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TECHNICAL NOTE - BRAIN TUMORS

TMS motor mapping in brain tumor patients: more robust maps with an increased resting motor threshold

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Abstract

Objective Navigated transcranial magnetic stimulation (nTMS) has found widespread usage across many clinical centers as part of their surgical planning routines. NTMS offers a non-invasive approach to delineation of the motor cortex, in which the region is outlined through electromagnetic stimulation and electromyographic recordings of target muscles. Several neurophysiological parameters such as the motor evoked potential (MEP) and its derivatives, the resting motor threshold (RMT) and motor latency, are collected. The present study investigates the clinical feasibility and reproducibility of increasing the MEP threshold in brain tumor patients, with the goal to improve the robustness of the procedure.

Materials and methods Twenty-three subjects with peri-motor cortex tumors underwent motor mapping with nTMS. RMT was calculated with both conventional 50-μV and experimental 500-μV MEP amplitude thresholds. Motor mapping was performed with 105% of both RMTs stimulator intensity using the FDI as the target muscle.

Results Motor mapping was possible in 20 patients with both the conventional and experimental thresholds. No significant differences in area size were found between motor area maps generated with a conventional 50-μV threshold in comparison to those generated with the higher 500-μV threshold (50 μV 272.56 mm^2 [170.47–434.31] vs. 500 μV 240.54 mm^2 [169.77–362.84], $P = 0.34$). Latency time was significantly reduced in 500-μV recordings relative to 50-μV recordings (50 μV 23.38 ms [22.55–24.51] vs. 500 μV 22.57 ms [21.41–23.70], $P < 0.001$). Both electric field intensity (50 μV 63.81 V/m [54.26–76.11] vs. 500 μV 77.83 V/m [65.21–93.94], $P < 0.001$) and RMT (50 μV 33 MSO% [28–36] vs. 500 μV 39.5 MSO% [32–44], $P < 0.001$) were significantly greater with the higher 500-μV threshold.

Conclusions Our study demonstrates the feasibility of increasing the MEP detection threshold to 500 μV in brain tumor patients for RMT determination and motor area mapping with nTMS.

Keywords nTMS · Motor mapping · Resting motor threshold · Latencies

Introduction

Preoperative planning for tumor resections of the central region revolves around a central idea: maximize the extent of tumor resection and minimize functional impairment. To accomplish this goal, delineation of the spatial relationship between the tumor and the primary motor cortex is needed. Navigated transcranial magnetic stimulation (nTMS) is a reliable tool that has been extensively validated to map motor-eloquent areas [10, 15, 21] and provides quantitative neurophysiological measurements including the motor evoked potential (MEP) and MEP derivatives such as the response latency time and the resting motor threshold (RMT).

Steven Lam and Giuseppe Lucente contributed equally to this work.

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Several lines of research suggest that these parameters provide assessments of the functional integrity of the motor system and are associated with surgical outcomes and subsequent motor function trajectory in brain tumor patients [23, 24]. Various manual and automated threshold-hunting methods for RMT determination exist, but the most commonly used estimation algorithm is the Rossini–Rothwell method, which generally yields less intra-subject variability [25, 33]. It defines the RMT as the minimum stimulation intensity capable of evoking 5 out of 10 MEP greater than a predetermined threshold amplitude in a target muscle at rest. As motor mappings are generally performed at an intensity level tethered to the RMT, it is of primary importance that RMT values reflect the actual excitability of the motor cortex.

At present, it remains a challenge in clinical practice to filter out electromyography (EMG) signal artifacts [14, 19], resulting in a variable degree of inter-/intra-subject variability. Inter-pulse MEP variability can be attributed to a myriad of confounding factors ranging from experimental issues or subject-related characteristics [34] to stimulation intensity [13] and frequency [8]. Moreover, cognitive states such as stimulation anticipation, motion imagery, and action observation have all been documented to produce inter-pulse MEP heterogeneity [1, 11, 12]. Differences in other subject-related parameters such as gender, age, and drugs have also been described to alter cortical excitability [2, 20, 3]. A recent analysis by Sollman et al. also identified several clinical factors related to inter-/intra-individual MEP heterogeneity in a brain tumor cohort including extent of motor impairment, cerebral edema, and coil operator proficiency [31, 30].

