Motor areas of the frontal cortex in patients with motor eloquent brain lesions

Lucia Bulubas,^{1,2} Jamil Sabih,^{1,2} Afra Wohlschlaeger, PhD,³ Nico Sollmann, MD,^{1,2} Theresa Hauck,^{1,2} Sebastian Ille, MD,^{1,2} Florian Ringel, MD,¹ Bernhard Meyer, MD,¹ and Sandro M. Krieg, MD, MBA^{1,2}

¹Department of Neurosurgery, ²TUM-Neuroimaging Center, and ³Section of Neuroradiology, Department of Radiology, Klinikum rechts der Isar, Technische Universität München, Germany

OBJECTIVE Because of its huge clinical potential, the importance of premotor areas for motor function itself and plastic reshaping due to tumors or ischemic brain lesions has received increased attention. Thus, in this study the authors used navigated transcranial magnetic stimulation (nTMS) to investigate whether tumorous brain lesions induce a change in motor cortex localization in the human brain.

METHODS Between 2010 and 2013, nTMS motor mapping was performed in a prospective cohort of 100 patients with brain tumors in or adjacent to the rolandic cortex. Spatial data analysis was performed by normalization of the individual motor maps and creation of overlays according to tumor location. Analysis of motor evoked potential (MEP) latencies was performed regarding mean overall latencies and potentially polysynaptic latencies, defined as latencies longer than 1 SD above the mean value. Hemispheric dominance, lesion location, and motor-function deficits were also considered.

RESULTS Graphical analysis showed that motor areas were not restricted to the precentral gyrus. Instead, they spread widely in the anterior-posterior direction. An analysis of MEP latency showed that mean MEP latencies were shortest in the precentral gyrus and longest in the superior and middle frontal gyri. The percentage of latencies longer than 1 SD differed widely across gyri. The dominant hemisphere showed a greater number of longer latencies than the nondominant hemisphere ($p < 0.0001$). Moreover, tumor location–dependent changes in distribution of polysynaptic latencies were observed ($p = 0.0002$). Motor-function deficit did not show any statistically significant effect.

CONCLUSIONS The distribution of primary and polysynaptic motor areas changes in patients with brain tumors and highly depends on tumor location. Thus, these data should be considered for resection planning.

<http://thejns.org/doi/abs/10.3171/2015.11.JNS152103>

KEY WORDS brain tumor; frontal motor areas; motor evoked potentials; premotor areas; transcranial magnetic stimulation; oncology; surgical technique

It is commonly known that the precentral gyrus (PrG) is the location of primary motor areas in the human cortex and is supported by the nonprimary motor areas: the premotor and supplementary motor cortex. Recently, several studies using different techniques have confirmed the existence of motor function located outside the PrG. In 1992, a study using implanted subdural grid electrodes showed frontal primary motor areas that were even more present in patients with brain lesions.²⁸ A study

using intraoperative direct cortical stimulation (DCS) also showed that monopolar as well as bipolar stimulation of the superior frontal gyrus (SFG) and middle frontal gyrus (MFG) evokes motor responses.¹⁰

There was also a recent study that used navigated transcranial magnetic stimulation (nTMS) in healthy volunteers, confirming the existence of primary motor areas in the SFG (Brodmann Areas 6 and 8).²⁷ Within patients with brain tumors, changes in motor-function location

ABBREVIATIONS ADM = abductor digiti minimi; APB = abductor pollicis brevis; BCS = biceps; DCS = direct cortical stimulation; EMG = electromyography; FCR = flexor carpi radialis; GCN = gastrocnemius; IFG = inferior frontal gyrus; MEP = motor evoked potential; MFG = middle frontal gyrus; nTMS = navigated transcranial magnetic stimulation; PMd = dorsal premotor area; PMv = ventral premotor area; PoG = postcentral gyrus; PrG = precentral gyrus; rMT = resting motor threshold; SD = standard deviation; SFG = superior frontal gyrus; SMA = supplementary motor area; TA = tibialis anterior.

SUBMITTED September 6, 2015. **ACCEPTED** November 25, 2015.

INCLUDE WHEN CITING Published online March 11, 2016; DOI: 10.3171/2015.11.JNS152103.

were observed and credited to cortical plastic reshaping.⁵ Moreover, in 3 independent studies preoperative nTMS motor mapping was recently proven to lead to superior functional and oncological outcomes in patients undergoing resection of motor eloquent lesions.^{6,12,14}

In brains with lesions, the premotor areas often play a more important role than in healthy brains^{7,24} because the PrG and the corticospinal tract are impaired by stroke or tumor. Not only was it possible to locate motor areas outside the PrG, but it was also shown that partial resection of the supplementary motor area (SMA) frequently leads to at least transient postoperative motor deficits.^{11,15,30}

Navigated TMS is the only noninvasive technique that is highly comparable to the gold standard of DCS, because both modalities elicit motor evoked potentials (MEPs), with comparable precision. Therefore, we used nTMS to investigate to what spatial extent such lesions cause plastic reshaping.^{9,13,19,26}

This study aimed to investigate the following hypotheses: 1) primary motor areas with short latencies can be found in wide parts of the frontal lobe; 2) the distribution of primary motor areas depends on tumor location; 3) nonprimary/polysynaptic motor areas can be identified via nTMS; and 4) the distribution of polysynaptic motor areas depends on hemispheric dominance and tumor location.

Methods

Study Ethics

The study was designed and performed in accordance with ethical standards of our university and the Declaration of Helsinki. It was approved by the local ethics committee. Prior to each nTMS examination, written informed consent was obtained from all patients.

Study Design

This study's design consisted of 2 parts: 1) the graphical analysis of nTMS motor maps depending on tumor location; and 2) the statistical latency analysis of the measured MEPs.

The statistical latency analysis itself also consisted of 2 separate steps: 1) the mean latency analysis, including all 100 patients' latencies, which examined latency lengths according to the gyri in which they were elicited; and 2)

the subgroup analysis, in which patients were divided into groups according to 3 subfactors: hemispheric dominance, tumor location, and paresis grade.

