Cortical plasticity of motor-eloquent areas measured by navigated transcranial magnetic stimulation in patients with glioma

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OBJECTIVE The goal of this study was to obtain a better understanding of the mechanisms underlying cerebral plasticity. Coupled with noninvasive detection of its occurrence, such an understanding has huge potential to improve glioma therapy. The authors aimed to demonstrate the frequency of plastic reshaping, find clues to the patterns behind it, and prove that it can be recognized noninvasively using navigated transcranial magnetic stimulation (nTMS).

METHODS The authors used nTMS to map cortical motor representation in 22 patients with gliomas affecting the precentral gyrus, preoperatively and 3–42 months postoperatively. Location changes of the primary motor area, defined as hotspots and map centers of gravity, were measured.

RESULTS Spatial normalization and analysis of hotspots showed an average shift of 5.1 ± 0.9 mm (mean ± SEM) on the mediolateral axis, and 10.7 ± 1.6 mm on the anteroposterior axis. Map centers of gravity were found to have shifted by 4.6 ± 0.8 mm on the mediolateral, and 8.7 ± 1.5 mm on the anteroposterior axis. Motor-eloquent points tended to shift toward the tumor by 4.5 ± 3.6 mm if the lesion was anterior to the rolandic region and by 2.6 ± 3.3 mm if it was located posterior to the rolandic region. Overall, 9 of 16 (56%) patients with high-grade glioma and 3 of 6 (50%) patients with low-grade glioma showed a functional shift > 10 mm at the cortical level.

CONCLUSIONS Despite the small size of this series, analysis of these data showed that cortical functional reorganization occurs quite frequently. Moreover, nTMS was shown to detect such plastic reorganization noninvasively.

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KEY WORDS brain tumor; motor cortex; brain mapping; neuronal plasticity; neurosurgery; oncology

Lesion-induced cerebral plasticity is a widely discussed and recently researched phenomenon. However, directly monitoring plasticity that might occur during the treatment of patients with glioma is not part of the clinical routine. Clinical evidence of cerebral plasticity stems mainly from postoperative neurological assessment or intraoperative direct cortical stimulation (DCS).9,32 However, data on the frequency and predictors of such plastic reorganization are not yet available.

The ability to recognize the redistribution of cortical functions without (or before) an operation could significantly enhance treatment options for patients with glioma, notably by optimizing surgical planning. It has, for example, been suggested that surgeons could choose to delay surgery to allow time for plastic reorganization to take place and shift cortical and subcortical white-matter functions away from the tumor. When this occurs, the chances of achieving total resection of the tumor are increased.15,24 To realize such an approach, however, a noninvasive and yet reliable diagnostic modality is required, and navigated transcranial magnetic stimulation (nTMS) has been touted as one such modality.10,14,28,32
The nTMS method has been shown to be safe, while causing no discomfort to patients, especially when used for mapping of the motor cortex.\textsuperscript{21,36} Crucially, recent studies have confirmed that its accuracy is comparable to that of DCS and functional MRI.\textsuperscript{21,27,37} Plastic reorganization has been observed using both these methods,\textsuperscript{1,10,29} a fact that bodes well for the chances of similar success using nTMS, which combines the excitatory approach of the former with the noninvasive nature of the latter. Moreover, the accuracy of nTMS motor mapping has proven to be unaffected by recurrent tumors and their accompanying lesions,\textsuperscript{22} and a limited number of reports on plastic changes observed by nTMS are available.\textsuperscript{14,34}

The goal of this study was to test the capability of nTMS motor mapping to detect plastic reorganization in the shape of changes in the distribution of cortical motor function in postsurgical patients with glioma, and to obtain an indication as to the frequency of this occurring.

**Methods**

**Patient Cohort**

We enrolled 22 patients with a mean age of 49.6 ± 3.2 years (mean ± SEM, range 26–78 years). To be considered for inclusion, patients had to be ≥ 18 years of age, and suffer from supratentorial gliomas located in or near the precentral gyrus (PrG) as identified by anatomical MRI scans. Each patient received a motor mapping using nTMS in preparation for surgery, and another mapping 3–42 months postoperatively. We applied the usual exclusion criteria for nTMS and MRI, such as cochlear implants or pacemakers.

