSMG</td>
<td>pSMG, SPL, mPrG, mPoG</td>
<td>1B</td>
</tr>
<tr>
<td>P11</td>
<td>30, F</td>
<td>AA</td>
<td>anG</td>
<td>pSMG, pSTG, pMTG</td>
<td>1A</td>
</tr>
<tr>
<td>P12</td>
<td>74, M</td>
<td>GBM</td>
<td>aSTG</td>
<td>mSTG, pMTG</td>
<td>2A</td>
</tr>
<tr>
<td>P13</td>
<td>41, M</td>
<td>AA</td>
<td>pSTG</td>
<td>mSTG, pMTG, anG</td>
<td>2B</td>
</tr>
<tr>
<td>P14</td>
<td>47, M</td>
<td>GBM</td>
<td>anG</td>
<td>SPL, pSMG</td>
<td>1A</td>
</tr>
<tr>
<td>P15</td>
<td>27, F</td>
<td>AVM</td>
<td>mSTG</td>
<td>NI</td>
<td>0</td>
</tr>
</tbody>
</table>

AA = anaplastic astrocytoma (WHO Grade III); AVM = arteriovenous malformation; C = cavernoma; DA = diffuse astrocytoma (WHO Grade II); GBM = glioblastoma (WHO Grade IV); NI = no infiltrated region.

* Patient characteristics include each patient’s preoperative aphasia grade, lesion type, and lesion location. The patients are grouped according to the location of their lesions, whether the lesions are located within the anterior language-related CPS regions (A1–12) or within the posterior language-related CPS regions (P1–15).

† CPS regions are defined in Table 2.

‡ Aphasia grades: 0 = no aphasia, 1 = mild aphasia, 2 = moderate aphasia, 3 = severe aphasia, A = predominantly nonfluent aphasia, B = predominantly fluent aphasia.
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Each site was stimulated 3 nonconsecutive times. The distance between 2 sites was approximately 10 mm. The coil position was tracked by the use of a stereotactic camera and reflectors fastened to the patient’s head with an elastic strap. Thus, the intracranial stimulation sites were visualized over the 3D reconstruction of the patient’s brain and were saved for later examination. By placing the coil perpendicular to the skull we obtained maximum field induction, and the induced electric field had a minimum cortical field strength of 55 V/m.

TMS Data Analysis

Since the baseline performance and the stimulation trials were video-recorded, rTMS language mappings were analyzed objectively and blinded to the stimulation sites and lesion location. In comparison with the baseline performance, we categorized the rTMS-induced language errors into 7 subgroups (no responses, performance errors, hesitations, neologisms, semantic paraphasias, phonologic paraphasias, and circumlocutions), rejected errors related to muscle stimulations or pain, and assigned the language errors to Corina’s cortical parcellation system (CPS) (Fig. 1, Table 2). Moreover, the definition of anterior (A) and posterior (P) language-related CPS regions is provided in Fig. 1. Subsequently, the error rate (number of errors per number of stimulations) was calculated for each region of the CPS. A CPS region was defined as language-positive in terms of rTMS, if any of the trains applied to this region led to any language error. Accordingly, a CPS region was defined to be language-negative, in terms of rTMS, if the region was stimulated but no language errors were generated. This was done to render better comparability to the results of fMRI language mapping, which were also analyzed without threshold.

Language Mapping During Awake Craniotomy

The setup and procedure of language mapping during awake craniotomy were performed as previously published by others. A bipolar-stimulation electrode with a distance of 5 mm (Inomed Medizintechnik GmbH) was used for cortical stimulation (intensity of 0–20 mA, frequency of 50 Hz, duration of 4 seconds). The distance between the stimulation sites was 5–10 mm, and we recorded a surface electroencephalogram (bandpass filter of 10 Hz to 1.5 kHz) to detect epileptic seizures. We used the same 3D MRI for the intraoperative mapping by DCS and for the preoperative mapping by rTMS, and we also used the same pictures for the object naming in both methods. The intraoperative naming task started with the matrix sentence, “This is a …,” and each cortical site was stimulated 3 times as well. The stimulated sites were considered to be language-positive in terms of DCS if at least 2 of 3 stimulations led to a language error (that is, the 2/3 rule). These positive sites were marked and transferred to the neuronavigation system (BrainLAB Vectorvision Sky or BrainLAB Curve, BrainLAB AG).