Graphical Analysis

Using SPM8 software (Functional Imaging Laboratory, Wellcome Trust Center for Neuroimaging, Institute of Neurology, University College London), we performed spatial normalization of each patient's 3D MRI sequence and upper-extremity nTMS motor map. Using MRICro software (McCausland Center for Brain Imaging), we created a mask of the tumor so that this area of pathological brain tissue was excluded from determining the algorithm used for normalization to standardized space, as reported previously.¹ The normalization results were manually checked. Normalization was repeated until the highest possible congruence of normalized brain and brain template was reached, considering the position of landmarks such as the cranium and ventricles. The resulting normalized motor maps of each tumor location group (frontal, rolandic, postcentral, temporodorsal, and parietal) were then fused and are presented within standardized brain templates (Fig. 1, Table 1). MRICron (McCausland Center for Brain Imaging) was also used for creation of 3D graphics included in this article.

Latency Analysis

Prior to analysis, nTMS mapping results were manually reviewed for accuracy of the automatic latency determination and location of MEP at the nTMS mapping station (eXimia 3.2 and eXimia 4.3; Nexstim). The latencies of each of the 6 muscles were then analyzed depending on the location of the MEP.

First, we tested differences of mean latency values among the 4 gyri (PrG, SFG, MFG, and postcentral gyrus [PoG]) in every muscle group (abductor pollicis brevis [APB], abductor digiti minimi [ADM], flexor carpi radialis [FCR], biceps (BCS), tibialis anterior [TA], and gastrocnemius [GCN]) using the Kruskal-Wallis test for nonparametric distribution and Dunn's test for multiple comparisons of ranks as a post hoc test (Fig. 2, Table 2).

Second, to differentiate primary and nonprimary motor areas, we defined latencies longer than 1 standard deviation (SD) above the mean value as transmitted via more

FIG. 1. Overview of location of motor function for the 5 tumor groups (frontal, rolandic, postcentral, temporodorsal, and parietal). These data were obtained by a fusion of normalized nTMS motor maps according to tumor location and overlay with a standardized brain template. Only upper-extremity muscles (APB, ADM, FCR, and BCS) are shown. Red areas show the highest overlap of normalized motor maps among all patients per group; blue areas show the lowest overlap. Figure is available in color online only.

TABLE 1. Patient demographic data and tumor group characteristics*

Tumor Group	No. of Pts	Mean Age of		Sex		Tumor Entity					Tumor Site		Tumor Dominance		Motor Function		Prior Surgery		
		Pts, Yrs		M	F	I	II	III	IV	Met	O	Rt	Lt	D	ND	NP	P	1st	2nd
Frontal	24	51.5	63	38	29	13	29	13	29	13	17	58	42	50	50	83	17	29	71
Rolandic	35	59.9	54	46	11	6	29	6	29	37	17	46	54	49	49	63	37	17	83
Postcentral	17	45.2	65	35	12	12	35	12	35	35	6	76	24	35	53	65	35	24	76
Temporodorsal	5	44.6	20	80	20	—	60	—	60	—	20	60	40	40	60	80	20	40	60
Parietal	19	57.1	58	42	—	16	63	16	63	16	5	74	26	26	63	79	21	16	84
Total	100	54.1	57	43	43	14	14	10	38	25	13	60	40	42	53	72	28	22	78

D = dominant; II = WHO Grade II glioma; III = WHO Grade III glioma; IV = WHO Grade IV glioblastoma; Met = metastasis; ND = nondominant hemisphere; NP = no paresis; O = others (e.g., arteriovenous malformation or cavernoma); P = paresis; Pts = patients; — = no data; 1st = patients' first surgery; 2nd = patients had prior surgery.

* Detailed overview of group size, mean age and sex of patients, tumor entity, tumor site, dominance of tumor hemisphere, patients' preoperative motor functions, and prior brain surgery (in patients with recurrent tumors at actual motor mapping) of the 5 tumor groups (frontal, rolandic, postcentral, temporodorsal, and parietal). Handedness was not obtained from all patients due to language difficulties. All values are expressed as percentages unless otherwise stated.

than 1 synapse. This distribution was tested separately for each muscle and each gyrus, depending on: 1) hemispheric dominance (dominant vs nondominant; Fig. 3, Tables 3 and 4); 2) tumor location (frontal, rolandic, postcentral, and parietal tumor groups vs temporal tumor group as the control group; Fig. 4, Tables 5 and 6); and 3) influence of tumor on motor function (without or with a paresis; Tables 7 and 8).

Group differences were tested using the chi-square test with absolute values of latencies > 1 SD. All results in this article are presented as the mean $\pm$ SD (GraphPad Prism 6.05). The level of significance was 0.05 for each statistical test.

Patient Population

We enrolled 100 patients with motor eloquent brain lesions scheduled for tumor resection into our study; only patients with intraaxial tumors (e.g., gliomas or metastases) were enrolled (Table 1). Between 2010 and 2013, the patients underwent preoperative MRI followed by nTMS mapping of the motor cortex. Navigated TMS-elicited MEPs were found in all patients in at least 1 upper-extremity muscle; in 34 of the 100 patients, MEPs were also found for lower-extremity muscles. Patients were divided into groups, according to their tumor location in relation to PrG, as follows: 1) the frontal tumor group, which included tumors frontal to PrG (SFG, MFG, and inferior frontal gyrus [IFG]); 2) the rolandic tumor group (PrG); 3) the postcentral tumor group (PoG); and 4) the parietal tumor group (dorsal to PoG). Because PoG itself is a partial origin of corticospinal tract neurons, although this is not described for the remaining parietal lobe, we decided to separate these 2 groups. A fifth group of temporodorsal tumors was included as the control group (Table 1).

Magnetic Resonance Imaging

All patients underwent MRI on a 3-T MR scanner in combination with an 8-channel phased-array head coil (Achieva 3T; Philips Medical Systems) for contrast-enhanced 3D gradient echo sequence and T2-weighted FLAIR imaging. The contrast-enhanced 3D gradient echo sequence data set was transferred to the nTMS system (eXimia 3.2 and eXimia 4.3) and was used for anatomical coregistration prior to the nTMS mapping.