At the time of enrollment, patients’ tumors included the following: 10 glioblastomas (WHO Grade IV), 5 anaplastic astrocytomas (WHO Grade III), 1 anaplastic oligodendroglioma (WHO Grade III), 4 diffuse astrocytomas (WHO Grade II), 1 oligoastrocytoma (WHO Grade II), and 1 mixed glioma (WHO Grade I) (Table 1).

To gauge potential positional shifts of motor areas relative to the positions of the patients’ tumors, patients were analyzed in 2 subgroups: Group A, including all patients whose tumor was judged to be situated anterior to the PrG; and Group P, with patients whose tumors were more posterior than the PrG.

**Ethical Standards**

Each patient was given detailed information on the study and the methods used for it, and gave his or her written consent prior to preoperative nTMS mapping. Our study was approved by the local ethics committee and is in accordance with the Declaration of Helsinki.

**MRI Procedures**

Each patient received a cranial MRI scan 1–7 days before and 3–42 months after surgery, using a 3-T MR scanner combined with an 8-channel phased-array head coil (Achieva 3T, Philips Medical Systems B.V.) for contrast-enhanced 3D gradient echo sequences as well as T2-weighted FLAIR imaging. The resulting MR images were used to navigate the nTMS mapping.

**Motor Mapping Using nTMS**

Motor mappings were performed using an established nTMS system (eXimia 4.3, Nexstim Oy) by the standard nTMS protocol, which has been published repeatedly.\textsuperscript{14,21,27,37} An infrared tracking system (Polaris Spectra) was used to track the relative positions of patients’ heads and the biphasic, 50-mm-radius, figure-8 magnetic stimulation coil. To measure the motor evoked potentials (MEPs) expected as the result of stimulation, we placed electromyography (EMG) electrodes (Ag/AgCl electrode, Neuroline 720, Ambu) on 5 different muscles: abductor pollicis brevis, abductor digitii minimi, flexor carpi radialis, tibialis anterior, and the gastrocnemius muscle. This, along with a grounding electrode on the patient’s elbow, helped us to continually monitor muscle activity during nTMS motor mapping. In some instances, individual muscles were deemed to be producing too many EMG artifacts, such as excessive baseline activity. The affected muscles and the corresponding EMG data were not considered in further analysis. As a result, in 6 patients, only 2 of the 3 aforementioned muscles of the upper limbs were analyzed.

Our mapping procedure followed the established recommendations by first determining the resting motor threshold (rMT).\textsuperscript{14,21,27,37} To achieve this, the PrG and surrounding areas of the cortex were stimulated with a standard intensity of 30% of the stimulator’s maximum output. The point at which the largest MEP was registered was then repeatedly stimulated to confirm that MEPs could reliably be triggered at that location. Further stimulation with decreasing or increasing intensity—depending on whether a response was registered after the respective preceding stimulation—served to determine the minimum stimulation intensity necessary to induce an MEP measuring > 50 mA. This intensity, quantified as a percentage of the stimulator’s maximum output, was then defined as the rMT. To map the cortical motor representation of the upper limb, the cortex was stimulated with an intensity of 110% of this rMT value. The lower-limb representation was mapped at ≥ 130% of the rMT (if no MEP of the lower limbs could be induced at 130% of the rMT).

Coil angulation was always perpendicular to the stimulated gyri. To minimize false negatives, we stimulated well beyond the areas appearing as positive for motor function. We considered a mapping point as positive for motor function when an EMG response > 50 mA was registered in 1 of the corresponding muscles upon its stimulation. All points were checked for artifacts after each mapping.

**Hotspot and Centers of Gravity Analysis**

We determined the hotspots (HSs) and the map centers of gravity (CoGs) for both maps of each patient. The HSs were defined as the points at which the highest MEPs could be triggered in the respective muscles upon stimulation at 110% of the rMT. Similar to Koenraadt et al.,\textsuperscript{20} the CoG (x, y, z) of the MEPS was calculated based on the 3D coordinates of the valid stimulation points (x, y, z) and the EF\textsubscript{max} (maximum electric field) amplitude of the corresponding valid MEPS.