Data Analysis

Anatomical Localization and Stimulation Assessment

The induced language errors by DCS and rTMS as well as the regions with a positive BOLD signal detected by fMRI were assigned to the CPS. Given that DCS represents the gold standard for language mapping, the intraoperative results determined by DCS provided the ground truth for every comparison. The assertion regarding language positivity or negativity of a CPS region defined by the noninvasive techniques of rTMS and fMRI was compared with the results of DCS language mapping as fol-
TABLE 2. Abbreviations of the anatomical cortical areas according to the CPS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Anatomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>aMFG</td>
<td>Anterior middle frontal gyrus</td>
</tr>
<tr>
<td>aMTG</td>
<td>Anterior middle temporal gyrus</td>
</tr>
<tr>
<td>aG</td>
<td>Angular gyrus</td>
</tr>
<tr>
<td>aSMG</td>
<td>Anterior supramarginal gyrus</td>
</tr>
<tr>
<td>aSTG</td>
<td>Anterior superior temporal gyrus</td>
</tr>
<tr>
<td>dPoG</td>
<td>Dorsal postcentral gyrus</td>
</tr>
<tr>
<td>dPrG</td>
<td>Dorsal precentral gyrus</td>
</tr>
<tr>
<td>mMFG</td>
<td>Middle middle frontal gyrus</td>
</tr>
<tr>
<td>mMTG</td>
<td>Middle middle temporal gyrus</td>
</tr>
<tr>
<td>mPoG</td>
<td>Middle postcentral gyrus</td>
</tr>
<tr>
<td>mPrG</td>
<td>Middle precentral gyrus</td>
</tr>
<tr>
<td>mSFG</td>
<td>Middle superior frontal gyrus</td>
</tr>
<tr>
<td>mSTG</td>
<td>Middle superior temporal gyrus</td>
</tr>
<tr>
<td>opIFG</td>
<td>Opercular inferior frontal gyrus</td>
</tr>
<tr>
<td>pMFG</td>
<td>Posterior middle frontal gyrus</td>
</tr>
<tr>
<td>pMTG</td>
<td>Posterior middle temporal gyrus</td>
</tr>
<tr>
<td>pSFG</td>
<td>Posterior superior frontal gyrus</td>
</tr>
<tr>
<td>pSMG</td>
<td>Posterior supramarginal gyrus</td>
</tr>
<tr>
<td>pSTG</td>
<td>Posterior superior temporal gyrus</td>
</tr>
<tr>
<td>SPL</td>
<td>Superior parietal lobe</td>
</tr>
<tr>
<td>trIFG</td>
<td>Triangular inferior frontal gyrus</td>
</tr>
<tr>
<td>vPoG</td>
<td>Ventral postcentral gyrus</td>
</tr>
<tr>
<td>vPrG</td>
<td>Ventral precentral gyrus</td>
</tr>
</tbody>
</table>

Statistical Analysis

We calculated the receiver operating characteristic (ROC) sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for each region of the CPS. In the context of our study, the sensitivity of the noninvasive mapping technique refers to the ability of rTMS or fMRI to correctly identify language-positive cortical regions as determined by the ground truth DCS. In contrast, the specificity of rTMS or fMRI refers to the ability to correctly identify language-negative cortical regions. The PPV of rTMS or fMRI indicates the probability that a language-positive cortical region in terms of rTMS or fMRI is afterward defined as language positive by DCS as well, while the NPV is the probability that a language-negative cortical region in terms of rTMS or fMRI will even be defined as language negative by DCS. As a first step, we summed up the results of all patients—that is, we analyzed the noninvasive methods versus DCS without dependency on lesion location. We separated the obtained ROCs into 3 subgroups: all mapped CPS regions, only the anterior language-related CPS regions (A), and only the posterior language-related CPS regions (P). The subgroups included the following CPS regions (Fig. 1, Table 2): 1) anterior (A): trIFG, opIFG, and vPrG; 2) posterior (P): aSMG, pSMG, aG, mSTG, and pSTG.