Navigated TMS Mapping of the Motor Cortex

We performed nTMS motor cortex mapping of the hemisphere with the lesion prior to surgery. Two different nTMS systems (eXimia 3.2 and eXimia 4.3) were used. Both systems used a biphasic figure-of-eight TMS coil with a diameter of 50 mm, which was attached to an infrared tracking system (Polaris Spectra), as reported earlier.^{5,13,19,23,26} Navigated TMS motor mapping was performed by 6 experienced users. The time for performing motor mapping ranged from 30 to 120 minutes with a median of 45 minutes, mostly depending on the ability of the patient to cooperate. MEPs were recorded by electromyography (EMG). According to the mapping protocol, which was also described previously,^{5,13,19,23,26} the resting motor threshold (rMT) of the tumor hemisphere was de-

FIG. 2. The mean MEP latencies for each muscle and each gyrus. Box-and-whiskers plots of mean MEP latency values of all 100 patients for each gyrus (PrG, SFG, MFG, and PoG), plotted for each muscle, are given. Kruskal-Wallis testing of differences among latencies of the 4 gyri (PrG, SFG, MFG, and PoG) was performed separately for each muscle and showed significant results for ADM and FCR only. For mean MEP latencies $\pm$ SD, see Table 2. n.s. = not significant.

terminated, and mapping was performed using 110% rMT for the upper extremity and 130% rMT for the lower extremity.^{5,13,19,23,26} The measured muscles were as follows: APB, ADM, FCR, and BCS for the upper extremity; and TA and GCN for the lower extremity. The electric muscle activity was continuously monitored by EMG using pregelled Ag/AgCl electrodes (Neuroline 720; Ambu). Finally, the positive upper- and lower-extremity motor mapping points (MEP threshold $\geq$ 50 mA in at least 1 of the measured muscles) were exported as Digital Imaging and Communications in Medicine file format for further analysis.

Results

Navigated TMS Mapping

The nTMS mappings of hemispheres with lesions were performed in all patients prior to surgery. The mean rMT

was $33.8\% \pm 9.3\%$ of the maximum stimulator output. We had 5008 positive motor points with a value greater than threshold ($\geq$ 50 mA) in at least 1 muscle and 8794 single MEPs, for an average of 1.8 MEPs per positive motor point due to overlapping representation of different muscles. On average, 50.1 ± 30.3 positive motor points were identified per nTMS mapping (median 42.5 positive motor points, range 10–167).

Graphical Analysis

The fusion of normalized motor maps from patients with comparable tumor locations (Fig. 1) showed that the main motor function (highest overlap, red) was located in the commonly expected area around the hand knob of the PrG. Yet, lower-overlap motor areas (blue) spread widely and up to SFG, MFG, and PoG. Moreover, all 5 tumor groups showed a high overlap of motor function (yellow-green) on the posterior part of the MFG. Only some tu-

TABLE 2. Mean MEP latency values of all patients combined*

Gyrus	APB	ADM	FCR	BCS	TA	GCN
PrG	23.53 $\pm$ 2.60	23.54 $\pm$ 2.79	18.05 $\pm$ 2.43	15.95 $\pm$ 3.12	32.64 $\pm$ 2.80	34.99 $\pm$ 4.41
SFG	23.43 $\pm$ 2.43	23.93 $\pm$ 3.07	18.22 $\pm$ 2.29	16.46 $\pm$ 3.26	32.75 $\pm$ 4.06	33.24 $\pm$ 3.79
MFG	23.69 $\pm$ 2.20	24.00 $\pm$ 2.39	18.56 $\pm$ 2.56	16.38 $\pm$ 3.35	35.00 $\pm$ 3.30	33.07 $\pm$ 3.49
PoG	23.54 $\pm$ 2.59	24.00 $\pm$ 3.33	18.53 $\pm$ 2.88	16.67 $\pm$ 3.20	32.37 $\pm$ 1.64	33.52 $\pm$ 3.65
All gyri	23.54 $\pm$ 2.54	23.72 $\pm$ 2.89	18.21 $\pm$ 2.54	16.17 $\pm$ 3.19	32.67 $\pm$ 3.01	34.15 $\pm$ 4.17

* Mean MEP latency values $\pm$ SD (msec) of all 100 patients for each gyrus (PrG, SFG, MFG, and PoG) and for all gyri. All 6 muscles are reported individually. For box-and-whiskers plots, see Figure 2.

FIG. 3. Latency distribution > 1 SD in both hemispheres. Percentage of latencies longer than 1 SD above mean latency as a measure for polysynaptic MEP in the dominant and nondominant hemispheres are shown. Latencies of all 100 patients and of all 6 muscles (APB, ADM, FCR, BCS, TA, and GCN) are counted together and demonstrated separately for each gyrus (PrG, SFG, MFG, and PoG). The chi-square test was used to determine differences in the distribution of latencies > 1 SD within the 4 gyri between the dominant and nondominant hemispheres ($p < 0.0001$). Figure is available in color online only.

mor groups (frontal, postcentral, and rolandic) showed this high overlap, also in the SFG. In general, motor function in the rolandic and temporal tumor groups spread to the least extent, whereas for parietal lesions, cortical motor function showed the widest spread.

General Latency Analysis

A total of 8774 MEP latencies were included in the analysis, in the following muscles: 2758 for APB, 2711 for

ADM, 2040 for FCR, 664 for BCS, 429 for TA, and 172 for GCN. For the latency analysis, we first determined mean latencies and the SD of all latencies in each gyrus for each muscle (box-and-whiskers plots in Fig. 2, mean values $\pm$ SD in Table 2). As known from the literature,²² APB and ADM showed longer latencies, whereas FCR and BCS showed shorter latencies due to the shorter distances to the measured muscles. In general, lower-extremity muscle latencies were, as expected, longer than upper-extremity muscle latencies. Considering the gyri, ADM, FCR, and BCS had the lowest mean latencies in PrG. Mean latencies in frontal gyri (SFG and MFG) were longer than in PrG for ADM, FCR, BCS, and TA. In APB, only MFG and PoG showed longer mean latency than PrG.

Distribution of MEP Latencies Was Dependent on Hemispheric Dominance

To determine patterns influencing the distribution of motor function, we compared the number of latencies longer than 1 SD above mean values as a model for polysynaptic latencies separately in every gyrus. First, we compared latencies longer than 1 SD above mean values of all 6 muscles together in the dominant versus nondominant hemispheres (Tables 3 and 4, Fig. 3). The percentage of latencies > 1 SD showed that there are significantly more latencies > 1 SD in the dominant hemisphere compared with the nondominant hemisphere ($p < 0.0001$). Additionally, in the dominant hemisphere, these latencies were more present in the frontal gyri (SFG and MFG), whereas in the nondominant hemisphere, the frontal gyri contained the fewest latencies > 1 SD.