Apart from the previously described confounding factors, it is not uncommon to encounter brain tumor patients with elevated electromyographic background activity owing to involuntary muscular contraction. This in turn leads to a higher pre-activation and facilitation of suprathreshold MEPs and an artificially wider motor map. Taken together, these false positive motor-eloquent points may result in suboptimal pre-surgical mapping and planning.

Aim of study

Extending upon our previous study which investigated the feasibility of motor mapping at a higher 500-μV MEP threshold in healthy subjects [18], the present study investigated the feasibility of the approach in brain tumor patients. Our primary objective was to analyze the internal consistency between the 50-μV and 500-μV MEP threshold-generated motor maps. Secondarily, we hoped to provide additional evidence in support of using a higher 500-μV MEP threshold to reduce inter-pulse MEP and EMG latency variability.

Materials and methods

Data collection was conducted in accordance with the ethical standards set forth by the ethics commission of the Charité University Hospital in Berlin (EA 2/135/14), local ethics committees, and the Declaration of Helsinki. Written informed consent was provided from every patient prior to onset of experiments.

Patient population

Between June 2017 and July 2018, 23 patients presenting with brain tumors in or near the motor cortex were recruited from the Department of Neurosurgery and referred to participate in the nTMS study by their attending surgeons. All patients received a thorough clinical assessment comprised of handedness,, motor functions, medical history, and current medication use. Every patient fulfilled the following inclusion criteria: no neurological disorders, no contraindication for TMS, and the ability to provide written informed consent. Handedness was assessed by the Edinburgh Handedness Inventory. Three patients were excluded from the final data analysis due to insufficient data points.

Of the 20 eligible patients included in the final analysis, the mean age was 49.3 ± 16.3 years (range 24.3–79.3 years). All patients were right-handed. Twelve patients (60%) were male. Mapping was performed pre-operatively in 18 patients and 12-months post-operatively in two patients. Nine tumors (45.0%) were localized in the motor cortex of the dominant hemisphere. One patient presented with bihemispheric tumors in whom we observed a tumor within the motor-eloquent region of the non-dominant hemisphere.

Stimulation preparations

All patients underwent pre-operative MR imaging. Each patient's structural MRI scan (Siemens, 1.5T, T1-weighted) was co-registered to his cranium through a 12-point registration process previously described in detail [28] and used by the Nexstim eXimia Navigated Brain Stimulation (NBS) software to create a patient-specific 3D navigational data set. After successful registration, nTMS was carried out using the eXimia's high-precision, figure-of-eight stimulation coil to deliver biphasic magnetic pulses to various points of the motor cortex. Muscle output was recorded by the integrated six-channel electromyogram (EMG) using pregelled silver-silver chloride surface electrodes attached to the first dorsal interosseous (FDI) muscle in a belly-tendon fashion, and a reference electrode was attached to the forearms of both arms. Patients were instructed to relax with their eyes opened throughout the stimulation session. All procedures were performed by the same technician to minimize inter-individual differences in technical proficiency.

Navigated brain stimulation

Prior to mapping, we checked that baseline EMG activity was acceptably low (< 50 μV). Stimulation was performed on both hemispheres and always on the tumorous hemisphere first. To locate the optimal stimulation site for the interosseous musculature, the mapping was conducted in the vicinity of the anatomically defined "hand knob" of M1. The coil was kept tangential to the scalp throughout the stimulation and during mapping; the direction of the electric field (elicited by each magnetic stimulus and calculated by the NBS image-guidance software) was kept perpendicular to the closest sulcus on the individual MR images. The optimal stimulation site, or "hotspot," was identified as the location at which TMS elicited the MEPs with the highest amplitudes. After determining the hotspot, optimal coil rotation, defined as the orientation evoking the highest amplitude MEPs, was verified through a series of magnetic pulses delivered at varying deviations between − 45 and + 45° from the initial coil rotation at the hotspot.