The selected CPS regions of subgroup A were based on predominantly motor-related language regions including the classic Broca's area, whereas the regions of subgroup P were based on predominantly sensory-related language regions including the classic Wernicke's area and the classic Geschwind's area.

Furthermore, we analyzed the noninvasive methods in comparison with DCS, with dependency on lesion location. Considering this, we divided the patient cohort into 2 subgroups (Table 1): 1) A1–12, patients with lesions within the anterior language-related CPS regions and 2) P1–15, patients with lesions within the posterior language-related CPS regions.

We then summed up the ROCs of the aforementioned 8 CPS regions (A and P) for 6 different subgroups and for each of the 2 comparisons: 1) anterior language-related CPS regions of patient P1–15 (w/o-a); 2) posterior language-related CPS regions of patient A1–12 (w/o-p); 3) without lesion in mapped CPS regions = (1) + (2) (w/o); 4) anterior language-related CPS regions of patient A1–12 (w/-a); 5) posterior language-related CPS regions of patient P1–15 (w/-p); and 6) with lesion in mapped CPS regions = (4) + (5) (w).

For interpretation of the obtained data and for the comparison of the 2 noninvasive methods in relation to the intraoperative results, we issued ROC curves for all subgroups. In Fig. 2 we plotted the results for sensitivity (y axis) against 1–specificity (x axis). Moreover, with the aim of outlining the results for the mapping of language-negative regions, we plotted the results for sensitivity (y axis) against the term 1–NPV (x axis) in Fig. 3.

Results

Patients

The 27 patients (18 male, 9 female) who met our inclusion criteria had a mean age of 46 ± 12 years. The mean age of the 12 patients (10 male, 2 female) of subgroup A was 44 ± 11 years, and the mean age of the 15 patients (8 male, 7 female) of subgroup P was 47 ± 12 years (Table 1). Regarding age, there was no significant difference between the 2 subgroups (p = 0.511).

Comparison of rTMS and fMRI With DCS Language Mapping

Across the 27 patients we compared the results of rTMS and DCS language mapping in 207 CPS regions in total. The results of fMRI language mapping using an
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Object-naming paradigm and DCS overlapped in 258 CPS regions in total. The overall ROCs of all mapped CPS regions without dependency on lesion location are demonstrated for both comparisons in Fig. 2 and Table 3. Table 3 also shows the overall results for the anterior as well as for the posterior language-related CPS regions.

Additionally, the ROCs were calculated for the dependency on lesion location. Table 4 outlines the results for the comparisons with and without a lesion in mapped regions (Fig. 3). For a more detailed analysis, we also show the results for only the anterior (w/-a) and the posterior (w/-p) language-related CPS regions, which met these requirements (Fig. 3, Table 4).

The NPV within the subgroup w/o-a could not be calculated for the comparison rTMS versus DCS because we did not obtain either true-negative or false-negative results for this analysis. This was also due to obviously less intraoperative results of regions without lesion (Fig. 3, Table 4).

Discussion

Noninvasive Mapping of Language-Negative Cortical Regions

In previous studies, rTMS yielded high overall sensitivity (90% and 90.2%) and NPV (99% and 83.9%) in comparison with DCS language mapping. In our study, we also found high overall sensitivity (97%) and NPV (91%) (Fig. 2, Table 3). Most importantly, we obtained a sensitivity and NPV of 100%, respectively, for both the anterior and posterior language-related CPS regions (Figs. 2 and 3, Tables 3 and 4). That these CPS regions are at least crucial cortical entry sites to the highly individualized language networks has already been proven in previous studies.