Regarding the 3 muscles with the most measured latencies (APB, ADM, and FCR) individually, corresponding results were achieved, although significantly only for ADM ($p = 0.011$, Table 3): Each of these muscles showed most latencies > 1 SD in frontal gyri of the dominant hemisphere, in the MFG (APB), the SFG (ADM), or both SFG and MFG (FCR). In general, all 3 muscles showed more latencies > 1 SD in the dominant hemisphere compared with the nondominant hemisphere.

Additionally, we investigated mean MEP latencies of every muscle in each gyrus. We observed that although there might be more latencies > 1 SD in a hemisphere (Table 3), this does not necessarily lead to an increased mean MEP latency in the same hemisphere (Table 4).

TABLE 3. Latency distribution > 1 SD in dominant and nondominant hemispheres for each muscle*

Gyrus	APB		ADM		FCR		BCS		TA		GCN	
	D	ND	D	ND	D	ND	D	ND	D	ND	D	ND
PrG, %	15	13	13	16	14	13	20	18	16	11	18	15
SFG, %	15	11	18	11	20	20	5	10	16	17	19	14
MFG, %	18	15	13	12	19	12	25	22	13	—	33	—
PoG, %	12	13	17	15	13	15	10	16	17	18	13	29
p Value	0.10		0.011		0.077		0.071		0.15		0.10	

* Percentage of latencies longer than 1 SD above the mean latency as a measure for polysynaptic MEP. Latencies of all 100 patients are counted and plotted separately for the dominant (D) and nondominant (ND) hemispheres for each gyrus (PrG, SFG, MFG, and PoG) and for each muscle (APB, ADM, FCR, BCS, TA, and GCN).

TABLE 4. Mean MEP latency in the dominant and nondominant hemispheres*

Gyrus	APB			ADM			FCR			BCS			TA			GCN		
	D	ND	D	D	ND	D	D	ND	D	D	ND	D	D	ND	D	D	ND	D
PrG	23.73 ± 2.52	23.33 ± 2.69	23.93 ± 3.11	23.23 ± 2.43	23.23 ± 2.43	18.23 ± 2.52	17.87 ± 2.36	15.81 ± 3.33	16.26 ± 2.92	33.06 ± 2.47	32.01 ± 3.12	33.24 ± 4.53	36.78 ± 3.47					
SFG	23.36 ± 2.37	23.54 ± 2.54	24.51 ± 3.44	22.82 ± 1.86	18.81 ± 2.36	17.30 ± 1.84	17.89 ± 3.15	13.89 ± 1.54	32.80 ± 4.17	32.17 ± 1.93	33.39 ± 4.01	32.23 ± 1.28						
MFG	23.62 ± 2.37	23.79 ± 1.96	24.22 ± 2.73	23.81 ± 2.03	18.90 ± 2.92	18.36 ± 2.31	16.21 ± 3.52	17.48 ± 1.44	35.00 ± 3.30									
PoG	23.89 ± 2.77	23.31 ± 2.44	25.13 ± 3.69	23.17 ± 2.75	19.51 ± 3.36	17.98 ± 2.52	17.69 ± 3.24	15.80 ± 2.92	32.46 ± 1.27	31.81 ± 1.72	30.73 ± 0.54	36.76 ± 3.36						

* Mean MEP latency values (msec) for individual muscles in each gyrus (PrG, SFG, MFG; and PoG) ± SD.

Distribution of MEP Latencies Was Dependent on Tumor Location Group

To detect differences in patterns of distribution of polysynaptic latencies among the 5 tumor locations, we compared each group to the temporal tumor group used as a control (Fig. 4). We did not include hemispheric dominance as a factor in this analysis. In the control group, most latencies > 1 SD were found in the SFG and MFG. Patients with frontal tumors showed fewer latencies > 1 SD in the frontal cortex than patients in the control group ($p = 0.013$). Patients with parietal tumors showed a very different distribution of latencies > 1 SD than patients in the control group, with only a few latencies in the MFG and PrG ($p = 0.0002$). In patients with tumors affecting the PoG, most latencies > 1 SD were found in the PrG itself, and fewer latencies were found in the PoG, which differed from the control group ($p = 0.013$). Patients with rolandic tumors showed almost the same number of latencies > 1 SD in the PrG and PoG as patients in the control group but fewer latencies in frontal gyri and especially small numbers in the SFG, although this did not achieve statistical significance ($p = 0.23$).

When analyzing statistical differences between individual muscles, APB, ADM, and FCR were the only muscles for which single-muscle analysis was reasonable due to the overall number of measured latencies. Significantly different results were only obtained for APB. When comparing the distribution of APB latencies only with the overall analysis (for which all 6 muscle latencies were calculated together (Table 5, Fig. 4), only the temporal tumor group differed, with clearly more latencies > 1 SD in the PrG and fewer in the SFG. Yet, we attribute these group differences to a smaller data set in the APB-only latency group and see higher reliability in the overall latency analysis.

To complete the analysis, we also investigated the mean MEP latency of each muscle in each gyrus among the 5 tumor groups. As reported above (Tables 3 and 4), we observed that even though there is a higher number of latencies > 1 SD above the mean value in a tumor group (Table 5), this does not necessarily mean that there is also an increase in mean MEP latency value nor does this lead to a larger SD (Table 6).

Distribution of MEP Latencies Depending on Motor Function

To consider preoperatively impaired motor function as a confounding factor, we also compared the number of latencies > 1 SD in patients with or without preoperative paresis due to tumor or edema. Again, we analyzed only APB, ADM, and FCR, because these muscles showed the highest counts of motor data and therefore the highest reliability. This analysis showed no significant differences between patients with or without preoperative paresis (p [APB] = 0.19, p [ADM] = 0.53, p [FCR] = 0.90; Table 7).