The electric field is the result of mathematical calculations that consider the intensity of the current generated by the TMS equipment, the coil, and the resistance of the tissues (including skin, the skull, the cortical layers, and the CSF). The equipment we used for this study automatically calculates the electric field value for each point of stimulation. The relevance of this value consists in that it gives a grade of the strength of the TMS pulse delivered, considering the local anatomical features and the distance between coil and cortex. It can therefore be regarded as a more accurate measure than the percentage of maximum stimulator output. The resting motor threshold was defined at the hotspot according to the traditional Rossini–Rothwell method, whereby the RMT is the minimal intensity level that elicits MEPs greater than a predetermined threshold in at least 5 out of 10 stimulations. RMT determination was performed at both 50-μV and 500-μV MEP amplitude thresholds and recorded as both a percentage of the maximum stimulator output and the induced electric field. To avoid intertrial-induced variability, RMT determination was randomized between the two threshold levels.

After determining the RMT, mapping of the FDI cortical functional area was performed with a stimulator output of 105% RMT. Mapping began from the outer MEP negative boundaries and proceeded inwards towards the hotspot. All stimulation points were spaced 1–5 mm apart, and all recordings were considered valid if the MEP amplitude exceeded the predefined threshold and the latency was between 15 and 30 ms.

Area calculation

The FDI motor cortical representation area was computed using the Convex Hull method in MatLab. Briefly, an ellipsoid was fitted to the cortical stimulation points to transform the 3D MRI coordinates onto a 2D plane and a convex hull was generated to outline all stimulation locations in the smallest convex polygon containing all the stimulation points. The areas of these convex hulls were considered as quantitative measurements of the size of the motor cortical representation areas.

Statistical analysis

The distribution of continuous data is reported as mean and median [IQR]. Differences in neurophysiological parameters (motor cortical representation area, distal latencies, electric field, RMT) between the 50-μV and 500-μV MEP thresholds were investigated using the paired Mann–Whitney signed-rank test. Levene's test for homogeneity of variances was used to explore equality of latency variability between the two thresholds. All statistical tests were conducted in an explorative manner on a two-sided 5% significance level.

Results

Three subjects were excluded from the data analysis due to insufficient FDI MEP recordings collected in either the 50-μV or the 500-μV threshold condition. No side effects were reported during the experiment. Area map characteristics and neurophysiological characteristics are shown respectively in Tables 1 and 2.

Motor area size

FDI motor maps generated with a 50-μV threshold showed no significant differences in motor map area size compared to 500-μV threshold maps in both tumorous (50 μV 331.05 mm^2 [179.12–530.05] vs. 500 μV 275.40 mm^2 [224.48–365.56] for 500 μV, $P = 0.47$) and healthy hemispheres (50 μV 228.50 mm^2 [166.00–337.10] vs. 500 μV 182.81 mm^2 [141.72–344.11], $P = 0.49$). Combining the maps

Table 1 Median motor area map and neurophysiological parameters according to resting motor threshold

	50 μV	500 μV	*P*
Map area (mm^2) [IQR]	272.56 [170.47–434.31]	240.54 [169.77–362.84]	0.34
Distal latencies (ms) [IQR]	23.38 [22.55–24.51]	22.57 [21.41–23.70]	< 0.001
Electric field (V/m) [IQR]	63.81 [54.26–76.11]	77.83 [65.21–93.94]	< 0.001
RMT (MSO%) [IQR]	33.00 [28–36]	39.50 [32–44]	< 0.001

RMT resting motor threshold, *MSO* maximum stimulator output

Table 2 Motor area map size in square millimeters according to resting motor threshold and tumor presence in our study subjects