By using negative mapping due to the perfect sensitivity and NPV, rTMS could once more yield excellent correlation to DCS, especially within critical cortical regions. Since sensitivity and NPV predict reliable negative results, high values for these 2 ROCs are of particular importance for the mapping of language-negative brain regions. This in turn is relevant given that some authors and surgeons also trust the mapping of language-negative sites when performing DCS during awake surgery. Moreover, the reliability of negative results allows a more extensive resection, which is essential regarding oncological considerations.

In contrast, fMRI language mapping using an object-naming task could not reach the results of rTMS concerning the mapping of language-negative sites (Figs. 2 and 3, Tables 3 and 4). Like previous studies, we obtained comparable overall specificity for the comparison of fMRI versus DCS when analyzing them without dependency on lesion location (Fig. 2, Table 3). However, we detected many false-negative results for the comparison fMRI ver-
sus DCS (fMRI vs DCS: 42 within all mapped regions and 29 within the anterior and posterior language-related regions; rTMS vs DCS: 2 within all mapped regions and 0 within the anterior and posterior language-related regions) (Fig. 2, Table 3). This determining factor seems to be dangerous regarding the abovementioned approach of mapping language-negative sites. Results of noninvasive techniques, incorrectly identified as language negative, could lead to harmful surgical decisions, as has recently been described for diffusion tensor imaging fiber tracking (DTI-FT).10 Alternatively, fMRI—like rTMS—cannot be used for the mapping of language-positive sites due to its limited PPV, which varies around chance level (Table 3).14 Giussani and colleagues reviewed 9 language mapping studies, which compared the results of fMRI and DCS in 2010. Despite the fact that these studies were not homogeneous, concerning several criteria, they found an incomplete match between fMRI and DCS: sensitivity ranged from 59% to 100% and specificity from 0% to 97%.18 In contrast, previous studies on rTMS language mapping, including the present study, showed robust results for the mapping of language-negative regions regarding the comparison with intraoperative results, independently from the performing institution.27,39,50,52 With these previous findings in mind, the present study is the first to show the advantages of rTMS language mapping as compared with fMRI within one patient cohort.

**Comparison With Dependency on Lesion Location**

The core of our study was to analyze the impact of left-sided perisylvian brain lesions on the results of rTMS and fMRI language mapping and their reliability when relating to DCS. As Fig. 3 and Table 4 show, we could not detect any impairment by lesions for rTMS mapping of language-negative cortical regions, either for subgroup w/-a or for subgroup w/-p. This is important because noninvasive methods, as part of the preoperative management of patients with brain lesions, should work with maximum accuracy, particularly in the vicinity of lesions.10 The stimulation by rTMS induces a transient virtual lesion.35 Accordingly, DCS, defining the gold standard for language mapping, also maps the cortex by creating a virtual lesion.8,19,33,34 Obviously, this electrophysiological approach seems to not be affected by the presence of a brain lesion.50

### Table 3. Overall results without dependency on lesion location*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All Mapped Regions</th>
<th>Anterior Regions</th>
<th>Posterior Regions</th>
<th>All Mapped Regions</th>
<th>Anterior Regions</th>
<th>Posterior Regions</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPV</td>
<td>34% (27–41)</td>
<td>56% (43–69)</td>
<td>22% (13–35)</td>
<td>48% (35–62)</td>
<td>61% (43–77)</td>
<td>33% (0–91)</td>
</tr>
<tr>
<td>NPV</td>
<td>91% (72–99)</td>
<td>100% (2–100)</td>
<td>100% (48–100)</td>
<td>79% (73–84)</td>
<td>53% (35–70)</td>
<td>79% (67–89)</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>97% (89–100)</td>
<td>100% (90–100)</td>
<td>100% (75–100)</td>
<td>40% (28–52)</td>
<td>58% (41–74)</td>
<td>7% (0–34)</td>
</tr>
<tr>
<td>Specificity</td>
<td>15% (9–22)</td>
<td>4% (0–18)</td>
<td>10% (3–22)</td>
<td>84% (78–89)</td>
<td>56% (38–74)</td>
<td>96% (87–100)</td>
</tr>
</tbody>
</table>