Additionally, we compared mean MEP latencies ± SD of each muscle in all 4 gyri among patients with and without paresis for these 3 muscles (Table 8). We did not observe any connection between a larger mean MEP latency and a higher number of latencies > 1 SD above the mean value in a gyrus. Corresponding results were also found regarding hemispheric dominance (Table 4) and tumor lo-

FIG. 4. Latency distribution > 1 SD among the 5 tumor groups. Percentages of latencies longer than 1 SD above the mean latency as a measure for polysynaptic MEP are shown. Latencies of all 100 patients and of all 6 muscles (APB, ADM, FCR, BCS, TA, and GCN) are counted together. The 5 tumor groups (frontal, rolandic, postcentral, and parietal tumor groups compared with the temporal tumor group as control) are illustrated separately for each gyrus (PrG, SFG, MFG, and PoG). The chi-square test was used to determine differences in the distribution of latencies > 1 SD within the 4 gyri between the tested tumor groups and the control tumor group. Figure is available in color online only.

cation (Table 6). Altogether, an increase of latencies > 1 SD did not correlate with larger mean MEP latencies.

Illustrative Case

Intraoperative Confirmation via DCS

We provide an illustrative case for the clinical use of data presented in our article. In a 48-year-old man suffering from a left-sided anaplastic astrocytoma (WHO Grade III) of the frontal lobe, preoperative nTMS data were implemented in the intraoperative neuronavigation and showed primary motor areas in the SFG and MFG. After placement of a strip electrode, even stimulation of the most frontal contact electrode with 10-mA train-of-five stimulation elicited MEPs in the SFG with very high amplitudes of 2 mV in the ADM (Fig. 5). Resection of these nTMS- and DCS-positive motor areas in SFG and MFG was avoided despite complete resection of the tumor. The patient did not show any preoperative nor any new postoperative motor deficits.

Navigated TMS has been repeatedly shown to correlate well with DCS in the literature.^{13,19,26} This was also confirmed in this illustrative clinical case, in which anterior motor areas in the SFG and MFG could be identified via nTMS and confirmed by even high-amplitude MEP responses with DCS.

Discussion

Primary Motor Areas of the Frontal Lobe

Studies on primates allowed a detailed classification of frontal premotor areas. It was possible to identify 6 premo-

tor areas (ventral premotor area [PMv]; dorsal premotor area [PMd]; SMA; and rostral, dorsal, and ventral cingulate motor areas), located on the lateral surface and medial wall of the hemispheres, which have direct projections to the spinal cord and for which intracortical stimulation leads to forelimb movement.^{2,3}

Uematsu et al. showed that it is possible to elicit primary motor responses outside the common M1 area in humans by using subdural grid electrodes in patients with seizure disorders. Patients with abnormalities in MRI (e.g., brain lesions) even had most of their primary motor responses located in more anterior areas than patients with no abnormalities.²⁸ Kombos et al. used direct monopolar and bipolar cortical stimulation for determining motor responses in patients with tumors during surgery and found that up to 37.85% of MEPs were located frontal to the PrG.¹⁰

Those findings correspond well with our results, where motor areas spread into the SFG and MFG (Fig. 1). Unfortunately, the definition of primary motor areas varies markedly in the literature. It ranges from the original definition of “motor areas” (with direct corticospinal projections located only in M1⁸) to frontal areas in which motor responses can be elicited after stimulation, although not in M1.¹⁰ This leaves space for all sorts of intermediate stages such as stimulation-sensitive, frontal nonprimary motor areas with direct corticospinal projections.²⁷

Distribution Depends on Tumor Location

The location of motor function in the human brain is not static; it is a dynamic process caused by the plastic reshaping of cortical and subcortical functions. There have been studies on primates showing that PMd and PMv are of ma-

TABLE 5. Latency distribution > 1 SD among tumor groups by muscle*

Gyrus	APB					ADM					FCR				
	Fr	Ro	PoC	Te	Pa	Fr	Ro	PoC	Te	Pa	Fr	Ro	PoC	Te	Pa
PrG, %	13	14	18	22	13	12	17	18	13	13	13	17	13	10	12
SFG, %	17	11	15	10	16	12	14	7	27	24	15	24	23	13	6
MFG, %	14	18	14	13	16	11	15	14	20	10	15	18	20	40	13
PoG, %	12	15	14	13	17	14	16	12	9	15	9	15	14	22	14
p Value	0.0056	0.014	0.015	—	0.0001	0.26	0.50	0.75	—	0.10	0.45	0.96	0.35	—	0.85

Fr = frontal tumor group; Pa = parietal tumor group; PoC = postcentral tumor group; Ro = rolandic tumor group; Te = temporal tumor group.
* Percentage of latencies longer than 1 SD above the mean latency of all 100 patients as a measure for polysynaptic MEP. All 5 tumor groups are outlined separately for each gyrus and individual muscle. Only APB, ADM, and FCR are plotted due to the small number of available MEP latencies for BCS, TA, and GCN. The temporal tumor group served as the control.

TABLE 6. Mean MEP latency for the 5 tumor groups*

Gyrus	APB					ADM					FCR				
	Fr	Ro	PoC	Te	Pa	Fr	Ro	PoC	Te	Pa	Fr	Ro	PoC	Te	Pa
PrG	23.45 ± 2.50	23.74 ± 3.04	23.34 ± 2.14	22.57 ± 2.05	23.93 ± 2.41	23.76 ± 2.92	23.66 ± 3.02	22.88 ± 1.79	22.51 ± 1.70	23.89 ± 2.89	18.33 ± 2.71	17.99 ± 2.76	17.29 ± 1.85	18.47 ± 1.25	18.11 ± 2.08
SFG	24.11 ± 2.22	22.94 ± 2.51	22.80 ± 1.92	24.20 ± 2.02	24.91 ± 2.65	25.14 ± 3.45	23.23 ± 2.80	22.62 ± 1.43	22.75 ± 1.74	25.58 ± 3.58	18.72 ± 2.60	19.06 ± 2.41	17.38 ± 1.62	19.81 ± 1.52	17.60 ± 2.38
MFG	24.60 ± 1.95	22.97 ± 2.30	22.81 ± 1.85	23.79 ± 1.95	24.08 ± 2.08	24.69 ± 2.68	23.20 ± 1.81	23.30 ± 1.37	21.81 ± 3.06	24.15 ± 2.07	18.94 ± 2.49	18.36 ± 2.77	18.47 ± 2.30	18.74 ± 0.95	18.28 ± 2.59
PoG	23.52 ± 3.33	24.26 ± 2.53	23.23 ± 2.10	21.35 ± 1.00	23.43 ± 2.21	24.73 ± 3.95	24.46 ± 3.00	21.74 ± 2.03	24.82 ± 2.51	23.86 ± 3.12	18.66 ± 2.46	19.12 ± 3.46	17.07 ± 2.11	19.54 ± 2.45	18.41 ± 2.36

* Mean MEP latency values (msec) of individual muscles in each gyrus (PrG, SFG, MFG, and PoG) are plotted separately for each tumor group. Only APB, ADM, and FCR are plotted due to the small number of available MEP latencies for BCS, TA, and GCN.