Subject	Tumor side		Healthy side	
	Area map 50 μV	Area map 500 μV	Area map 50 μV	Area map 500 μV
1	130.58	283.49	174.81	193.53
2	353.05	301.73	130.59	191.60
3	527.51	368.35	491.41	419.29
4	151.40	240.41	431.25	135.21
5	537.69	200.90	175.97	230.92
6	190.12	267.30	322.48	502.30
7	352.20	267.30	1331.94	1302.00
8	625.66	664.21	103.16	53.83
9	382.27	210.37	443.52	174.03
10	59.41	29.87	125.75	270.86
11	474.91	426.55	117.27	350.23
12	602.15	441.57	197.01	342.07
13	309.89	351.35	344.24	444.58
14	186.34	205.21	334.77	167.14
15	108.34	76.81	189.23	170.65
16	3822.77	362.24	209.90	157.87
17	580.94	716.56	272.50	143.89
18	157.48	240.68	247.10	100.04
19	192.90	364.63	139.38	119.72
20	272.62	229.19	282.72	74.33

generated in both hemispheres, motor area size remained non-significantly different between thresholds (50 μV 272.56 mm^2 [170.47–434.31] vs. 500 μV 240.54 mm^2 [169.77–362.84], $P = 0.34$). Similarly, no significant differences in map area size were found between tumorous and healthy hemispheres (tumor 292.61 mm^2 [198.90–430.31] vs. healthy 195.27 mm^2 [142.76–342.61], $P = 0.17$).

Latencies, electric field, and resting motor threshold

MEP recordings generated with a 500-μV threshold exhibited a significant reduction in latency in comparison to those generated with the conventional 50-μV threshold for both tumor (50 μV 23.27 ms [22.68–24.22] vs. 500 μV 22.44 ms [21.23–23.20], $P < 0.001$) and healthy hemispheres (50 μV 23.69 ms [22.55–24.56] vs. 500 μV 22.57 ms [21.60–23.99], $P < 0.001$). Removing stratification by hemispheric tumor presence, MEP latency remained significantly lower in 500-μV MEP recordings than 50-μV recordings (50 μV 23.38 ms [22.55–24.51] vs. 500 μV 22.57 ms [21.41–23.70], $P < 0.001$). No significant difference in latency was observed, however, between tumorous and healthy hemispheres (tumor 23.09 ms [21.45–23.83] vs. healthy 23.05 ms [21.88–24.36], $P = 0.06$). Analyzed separately, distal latency variability of 500-μV threshold recordings was not significantly different from that of the lower 50-μV threshold recordings across tumor ($F = 0.1589$, $P = 0.60$), healthy ($F = 0.1715$, $P = 0.6811$), and pooled ($F = 0.0066$, $P = 0.94$) hemispheric groups. Similarly, no significant difference in latency variability was observed between tumor and healthy hemispheres ($F = 0.2708$, $P = 0.60$).

Concerning electric field intensity, 500-μV threshold positive points exhibited greater electric field intensity compared to that of 50-μV threshold in both tumorous (50 μV 67.94 V/m [57.55–78.83] vs. 500 μV 78.70 V/m [66.20–106.53], $P < 0.001$) and healthy hemispheres (50 μV 62.84 V/m [53.49–72.60] vs. 500 μV 75.81 V/m [64.06–86.45], $P < 0.001$). Elimination of tumor stratification did not alter the positive association between threshold and electric field intensity (50 μV 63.81 V/m [54.26–76.11] vs. 500 μV 77.83 V/m [65.21–93.94], $P < 0.001$). Tumorous hemispheres also exhibited significantly greater electric field intensity values than non-tumorous hemispheres (tumor 70.95 V/m [59.54–89.14] vs. healthy 67.70 V/m [60.57–79.66], $P = 0.01$).

We found a significant association between RMT and threshold levels across both tumorous (50 μV 34 MSO% [29.75–36] vs. 500 μV 40.5 MSO% [33–44], $P < .001$) and healthy hemispheres (50 μV 32 MSO% [27–35.75] vs. 500 μV 37.5 MSO% [31.5–44.25], $P < .001$). Pooling the RMT values together for both hemispheres, we similarly found a significant positive association between RMT and higher threshold levels (50 μV 33 MSO% [28–36] vs. 500 μV 39.5 MSO% [32–44], $P < 0.001$). No significant association was found between RMT and tumor presence (tumor 35 MSO% [30.75–43] vs. healthy 33 MSO% [28–41], $P = 0.09$).