* This table shows the overall results including all mapped CPS regions for the comparisons of rTMS versus DCS and fMRI versus DCS. We additionally demonstrate the results for anterior (trIFG, opIFG, and vPrG) and posterior (aSMG, pSMG, anG, pSTG, and mSTG) language-related CPS regions (Fig. 1, Table 2). The ROCs of these results were calculated without dependency on lesion location. The 95% CI is indicated in parentheses.

### Table 4. Results with dependency on lesion location*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Anterior Regions w/ Lesion Anterior</th>
<th>Posterior Regions w/ Lesion Posterior</th>
<th>w/ Lesion in Mapped Regions</th>
<th>Anterior Regions w/ Lesion Anterior</th>
<th>Posterior Regions w/o Lesion Posterior</th>
<th>w/o Lesion in Mapped Regions</th>
</tr>
</thead>
</table>

* Results of rTMS and fMRI language mapping in comparison with DCS language mapping. The ROCs in column 3 (w/ Lesion in Mapped Regions) respectively include the results of column 1 (Anterior Regions w/ Lesion Anterior) and column 2 (Posterior Regions w/ Lesion Posterior). Accordingly, the ROCs in column 6 (w/o Lesion in Mapped Regions) were calculated by the summed results of column 4 (Anterior Regions w/o Lesion Anterior) and column 5 (Posterior Regions w/o Lesion Posterior). The NPV within the subgroup w/-a could not be calculated for the comparison rTMS versus DCS because neither true-negative nor false-negative results were obtained for this analysis. The anterior regions comprise the CPS regions trIFG, opIFG, and vPrG, whereas the posterior regions comprise the CPS regions aSMG, pSMG, anG, pSTG, and mSTG (Fig. 1, Table 2). The 95% CI is indicated in parentheses.
This is reflected by a robust correlation between rTMS and DCS, whether analyzed for regions with or without a lesion, even when specificity and PPV are around chance level or far below (Fig. 3, Table 4). Especially the plotting of sensitivity against 1–NPV in Fig. 3 shows that rTMS was able to detect all language-positive sites as determined by DCS, equivalent to the fact that the comparison of these 2 methods revealed not a single false-negative result within language-related cortical regions. In contrast, the blood flow–dependent approach of fMRI seems to be more affected by the presence of cerebral pathologies, as shown in many previous studies. This is probably based on methodological differences. The task-related increase of deoxyhemoglobin from activated neurons is supposed to be the basic principle of fMRI. The measured BOLD signals should then show activated cortical regions because of their increased consumption of oxygen. In particular, the dependency on oxygen extraction seems to be the crucial point of the disappointing results for fMRI in patients with brain lesions. On the one hand, tumors induce the proliferation of vessels; hence, the blood volume of the affected region is increased, which is associated with an additional extraction of oxygen and a higher baseline blood flow, resulting in smaller changes in the concentration of deoxyhemoglobin. On the other hand, when healthy parenchyma is infiltrated by gliomas, the contact between capillary cells and astrocytes is decreased, and neurotransmitters cannot be released as they should. This in turn alters the relations of blood flow and the extraction of oxygen. Furthermore, it is known that tumor vascularity in malignant gliomas is unable to autoregulate, and the existing neural activity cannot be measured by the change of regional blood flow and BOLD signals. All of these mechanisms result in decreased or unavailable BOLD signals, which is potentially dangerous regarding the use for any preoperative assessment in brain tumor patients. Even though the following is speculative, the listed essentials of decreased BOLD signals in patients also explain our results. We obtained higher specificity and NPV in subgroup w/ than in subgroup w/o lesion (Fig. 3, Table 4). This bodes well for its clinical applicability despite the fact that even these results do not provide a safe and precise mapping of language-negative sites. The detection of language-negative sites by fMRI may be due to the lack of BOLD signals based on the affection by lesions. Thus we suspect that fMRI revealed a high rate of true-negative results in comparison with DCS but also a crucial high rate of false-negative results. In contrast, there were no false-negative results within language-eloquent brain regions for rTMS language mapping.