TABLE 7. Latency distribution > 1 SD considering motor deficit for single muscles*

Gyrus	APB		ADM		FCR	
	NP	P	NP	P	NP	P
PrG, %	14	10	14	13	14	13
SFG, %	16	5	17	13	16	23
MFG, %	18	12	15	19	14	23
PoG, %	13	8	14	18	14	14
p Value	0.19		0.53		0.90	

* Percentage of latencies longer than 1 SD above the mean latency of all 100 patients as a measure for polysynaptic MEP. Patients without paresis (NP) are shown on the left; patients with any grade of paresis (P) are shown on the right. Results are plotted separately for each gyrus (PrG, SFG, MFG, and PoG), and individual muscle (APB, ADM, and FCR). The chi-square test was used to determine differences in the distribution of latencies > 1 SD within the 4 gyri between the nonparetic and the paretic groups.

for importance for maintaining motor functions when M1 is impaired.¹⁶ Another study on patients showed that TMS to the ipsilesional PMd affects movement of the paretic hand in patients after rolandic stroke.⁷ These studies imply that nonprimary motor cortices might be able to take over motor function if the primary motor cortex is affected.

The frontal regions shown in Fig. 1 correspond well with the location of nonprimary motor areas. They might even be in accordance with the location of PMd (posterior part of MFG)^{4,7} and SMA (rostral to the PrG on the medial wall of the hemisphere,^{18,25} projecting in lateral view used for nTMS mapping on the posterior part of the SFG), although we did not restrict our measurement to those regions.

Nonprimary/Polysynaptic Motor Areas Can Be Identified via nTMS

It is still not known whether frontal premotor areas work only through connections to the PrG or whether there are direct pathways to the spinal cord. In primates, the existence of those direct spinal projections was shown.² Fridman et al. showed that in affected hemispheres of patients who had rolandic stroke, MEPs elicited in PMd have shorter latencies than those MEPs elicited in M1, and assumed that this was caused by the PMd of the hemisphere with lesion having corticomotoneuronal connections similar to M1. However, in healthy volunteers and nonlesional hemispheres, PMd seemed to have longer latencies than M1.⁷ Teitti et al. also found frontally evoked MEPs (Brodmann

Areas 6 and 8), with latencies shorter than those of M1. These authors assumed that those might originate from direct spinal projections.²⁷ Nevertheless, Teitti et al. examined 15 healthy volunteers, whereas Fridman et al. examined 4 patients who had suffered strokes and 5 healthy volunteers as a control group.

Our latency analysis of 100 patients with brain tumors shows that there are shorter latencies in the PrG and longer latencies in both frontal gyri for most of the muscles. Because the difference between these mean latencies is rather small, our data are in accordance with direct motor projections within nonprimary motor cortices, which lead to fast muscle responses. But there were, at least in our cohort of patients with brain tumors, also many long latency projections (presumably polysynaptic) identified via nTMS, leading to higher mean values in latency analysis (Figs. 2–4).

We used mean values and the percentage of latencies longer than 1 SD above the mean value to distinguish between monosynaptic and polysynaptic motor areas. There are definitely more factors that influence MEP latency, such as height or stimulus intensity,²⁹ but these confounders are minimized by the size of our patient cohort, and we can use the number of latencies > 1 SD as a model for polysynaptic neuronal activation.

Long Latencies and Hemispheric Dominance

Other studies did not show any differences of MEP latency dependent on handedness and hemispheric dominance.^{17,29} Those studies mainly investigated healthy subjects, whereas our study cohort enrolled only subjects suffering from intraaxial tumors, which can impair cortical and subcortical motor function. The main effect seen in our patient cohort was a higher number of longer latencies, which we assume was due to polysynaptic MEP transduction in frontal cortices, mostly in the dominant hemisphere (Fig. 3).

Still, there are differences in the organization of dominant and nondominant hemispheres. There have been studies showing the importance of the SMA of the dominant (left) hemisphere.²¹ Moreover, a stronger coupling between SMA and M1 was observed in the dominant hemisphere compared with the nondominant hemisphere.²⁰ According to these data, we assume that there are more projections from SMA or other frontal areas within the SFG and MFG to the PrG in the dominant hemisphere than the nondominant hemisphere. These are shown in our study by longer and thus polysynaptic MEP latencies in frontal cortices (i.e., SFG and MFG; Fig. 3).

TABLE 8. Mean MEP latency in patients with or without paresis*

Gyrus	APB		ADM		FCR	
	NP	P	NP	P	NP	P
PrG	23.45 ± 2.56	23.76 ± 2.74	23.57 ± 2.62	23.47 ± 3.26	18.13 ± 2.37	17.78 ± 2.56
SFG	23.37 ± 2.35	23.86 ± 2.90	23.89 ± 2.80	24.11 ± 3.91	18.50 ± 2.33	17.13 ± 1.76
MFG	23.77 ± 2.20	23.27 ± 2.19	23.69 ± 1.95	25.69 ± 3.58	18.60 ± 2.63	18.29 ± 2.03
PoG	23.31 ± 2.41	24.33 ± 2.99	23.78 ± 2.95	24.73 ± 4.29	18.49 ± 2.82	18.66 ± 3.04

* Mean MEP latency values (msec) of individual muscles in each gyrus (PrG, SFG, MFG, and PoG), plotted for patients without paresis (NP) and patients with any grade of paresis (P).

FIG. 5. Intraoperative confirmation via DCS. This glioma (WHO Grade III) case, which had very frontal motor areas with short latencies, was also confirmed intraoperatively. The **upper right** panel shows the intraoperative neuromonitoring by EMG of the hand muscles. The other 3 panels show the location of the stimulated strip electrode via intraoperative neuronavigation (= IntraOp Point #01), which elicited MEP in the SFG with 10-mA train-of-five stimulation. **Green** shows the preoperative nTMS data implemented in the neuronavigation data. Flexor = FCR muscle; Hth = ADM muscle; Thenar = APB muscle; Tib Ant = TA muscle. Figure is available in color online only.