Discussion

The vital and functional prognosis of brain tumor patients is strongly related to the completeness of the resection and the avoidance of removing eloquent cerebral areas. The nTMS pre-surgical mapping allows the evaluation of the functional and anatomical status of the motor areas before undergoing the actual surgery. Indeed, optimal pre-surgical planning allows the surgeon to tailor the correct surgical approach strategy for each patient and to inform the patients of the possible risks of the intervention with more precise probabilities. This renders the optimization of motor mapping to be of crucial importance, particularly in patients with difficulty relaxing, as pre-elevated cortical excitability may result in false positives that generate artificially larger motor maps as shown in Fig. 1.

This study expanded upon our previous study [18] in its investigation of the reliability of motor maps generated with

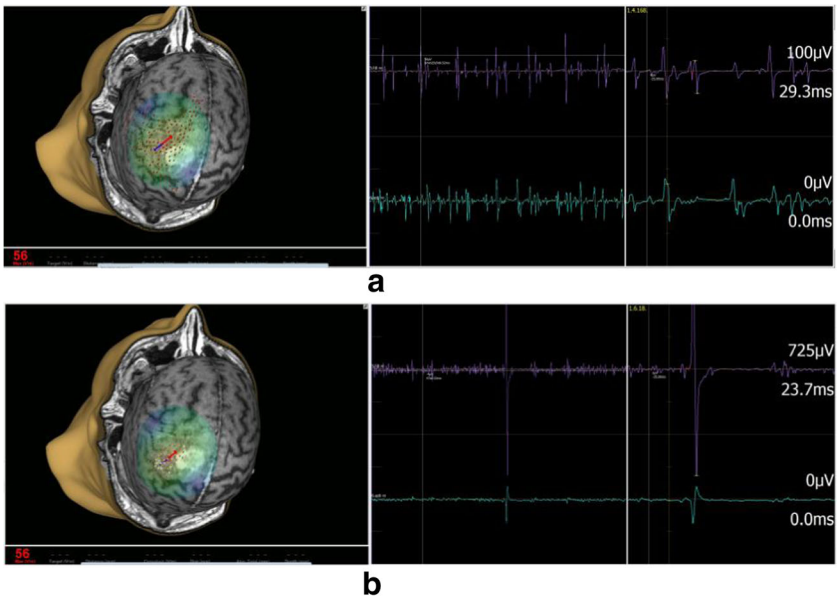

Fig. 1 **a** Patient with difficulty relaxing; 50-μV MEP threshold-generated nTMS motor map showing the functional points of the motor cortex in spatial relation to the tumor along with a corresponding "noisy" EMG readout. Both FDI and APB responses are shown. The color coding is as follows: gray = no response or MEP (peak-to-peak amplitude) < 50 μV, red = MEP 50 to 500 μV, yellow = 500 to 1000 μV, white > 1000 μV. **b** Patient with difficulty relaxing; 500 μV MEP threshold-generated nTMS motor map showing the functional points of the motor cortex in spatial relation to the tumor along with a corresponding less "noisy" EMG readout. Both FDI (purple) and APB (turquoise) responses are shown. The color coding is as follows: gray = no response or MEP (peak-to-peak amplitude) < 50 μV, red = MEP 50 to 500 V, yellow = 500 to 1000 μV, white > 1000 μV

different MEP thresholds in brain tumor subjects. Based off our findings in healthy subjects, we hypothesized that FDI motor area maps generated with a higher 500-μV MEP threshold would be similar to those produced by a conventional 50-μV threshold while removing noise artifacts. The noise artifacts are a common unwanted complication of motor mapping in patients with difficulties to relax. Within our in-house cohort of 650 patients that have undergone presurgical motor mappings, an estimated 15–20% demonstrate noisy EMGs that are subsequently reflected in imprecise motor maps (data not published). This could lead to large, likely unreliable preoperative motor maps. We provide an anecdotic example in one of our study patients who shows a very large 50-μV threshold motor map but a significantly more constrained and reliable 500-μV threshold motor map (Fig. 1).