Conceptually, the CoG of x is a weighted mean of x, where the weight (notated as w) is the relative EF\textsubscript{max} amplitude. Accordingly, the CoG of x (notated as CoG\textsubscript{x}) of n
trials was computed as the mean of (x at stimulation point
i weighted by $EF_{max}$ at stimulation point i). The definitional
formula for CoG$_x$ is

$$CoG_x = \sum_{i=1}^{n} w_i \times x_i,$$

where

$$w_i = EF_{max_i} / \sum_{i=1}^{n} EF_{max_i}.$$

To simplify, the computational formula for CoG$_x$ is

$$CoG_x = \frac{\sum_{i=1}^{n} (EF_{max_i} \times x_i)}{\sum_{i=1}^{n} EF_{max_i}}.$$

Extending this formula to CoG$_y$ and CoG$_z$:

$$CoG_y = \frac{\sum_{i=1}^{n} (EF_{max_i} \times y_i)}{\sum_{i=1}^{n} EF_{max_i}};$$

$$CoG_z = \frac{\sum_{i=1}^{n} (EF_{max_i} \times z_i)}{\sum_{i=1}^{n} EF_{max_i}}.$$

The abductor digitii minimi, abductor pollicis brevis, and
flexor carpi radialis muscles were each analyzed separately,
so that each mapping produced 3 HSs and 3 CoGs. Mapping data on lower-extremity muscles were not used
for further analysis, because the deep-lying cortical repre-
sentation of the leg could result in reduced accuracy of the
nTMS motor mapping.$^{12,21,35}$

All HSs, as well as stimulation points corresponding to

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**TABLE 1. Demographic data and clinical characteristics of patient cohort**

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Mean 49.6  3.1   12.1     0.3 0.3
SEM 3.2  0.2   2.2     0.025 0.02
Min 26  1   3.0     0.24 0.22
Max 78  4   41.2     0.72 0.62
Median 48.5  3   7.0     0.325 0.31

p value 0.5098  0.6430

EOR = extent of resection; max = maximum; min = minimum.
* The rMTs at patients' first and second motor mappings (rMT1 and rMT2) are described relative to the stimulator's maximum output.
the coordinates calculated for the CoGs, were exported to the DICOM format using nTMS analysis software (eXimia 4.3, Nexstim Oy).

Spatial Normalization
Each patient’s MRI scan, as well as the corresponding HSs and CoGs, were exported to DICOM, and then converted to the Neuroimaging Informatics Technology Initiative format using dcm2nii (McCausland Center for Brain Imaging, University of South Carolina). To filter out the effects of brain shift because of the tumor (or, in the cases of patients’ second scans, the resection cavity), we used cost-function masking, as described by Brett et al., which remains the standard method for normalization of brain images with focal lesions. Both the native images and the images with exported points were then normalized in SPM12 (Functional Imaging Laboratory, Wellcome Trust Center for Neuroimaging, Institute of Neurology, University College London), with the standard “single_subj_T1.nii” 2-mm-resolution image from the SPM12 catalog serving as template. The coordinates for each HS and CoG were then measured using MRIcron (McCausland Center for Brain Imaging, University of South Carolina).

These coordinates were then transposed to the following 1-mm-based coordinate system: x represents the mediolateral axis, originating from the median line. Thus, higher values for x imply greater distance to the midline. The y coordinate represents the posteroanterior axis, whereas z is a measure for the inferior-superior axis.

Shift Measurement
To quantify positional changes along the mediolateral x axis and the posteroanterior y axis, the coordinates from the first mapping were subtracted from those obtained in the second. As a result, positive values for x denoted movement in a lateral direction, whereas positive values for y stood for a shift in an anterior direction. Correspondingly, negative values denoted positional change in the respective opposite directions.

Statistical Analysis
All statistical analysis was performed using GraphPad Prism software version 6.04. The absolute values in millimeters of the extent of the positional shifts of HSs and CoGs along the posteroanterior axis were compared with those along the mediolateral axis with Wilcoxon matched-pairs signed-rank tests. To further analyze the shift of motor function along the posteroanterior axis and to take the direction of this shift into account, redistribution along the y axis was compared for Groups A and P. The significance of differences between the groups was tested with Mann-Whitney U-tests.