Long Latencies and Tumor Location

Another important issue is detection of how tumor location influences motor function. In the latency analysis, patients with temporal tumors had the most latencies > 1 SD above the mean value (which we assume were polysynaptic projections) located in frontal gyri, suggesting many projections from the SFG and MFG to the PrG (Fig. 4). In the frontal and postcentral tumor groups, fewer latencies > 1 SD were found in the directly impaired gyrus (frontal gyrus for the frontal tumor group, PoG for the postcentral tumor group). This might suggest that polysynaptic projections are being disturbed earlier than monosynaptic projections by structural changes.

When the rolandic and temporal tumor groups were compared, both groups showed many presumably polysynaptic latencies in total and in the MFG compared with the other groups (Fig. 4). The MFG is an area that corresponds well with PMd, as assumed above. Surprisingly, the fewest latencies > 1 SD found in the SFG (which corresponds to SMA) were present in patients with rolandic tumors. The SMA in primates was shown to include direct spinal projections,^{2,3} which in our case seems to be represented by a higher number of monosynaptic latencies. This implies that the SMA overtakes direct corticospinal, fast

motor responses due to lesions in M1, whereas the PMd remains a supporting region with polysynaptic projections to the remaining primary motor areas.

Long Latencies and Preoperative Paresis

When comparing patients with or without paresis, we did not observe any statistically significant differences in distribution of long latencies for APB, ADM, or FCR (Table 7). Although there were variable differences among these groups within 1 gyrus, we could not observe any effect of 1 of the groups leading to an increased or decreased number of latencies > 1 SD in all 4 gyri. Therefore, the changes in motor function that we observed and described can indeed be seen as a result of hemispheric dominance (Table 3, Fig. 3) and tumor location (Table 5, Fig. 4), and they are not influenced by a patient's motor function deficit.

Clinical Implications

Detecting those primary motor areas outside the PrG prior to surgery is important for preoperative planning. Thus, the finding of our study might be the reason for superior outcome of patients who underwent preoperative nTMS mapping in 3 independent studies.^{6,12,14}

Still, the existence of those widely spread motor areas, such as within SFG and MFG, does not necessarily mean these areas are absolutely essential for motor function. There are motor eloquent regions within the SMA or SFG, because surgery in this region often causes transient motor deficits that fully recover over time.^{11,15,30} Moreover, the inactivation of the PMd and PMv in monkeys with lesioned M1 led to worsening motor functions, which also implies the essential roles of the PMd and PMv in brains with a lesion within the PrG.¹⁶

Thus, further studies should target the motor eloquence of nTMS-positive motor areas in patients with brain tumors. The correlation of resected nTMS-positive motor areas with patients' postoperative motor deficits has to be shown to actually prove the essential role of these regions (i.e., SFG and MFG) for primary motor function in the human brain.

Limitations

In the enrolled cohort, there are huge differences among patients, individual brain anatomy, tumors, tumor size, malignancy, and speed of growth. There are many subfactors that also might have effects on measured MEPs, such as patient age, sex, height, and medication. It is important to keep in mind that 22% of our patients underwent operations on recurrent tumors, and most of these patients also underwent radiotherapy or chemotherapy; these factors could also influence our results (Table 1). We tried to minimize these effects by spatial normalization, dividing patients according to tumor location, and considering group characteristics. However, group size was still too small to additionally analyze chemo- or radiotherapy effects.

Moreover, there are technical limitations to the graphical analysis by spatial normalization; in brains with lesions, the lesion tends to impair the process of normalization. This effect can be minimized by masking the lesion, as was done in this study, but interference still cannot be fully discounted.¹

Mathematical limitations to our study are caused by different sizes of data sets. APB and ADM are muscles for which motor responses can be elicited easily; therefore, we obtained the largest data sets for these muscles. Lower-extremity muscle MEPs, however, are more difficult to obtain, leading to smaller data sets for these examined muscles. Numbers of latencies > 1 SD also showed a huge amount of variability among the analyzed factors and gyri.

In this study, we did not correlate nTMS-positive motor points to intraoperatively elicited DCS-positive motor points in all patients, nor did we correlate the extent of resection of nTMS-positive motor points to postoperative motor deficits. These correlations would exceed the scope of this pilot study. Thus, these questions will be the topics of future studies by our group.

Conclusions

This study is based on a large cohort of patients and provides additional information for fundamental theories on functionality and plastic changes in the human brain. We showed that primary motor areas could be found in wide parts of the frontal lobe by using nTMS and there-

fore confirmed intraoperative DCS data by a noninvasive technique. Additionally, nonprimary, polysynaptic motor areas can also be identified via nTMS in these regions. The distribution of these motor areas (primary as well as nonprimary) depends on tumor location, which needs to be considered preoperatively for individual resection planning.

Acknowledgments

The study was completely financed by institutional grants from the Department of Neurosurgery and the Section of Neuroradiology of Technische Universität München.