Clinical Implications and Future Aspects of rTMS

It must be first highlighted that the results of DCS during awake surgery are indispensable in patients suffering from lesions within or adjacent to language-eloquent brain regions. Given our current knowledge, the aim should not be to replace DCS with rTMS; DCS is and will remain the gold standard for language mapping, justified by comprehensive experience with this technique. Particularly for the mapping of cortical language function, noninvasive methods should be more sophisticated, directed toward a multimodal approach that includes intraoperative mapping as the last step. The preference for multimodality is based on the principle of combining the advantages of each method to ultimately gain the best possible understanding of each patient’s functional anatomy. Currently, rTMS language mapping is able to play a supportive role in this effort, and there are 2 main advantages regarding clinical procedures, not least proven by the present study: First, based on its high sensitivity, language-positive sites near critical regions identified by rTMS can be transferred to intraoperative neuronavigation systems for the verification by DCS. This might accelerate the intraoperative procedure. Second, because of the excellent NPV in the vicinity of lesions, surgeons can be more confident of language-negative sites in cases of preand intraoperative identification and may be able to plan a more extensive resection beforehand.

Moreover, rTMS represents a noninvasive method that could be consulted for the preoperative management of patients unwilling or unable to undergo the physically and sometimes psychologically demanding procedure of awake surgery. Currently, this should only be done in combination with other noninvasive mapping techniques such as PET, fMRI, or DTI-FT, and even then it carries the risk of surgery-related deficit or limited extent of resection. Even if DTI-FT requires further development and validation before it can be included in decision making, the combination of rTMS and DTI-FT may yield useful and supportive information with respect to the hodotopical model of human language function and for the resection of brain lesions in the future. The feasibility of this combination has already been shown for the motor system. Also, by performing noninvasive language mapping, we are able to provide longitudinal follow-up examinations. Thus, it might be possible to incorporate information about plastic reshaping of language function received by rTMS when considering oncological reoperation of recurrent tumor. This additional information could even be supportive and useful regarding the approach of consecutive awake surgery of brain tumor patients.

Limitations

One of the limitations of our study is the analysis of hesitation errors. To date, we are not able to categorize these errors objectively, but only in comparison with baseline performance. Despite this having been done by experienced examiners blinded to the results of intraoperative language mapping, subjectivity cannot be ruled out. This type of error is contrarily discussed anyway while some authors do not even include them in their analysis. With this in mind, the interpretation of hesitation errors might be a reason for the high rate of false-positive results as compared with DCS. Apart from that, particularly with regard to current models of language processing, hesitation errors should be deemed a correlate of disrupted language processing. Most certainly, the analysis of raw data obtained by mapping methods and its reliability are crucial. Based on the functional imaging analysis contest in 2005, Bennett and Miller described that the same fMRI raw data set leads to different results when analyzed by different examiners. However, certain discrepancies have also been
reported for rTMS language mapping, even though variability was relatively low regarding the most important no response errors. Another determining factor, and simultaneously a potential limitation, lies in the CPS map to which the results are assigned. Despite Corina’s CPS being well established and the subregions especially reflecting critical cortical areas for the mapping of language, the error margins exceed the size of 10 mm. Moreover, by combining DCS with direct subcortical stimulation, the spatial resolution is even smaller than 10 mm. Hence, optimized systems and methods for the comparison of rTMS and DCS should be taken into account in future studies. It might be that this aspect could decrease the occurrence of false-positive results of rTMS language mapping in comparison with DCS, too. Yet, the CPS is used since the different regions allow us statistical comparisons of different approaches to further improve our rTMS setup.