We used linear regression to analyze the relationship between the changes in HS and CoG location and the time intervals between mappings. Furthermore, the Pearson and Spearman correlation coefficients were computed to help describe this relationship. These calculations were also computed separately for patients suffering from low- or high-grade glioma. Because the time intervals cannot be presumed to be samples from a gaussian distribution, confidence intervals and p values for this correlation were not evaluated.

The above measurements were repeated, with the modification that only changes ≥ 10 mm were considered actual positional shifts. The remaining values were set to 0. We consider this 10-mm cutoff to be a way of accounting for the inaccuracy of the neuronavigational part of the nTMS system, which recent theoretical calculations (but also clinical studies) have found to lie in the region of 6.7 mm, 6,13,25,30,31,39,40 as well as the 2-mm resolution of the SPM12 normalization template and the 1-mm resolution of the original MR images.

Differences regarding the rMTs of each patient’s first and second mapping were evaluated by calculating the coefficient of variance (CV). The average CV of all 22 patients was then computed. A paired t-test was used to gauge whether rMTs differed significantly between mappings. All results are presented as the mean ± SEM, and a p value < 0.05 was considered to be statistically significant.

Visual Confirmation
To verify that the measured positional changes of HSs and CoGs were not artifacts resulting from the normalization process, screenshots of the 3D head model generated by the nTMS analysis software (eXimia 4.3, Nexstim Oy), featuring the visualized HSs and CoGs, were compared for each patient. Visually observed changes in position were then compared with the calculated shift. To help illustrate this process with an example, we have provided an image consisting of the screenshots based on the mappings of the patient in Case 2 (Fig. 1).

Results
Overall Positional Shift by Axis
Overall, the average absolute value of positional shifts of HSs was 5.1 ± 0.9 mm on the mediolateral x axis and 10.7 ± 1.6 mm on the posteroanterior y axis. For CoGs, the corresponding values were 4.6 ± 0.8 mm on the x axis and 8.7 ± 1.5 mm on the y axis. The average magnitudes of the resulting vectors were 12.4 ± 1.6 mm for HSs and 10.4 ± 1.5 mm for CoGs. Shifts along the y axis were significantly greater than those on the x axis (p_HS = 0.0011; p_CoG = 0.0075; Table 2, Figs. 2 and 3).

Applying the 10-mm cutoff to average shift vectors at the brain surface level resulted in the discounting of 11 of 22 (50%) HS shift vectors and 13 of 22 (59%) CoG shift vectors.

Influence of Tumor Location
Average Shift
To compare Group A (including all patients with tumors situated anterior to the PrG) with Group P (with those patients whose tumors were further posterior), we used the coordinate system as explained in Spatial Normalization. We found that HSs and CoGs of Group A had moved, on average, +4.5 ± 3.6 mm on the y axis, denoting change in an anterior direction, toward the tumor. Correspondingly, in Group P, HSs and CoGs had shifted further posterior, as...
shown by an average shift of $-2.6 \pm 3.3$ mm. The statistical significance of these shifts in opposite directions, and thereby toward the respective tumors or resection cavities, could not be confirmed by a Mann-Whitney U-test ($p = 0.1802$). Analysis of HS and CoG shifts individually delivered slightly lower $p$ values ($p_{\text{HS}} = 0.1402$; $p_{\text{CoG}} = 0.1745$) (Fig. 3).

Shifts measured along the x axis were, on average, $-1.9$ ± 2.0 mm in Group A, and $-0.2$ ± 1.5 mm in Group P ($p = 0.6619$; $p_{\text{HS}} = 0.4078$; $p_{\text{CoG}} = 0.7096$). For further details, see Tables 3 and 4. The HSs and CoGs of Groups A and P are visualized in Fig. 4.

**Cutoff Rule of 10 mm**

In Group A, HS shifts of ≥ 10 mm at the cortical surface level were measured in 6 of 12 patients. In 4 of these 6 patients, surface-level CoG measurements also reached ≥ 10 mm.