References

1. Brett M, Leff AP, Rorden C, Ashburner J: Spatial normalization of brain images with focal lesions using cost function masking. **Neuroimage** **14**:486–500, 2001
2. Dum RP, Strick PL: Motor areas in the frontal lobe of the primate. **Physiol Behav** **77**:677–682, 2002
3. Dum RP, Strick PL: The origin of corticospinal projections from the premotor areas in the frontal lobe. **J Neurosci** **11**:667–689, 1991
4. Fink GR, Frackowiak RS, Pietrzyk U, Passingham RE: Multiple nonprimary motor areas in the human cortex. **J Neurophysiol** **77**:2164–2174, 1997
5. Forster MT, Senft C, Hattingen E, Lorei M, Seifert V, Szélenyi A: Motor cortex evaluation by nTMS after surgery of central region tumors: a feasibility study. **Acta Neurochir (Wien)** **154**:1351–1359, 2012
6. Frey D, Schilt S, Strack V, Zdunczyk A, Rösler J, Niraula B, et al: Navigated transcranial magnetic stimulation improves the treatment outcome in patients with brain tumors in motor eloquent locations. **Neuro Oncol** **16**:1365–1372, 2014
7. Fridman EA, Hanakawa T, Chung M, Hummel F, Leiguarda RC, Cohen LG: Reorganization of the human ipsilesional premotor cortex after stroke. **Brain** **127**:747–758, 2004
8. Fulton J: A note on the definition of the “motor” and “premotor” areas. **Brain** **58**:311–316, 1935
9. Ille S, Sollmann N, Hauck T, Maurer S, Tanigawa N, Obermueller T, et al: Impairment of preoperative language mapping by lesion location: a functional magnetic resonance imaging, navigated transcranial magnetic stimulation, and direct cortical stimulation study. **J Neurosurg** **123**:314–324, 2015
10. Kombos T, Suess O, Kern BC, Funk T, Hoell T, Kopetsch O, et al: Comparison between monopolar and bipolar electrical stimulation of the motor cortex. **Acta Neurochir (Wien)** **141**:1295–1301, 1999
11. Krainik A, Lehericy S, Duffau H, Vlaiu M, Poupon F, Capelle L, et al: Role of the supplementary motor area in motor deficit following medial frontal lobe surgery. **Neurology** **57**:871–878, 2001
12. Krieg SM, Sabih J, Bulubasova L, Obermueller T, Negwer C, Janssen I, et al: Preoperative motor mapping by navigated transcranial magnetic brain stimulation improves outcome for motor eloquent lesions. **Neuro Oncol** **16**:1274–1282, 2014
13. Krieg SM, Shiban E, Buchmann N, Gempt J, Foerschler A, Meyer B, et al: Utility of presurgical navigated transcranial magnetic brain stimulation for the resection of tumors in eloquent motor areas. **J Neurosurg** **116**:994–1001, 2012
14. Krieg SM, Sollmann N, Obermueller T, Sabih J, Bulubas L, Negwer C, et al: Changing the clinical course of glioma patients by preoperative motor mapping with navigated transcranial magnetic brain stimulation. **BMC Cancer** **15**:231, 2015
15. Laplane D, Talairach J, Meininger V, Bancaud J, Orgogozo

- JM: Clinical consequences of corticectomies involving the supplementary motor area in man. **J Neurol Sci** 34:301–314, 1977
16. Liu Y, Rouiller EM: Mechanisms of recovery of dexterity following unilateral lesion of the sensorimotor cortex in adult monkeys. **Exp Brain Res** 128:149–159, 1999
 17. Livingston SC, Goodkin HP, Ingersoll CD: The influence of gender, hand dominance, and upper extremity length on motor evoked potentials. **J Clin Monit Comput** 24:427–436, 2010
 18. Penfield W: The supplementary motor area in the cerebral cortex of man. **Arch Psychiatr Nervenkr Z Gesamte Neurol Psychiatr** 185:670–674, 1950
 19. Picht T, Schmidt S, Brandt S, Frey D, Hannula H, Neuvonen T, et al: Preoperative functional mapping for rolandic brain tumor surgery: comparison of navigated transcranial magnetic stimulation to direct cortical stimulation. **Neurosurgery** 69:581–588, 2011
 20. Pool EM, Rehme AK, Fink GR, Eickhoff SB, Grefkes C: Handedness and effective connectivity of the motor system. **Neuroimage** 99:451–460, 2014
 21. Rogers BP, Carew JD, Meyerand ME: Hemispheric asymmetry in supplementary motor area connectivity during unilateral finger movements. **Neuroimage** 22:855–859, 2004
 22. Rossini PM, Barker AT, Berardelli A, Caramia MD, Caruso G, Cracco RQ, et al: Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: basic principles and procedures for routine clinical application. Report of an IFCN committee. **Electroencephalogr Clin Neurophysiol** 91:79–92, 1994
 23. Ruohonen J, Karhu J: Navigated transcranial magnetic stimulation. **Neurophysiol Clin** 40:7–17, 2010
 24. Seitz RJ, Höflich P, Binkofski F, Tellmann L, Herzog H, Freund HJ: Role of the premotor cortex in recovery from middle cerebral artery infarction. **Arch Neurol** 55:1081–1088, 1998
 25. Tanji J: The supplementary motor area in the cerebral cortex. **Neurosci Res** 19:251–268, 1994
 26. Tarapore PE, Tate MC, Findlay AM, Honma SM, Mizuiri D, Berger MS, et al: Preoperative multimodal motor mapping: a comparison of magnetoencephalography imaging, navigated transcranial magnetic stimulation, and direct cortical stimulation. **J Neurosurg** 117:354–362, 2012
 27. Teitti S, Määttä S, Säisänen L, Könönen M, Vanninen R, Hannula H, et al: Non-primary motor areas in the human frontal lobe are connected directly to hand muscles. **Neuroimage** 40:1243–1250, 2008
 28. Uematsu S, Lesser R, Fisher RS, Gordon B, Hara K, Krauss GL, et al: Motor and sensory cortex in humans: topography studied with chronic subdural stimulation. **Neurosurgery** 31:59–72, 1992
 29. van der Kamp W, Zwiderman AH, Ferrari MD, van Dijk JG: Cortical excitability and response variability of transcranial magnetic stimulation. **J Clin Neurophysiol** 13:164–171, 1996
 30. Zentner J, Hufnagel A, Pechstein U, Wolf HK, Schramm J: Functional results after resective procedures involving the supplementary motor area. **J Neurosurg** 85:542–549, 1996

Disclosures

Drs. Krieg and Ringel are consultants for Brainlab AG.

Author Contributions

Conception and design: Krieg. Acquisition of data: Krieg, Bulubas, Sabih, Sollmann, Hauck, Ille. Analysis and interpretation of data: Krieg, Bulubas, Wohlschlaeger. Drafting the article: Krieg, Bulubas. Critically revising the article: Krieg. Reviewed submitted version of manuscript: Krieg, Bulubas, Sabih, Sollmann, Hauck, Ille, Ringel, Meyer. Approved the final version of the manuscript on behalf of all authors: Krieg. Statistical analysis: Krieg, Bulubas. Administrative/technical/material support: Krieg, Meyer. Study supervision: Krieg, Wohlschlaeger, Ringel, Meyer.

Correspondence

Sandro M. Krieg, Department of Neurosurgery, Klinikum rechts der Isar, Technische Universität München, Ismaninger Str. 22, Munich 81675, Germany. email: sandro.krieg@tum.de.