Our results affirmed our initial hypothesis since we observed consistency between 50-μV and 500-μV FDI motor maps, as demonstrated by the lack of significant differences in motor map area sizes. Furthermore, the 50-μV motor maps exhibited a large quantity of low-amplitude motor responses stemming from non-motor eloquent regions (Fig. 1a, b), indicating the presence of false positive responses. In contrast, while the 500-μV motor maps featured less motor responses in total, the motor responses were largely concentrated in essential motor regions, as shown in anecdotal examples in Fig. 2a, b.

Every point of stimulation was elicited at about 5 mm of distance from the previous, in an outside to inside manner delineating the motor area. We do not provide the density of motor responses, but according to our method, the statistically equal area size should include approximately the same number of motor eloquent points.

Moreover, no side effects or discomfort were reported when performing the motor mapping with a higher threshold.

Tumor presence was positively associated with higher RMT, although the association narrowly failed to reach significance. These results contradicted observations from a previous study in which RMT was found to be higher in tumorous brain hemispheres than in healthy hemispheres as a result of tumor-induced functional compromise of the primary motor cortex, regardless of the patients' motor status [23]. Of note, the study also reported several patients with lower RMTs in tumorous hemispheres likely stemming from malignant tumors in the secondary motor cortex that damaged inhibitory pathways. Cicinelli et al. reported similar inter-hemispheric asymmetries of motor cortex excitability in subacute stroke patients, specifically significantly higher RMT to a single magnetic pulse over the M1 in affected hemispheres than in unaffected hemispheres [5]. Still, other studies have described in stroke patient groups that RMT is similar across affected and healthy hemispheres [4, 32]. Given the differential effects of stroke and tumor pathology on motor excitability and dynamics, further research is needed to fully characterize the relationship between motor system excitability and corticospinal tract impairment in both stroke and brain tumor models.

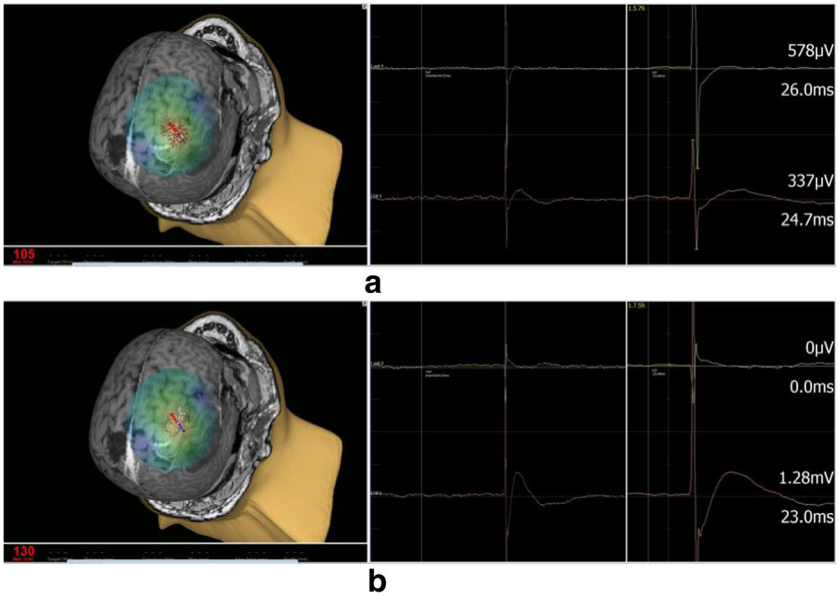

Fig. 2 **a** Patient without difficulty relaxing; 50-μV MEP threshold-generated nTMS motor map showing the functional points of the motor cortex in spatial relation to the tumor along with a corresponding EMG readout. Both FDI (orange) and APB (light green) responses are shown. The color coding is as follows: gray = no response or MEP (peak-to-peak amplitude) < 50 μV, red = MEP 50 to 500 μV, yellow = 500 to 1000 μV, white > 1000 μV. **b** Patient without difficulty relaxing; 500-μV MEP threshold-generated nTMS motor map showing the functional points of the motor cortex in spatial relation to the tumor along with a corresponding EMG readout. Both FDI (orange) and APB (light green) responses are shown. The color coding is as follows: gray = no response or MEP (peak-to-peak amplitude) < 50 μV, red = MEP 50 to 500 μV, yellow = 500 to 1000 μV, white > 1000 μV