In Group P, HS shifts made the 10-mm cutoff at the brain surface level in 5 of 10 patients. In 4 of these 5 patients, CoG shift vectors also reached ≥ 10 mm.

Differences between Groups A and P regarding the distribution of shifts of ≥ 10 mm were analyzed using contingency tables, and no significant differences were observed between groups ($p_{\text{HS}} = 1.0$; $p_{\text{CoG}} = 0.6656$). To summarize, 12 of 22 patients presented shifts of HSs, CoGs, or both of ≥ 10 mm at the cortical surface level. In 8 of these 12 cases, both HSs and CoGs had shifted by ≥ 10 mm. Nine of these 12 patients suffered from high-grade glioma (WHO Grades III and IV), and the remaining 3 suffered from low-grade glioma (WHO Grades I and II).

**Visual Analysis**

Visual analysis of the screenshots taken at each mapping confirmed the direction and approximate extent of every measured shift. Although edema, as well as particularly large tumors and subsequent resection cavities, were observed in some patients, these characteristics were distributed across patients with shifts both higher and lower than the 10-mm cutoff. Concerning the positions of shifts relative to the PrG, HSs and CoGs were judged not to have left the PrG in 12 of 22 cases (54%). In 3 cases (14%), HSs and CoGs appeared to have shifted out of the PrG—twice into the superior frontal gyrus (SFG), and once into the middle frontal gyrus (MFG). We observed an apparent shift back into the PrG in 7 cases (32%) (Table 4). For an example of how visual analysis was conducted, see Fig. 1.

**Resting Motor Threshold**

The rMT averaged 35% ± 2% across the first mappings and 34% ± 2% across the second mappings ($p = 0.6430$). The average CV was 0.16.

**Time Interval as a Factor**

Linear regression rendered a positive slope value of $0.2642 \pm 0.1473$ (95% CI $-0.04298$ to 0.5714) for HS shifts and $0.2206 \pm 0.1446$ for CoG shifts (95% CI $-0.08109$ to 0.5222). Correlating the time intervals between mappings 1 and 2 with the vector magnitudes of shifts measured at the brain surface level delivered Spearman correlation coefficients of $r_{\text{HS}} = 0.5486$ and $r_{\text{CoG}} = 0.4878$, as well as Pearson correlation coefficients of $r_{\text{HS}} = 0.3723$ and $r_{\text{CoG}} = 0.3228$. Although CIs could not be computed for either type of correlation coefficient due to the non-gaussian distribution of data, both values, as well as the slope rendered by linear regression, indicate a trend toward positive correlation, meaning that shifts tended to be larger in patients whose time interval between mappings was long (Fig. 5). The following subsections detail the corresponding calculations for patients suffering from high- or low-grade gliomas.

**Low-Grade Gliomas**

When only the 6 patients with low-grade gliomas were considered, linear regression rendered a positive slope value of $0.3921 \pm 0.4103$ (95% CI $-0.7470$ to 1.531) for HS shifts and $0.2151 \pm 0.4686$ for CoG shifts (95% CI $-1.086$ to 1.516). Spearman correlation coefficients between shift and time span between mappings were $r_{\text{HS}} = 0.6571$ and $r_{\text{CoG}} = 0.08571$, with Pearson correlation coefficients amounting to $r_{\text{HS}} = 0.4311$ and $r_{\text{CoG}} = 0.2236$.

**High-Grade Gliomas**

Regarding patients with high-grade glioma, linear regression produced positive slope values of $0.2215 \pm 0.1593$ (95% CI $-0.1201$ to 0.5632) for HS shifts and $0.2206 \pm 0.1393$ for CoG shifts (95% CI $-0.07810$ to 0.5193). The Spearman correlation coefficients between shift and time span between mappings were $r_{\text{HS}} = 0.3956$ and $r_{\text{CoG}} = 0.6498$, and the Pearson correlation coefficients were $r_{\text{HS}} = 0.3484$ and $r_{\text{CoG}} = 0.3899$. 