Moreover, the 3 mapping modalities were performed by the sole use of an object-naming task. As Rutten and Ramsey concluded in their review, the combination of multiple fMRI language tasks is the best strategy for reproducible and reliable results. This might be true, but this would protract the mapping procedures at the same time. The difficulty of checking the patient’s compliance regarding the performance of tasks within the MR scanner has to be considered anyway. By the use of more than one task, especially for the mapping of patients, it must be assumed that the patient’s concentration and the effect on the results will be impaired. Of course, this pertains to all mapping techniques. Anyway, we used only one task for all modalities, providing that the present results are comparable. Most importantly, the object-naming task has shown to mirror the entire word production process and includes all language-eloquent brain regions. Furthermore, as recently described, object naming has to be considered a cornerstone for intraoperative language mapping. The reproducibility and reliability of this task have been shown for both fMRI and rTMS language mapping as well. However, the use of more than 1 task for studying further stages of language is recommended, in particular for examinations with healthy subjects and in basic research of human language function per se.

Despite the encouraging results of rTMS language mapping, further and, in particular, randomized studies are required to check the reproducibility of our results. This is necessary not least due to the fact that our patient cohort is not homogenous with regard to the distribution of lesion types in the 2 subgroups (Table 1). Yet, the finding that different types of lesions lead to different results of rTMS language mapping has not been described, but this interrogation has to be evaluated in future studies. The present study is not the first to compare rTMS and DCS; however, in relation to others, rTMS is still a novel technique, especially in the field of language mapping. As with each method, it must be refined—for example, regarding its specificity and PPV. Further, since rTMS is noninvasive and lesion based, it may contribute substantially to the basic research of human language function.

Nonetheless, we must also point out that several brain areas cannot be mapped with high reliability (e.g., the temporo-basal regions) because rTMS may induce pain. This is a serious limit for many lesions located in these areas. In addition, the specificity of rTMS is only around 8%, with a PPV of 34%. This means that rTMS is currently too sensitive for the mapping of language-positive cortical regions and that the wrong interpretation of rTMS can be very dangerous in clinical practice, because it could lead surgeons not to select patients for surgery due to a false-positive result during rTMS while the lesion was in fact resectable. This is another crucial issue. These false-positive regions in terms of DCS might only be language involved. However, our suggested clinical procedure permits the intraoperative verification of language-positive cortical regions in terms of rTMS.

Conclusions

The present study is the first to investigate distinct results of language mapping by rTMS and fMRI within a single patient cohort. With certainty, fMRI for language mapping is an enormously important mapping tool for studying human language function in healthy subjects. However, its results regarding the comparison with intraoperative language mapping during awake surgery are considerably affected by the presence of a brain lesion. In contrast, we showed that rTMS language mapping in patients suffering from brain lesions is less affected by these circumstances, especially when performing mapping of language-negative cortical regions based on sensitivity and NPV.

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Conception and design: Krieg. Acquisition of data: Krieg, Ille, Sollmann, Hauck, Maurer, Negwer, Droese, Boeckh-Behrens, Ringel. Analysis and interpretation of data: Krieg, Ille, Obermueller. Drafting the article: Krieg, Ille. Critically revising the article: Krieg, Ille, Obermueller, Negwer, Droese, Boeckh-Behrens, Meyer. Reviewed submitted version of manuscript: Krieg, Ringel. Approved the final version of the manuscript on behalf of all authors: Krieg. Statistical analysis: Ille, Tanigawa. Administrative/technical/material support: Krieg, Boeckh-Behrens, Meyer, Ringel. Study supervision: Krieg, Meyer, Ringel.

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