Between the two thresholds, 500-μV MEP recordings demonstrated significantly less latency compared to 50-μV recordings. Higher stimulation intensities are more likely to directly evoke corticospinal neurons near the initial segment and to generate short latency d-waves [6, 26, 7, 27]. In contrast, lower stimulation intensities preferentially activate corticospinal neurons via corticocortical inter-neuron projections that in turn result in long latency i-waves. A shorter latency value during MEP generation is related to stronger direct activation of cortical motor neuron which might be translated in an "effective" activation of the actual motor neurons pool correspondent to the site of stimulation. In brief, by filtering out smaller MEPs with larger latencies, we could assume that the MEPs generated correspond to the "true" directly activated motor neurons and not a distant pool activated by inter-neurons. A shorter latency value during MEP generation is related to stronger direct activation of cortical motor neuron which might be translated in an effective activation of the actual motor neurons pool correspondent to the site of stimulation [29]. In brief, by filtering out smaller MEPs with larger latencies, we could assume that the MEPs generated correspond to the true directly activated motor neurons and not a distant pool activated by inter-neurons. We also speculated that a large degree of synchronization of CST pyramidal neurons would be necessary to overcome the high 500-μV amplitude threshold level, thereby increasing concomitant muscular contractions, resulting in less MEP latency variance. No significant differences in latency variability were observed between the two threshold conditions across healthy, tumorous, and pooled hemispheres, although we suspect that our limited sample size masked the effect.

Addressing possible limitations of our study, one potential limitation of using a 500-μV threshold includes masking of MEPs generated in the amplitude range of sub-500 μV, although the high internal consistency between the two motor maps shows that any possible masking is insignificant. Second, our study included both pre-operative and post-operative patients under the assumption that post-op motor excitability would not differ significantly from pre-op excitability levels. Unfortunately, spare literature exists concerning differences in functional motor integrity between pre-op and post-op patients, although a study in patients with recurrent gliomas reported significant correlations between pre-op subsequent post-op motor maps [16].

EMG recordings were collected solely from the FDI in accordance with previous studies that have demonstrated moderate to good RMT reliability when measured from the FDI [17]. Limiting our measurements to the FDI potentially restricts the generalization of our findings to motor area maps of other hand or upper limb muscles, although we would not expect differing results.

Lastly, we could not provide direct comparison with direct cortical stimulation which is the gold standard for motor mapping. However, the strong correlation between non-invasive motor mapping and intra-operative motor map has been demonstrated by different groups during the last years [9, 22].

Statistically, we describe a strong correlation between 50 and 500 μV; so accordingly, we can affirm that conventional DCS maps should show a good correlation with our 500-μV motor maps.

Conclusion

In conclusion, we demonstrated the feasibility of increasing the amplitude threshold for non-invasive motor area mapping. The higher threshold delineated motor cortical outlines consistent with those produced by the conventional 50-μV threshold and filtered out signal artifacts present in 50-μV maps of patients with elevated baseline EMG activity. Based on these findings, we propose that the higher threshold level generates more robust motor maps and shows particular promise in mapping patients with high levels of baseline EMG noise.

Based on our findings, it seems justified to propose the new higher amplitude threshold mapping, especially in patients with high levels of baseline EMG noise to achieve a reliable presurgical motor map.

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Compliance with ethical standards Data collection was conducted in accordance with the ethical standards set forth by the ethics commission of the Charité University Hospital in Berlin (EA 2/135/14), local ethics committees, and the Declaration of Helsinki.

Conflict of interest TP has served as speaker for NexStim Oy. GL, HS, and SL certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements) or non-financial interest (such as personal or professional relationships, affiliations, knowledge, or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (name of institute/committee) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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