![FIG. 1. Case 2. Example of visual analysis. The image consists of screenshots taken from the 3D brain model used for the nTMS motor mapping of the patient, who suffered from a diffuse astrocytoma (WHO Grade II). The patient’s first (preoperative) mapping (left) and second mapping (right) are displayed. Gray markers represent individual stimuli. White markers represent stimuli corresponding to the positions of HSs and map CoGs. To help compare the positions of these points in the respective mappings, an overlay of white lines along selected nearby gyri was added to the respective images. It becomes apparent that in the second mapping, these markings were found to be further anterior than in the first, in some cases beyond the PrG. Most markers remained in the PrG; thus visual analysis confirmed the calculated slight overall shift of markers in an anterior direction. Red and orange markers were used for navigation during the stimulation process and are not relevant to the analysis of these images. Figure is available in color online only.](image-url)
Differentiating Between Artifacts and Location Changes

The first question that needs to be answered with regard to the shifts we measured is whether they were the result of the inaccuracy of our methods, or whether the cortical representations of the muscles analyzed actually changed location in certain patients. To evaluate this, we compared both the extent and orientational components of shifts measured in our study to observations from previous neuronavigated studies describing the retest reliability of nTMS motor mapping in healthy participants. With regard to the pure, average extent of the shifts we measured, our results only marginally exceed the average of inaccuracies (6.7 mm) observed by these studies.6,13,25,30,31,39,40 However, individual measurements in several of our patients deviated far more from this usual range, as reflected in our relatively high SEM values. This is despite our application of the same nTMS protocol as used for a number of these studies. Notably, one these studies, by Sollmann et al.,31 was conducted by our own study group. Hence, the

**TABLE 2. Overall HS and CoG shift by axis**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Group</th>
<th>Time Interval, Mos</th>
<th>Motor Deficit at Map 2 (yes = 1, no = 0)</th>
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<th>HS Shift</th>
<th>CoG Average 2D-Shift, mm</th>
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Average absolute values of differences measured between Maps 1 and 2 for HSs, CoGs, and their combined averages. Values are given for the x axis and y axis individually. In addition, the magnitudes of the vectors of x and y, representing the extent of shift measured at the brain surface level, feature as 2D shift.

Discussion

**Differentiating Between Artifacts and Location Changes**

The first question that needs to be answered with regard to the shifts we measured is whether they were the result of the inaccuracy of our methods, or whether the cortical representations of the muscles analyzed actually changed location in certain patients. To evaluate this, we compared both the extent and orientational components of shifts measured in our study to observations from previous neuronavigated studies describing the retest reliability of nTMS motor mapping in healthy participants. With regard to the pure, average extent of the shifts we measured, our results only marginally exceed the average of inaccuracies (6.7 mm) observed by these studies.6,13,25,30,31,39,40

However, individual measurements in several of our patients deviated far more from this usual range, as reflected in our relatively high SEM values. This is despite our application of the same nTMS protocol as used for a number of these studies. Notably, one these studies, by Sollmann et al.,31 was conducted by our own study group. Hence, the

**FIG. 2. Extent of shift by axis. Column chart shows the average absolute values of shifts recorded along the mediolateral and posteroanterior axes. Whiskers represent the SEM. A Wilcoxon matched-pairs signed-rank test showed the differences to be significant (p = 0.0008).**
deviation from this standard range of shift values in the present study seems unlikely to have been caused by flaws in the nTMS mapping procedure. As for the orientation of these shifts, most studies either found more variability of HS and CoG positions along the mediolateral axis, with relatively stable results on the posteroanterior axis,\textsuperscript{13,25,26,31} or very little variability on either.\textsuperscript{39}

Although Sparing et al.\textsuperscript{33} and Wolf et al.\textsuperscript{40} found the opposite to be true, this seems to have been an exception. Also, the latter study used non-navigated TMS, leaving it open to coil-positioning issues.\textsuperscript{18,30,31} Thus, we view the opposite to be true, this seems to have been an exception.

Interpretation of Data

Under the premise that our measurements were accurate, and the location changes of cortical motor represen-
fore seem possible that a similar process is responsible for the changes we found in our patients, i.e., a process linked directly to the immediate effects of surgery itself, rather than a gradual reorganization of the motor cortex over time.

On the other hand, in our study, the extent of shifts observed tended to correlate with the length of the time intervals between examinations. This seems indicative of long-term plasticity, as opposed to the immediate, intraoperative changes referenced above. The fact that motor function seems to have moved further toward the tumor site, however, would at first appear to be in contrast to recent reports of such long- or medium-term plasticity.28,32 Yet, this need not necessarily be viewed as contradictory.

First, these publications were based on changes observed intraoperatively. In the case of the findings of Southwell et al.,32 previously DCS-positive sites in proximity to tumors were found to be DCS-negative during second operations. Due to the minimization of craniotomy size, however, these DCS mappings cannot be viewed as extensive and complete mappings of the motor cortex. Whereas Southwell et al. revealed changes in individual, specific sites, our study focused on HS and CoG measurements—thereby describing changes in the overall distribution of cortical motor function representation.

Second, a shift of function away from the tumor site may be followed by a subsequent shift in the opposite direction after resection or partial resection of the tumor that induced the initial reorganization. Temporary redistribution of motor function has already been reported in stroke patients,8,23 suggesting that a similar mechanism may be the cause of our observations.

It must be noted that recently published atlases of functional plasticity17 and functional resectability19 found the primary motor cortex to be an area of low plastic potential compared with other cortical areas, including the adjacent premotor cortex. Although this may generally hold true, our results indicate that a certain extent of primary motor cortex plasticity is possible, a finding which in turn is in line with a number of reports.2,5,9–11,16

Limitations of the Study

The main limitation of this study is its relatively small sample size of 22 patients. Some arguments in the Discussion must therefore be seen in the context of findings that, in part, do not exceed trend-level significance. Further studies with more patients need to be conducted to conclusively confirm or deny these findings. Also, because the time between surgery and follow-up mappings seems to be a factor, predetermined follow-up periods, potentially with >1 repeat mapping, could enhance the findings of any future study. Thus, the current study more or
less represents a pilot study to provide sufficient data for estimates of future sample sizes, but not final evidence for tumor-induced functional reorganization of cortical motor areas.

Of course, it is never possible to fully exclude the possibility of edema or lesions interfering with the accuracy of nTMS. However, the likelihood of this happening has, in our estimation, been shown to be sufficiently low. Equally, the normalization process we applied to the images must always find a compromise between accuracy and conformity to the template used. Therefore, slight distortions of the MR images are to be expected.

Visual analysis of screenshots taken during mappings is, by nature, a subjective method of evaluation. It should therefore be seen as mere confirmation of results produced by more objective methods. However, we believe that it is a valid approach, given that the level of detail we deduced from this part of our analysis was kept to a realistic minimum.

Conclusions

nTMS can be used to detect cortical plasticity in patients with glioma. The data that emerged from this study seem to point to a shift of motor function back toward the resection cavity after tumor removal. However, further studies with more participants need to be undertaken for any underlying patterns to be analyzed and established with a satisfactory level of certainty. Whatever the underlying mechanism, plastic reorganization of the cortical representation of motor function seems to occur quite frequently. Using nTMS motor mapping to track this reorganization in patients with glioma on a wider scale could benefit both our understanding of it, as well as, ultimately, the patients involved.

Acknowledgments

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References

3. Brett M, Leff AP, Rorden C, Ashburner J: Spatial normaliza-


Disclosures
Dr. Krieg is a consultant for BrainLAB and Nexstim.

Author Contributions
Conception and design: Krieg. Acquisition of data: Krieg, Conway, Wildschuetz, Moser, Bulubas, Sollmann. Analysis and interpretation of data: Conway, Wildschuetz, Moser, Bulubas, Sollmann, Tanigawa. Drafting the article: Krieg, Conway. Critically revising the article: Krieg. Reviewed submitted version of manuscript: Krieg, Wildschuetz, Moser, Bulubas, Sollmann, Tanigawa, Meyer. Approved the final version of the manuscript on behalf of all authors: Krieg. Statistical analysis: Conway, Krieg, Tanigawa. Administrative/technical/material support: Krieg, Meyer. Study supervision: Krieg, Meyer.

Supplemental Information
Previous Presentations
Portions of this work were presented at the 84th AANS Annual Scientific Meeting, Chicago, IL, April 30–May 4, 2016.

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