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ORIGINAL ARTICLE - BRAIN TUMORS

Neurophysiological examination combined with functional intraoperative navigation using TMS in patients with brain tumor near the central region—a pilot study

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Abstract

Objective Feasibility and value of non-invasive transcranial magnetic brain stimulation (TMS MAGVENTURE® MagPro R30 Denmark) for preoperative diagnosis and surgical planning of brain tumor operations in everyday clinical practice.

Methods A prospective monocentric study was conducted, which included preoperative neurological and electrophysiological examination, TMS, and display of functional data in the navigation system (LOCALITE® TMS Navigator Germany). During surgery, the TMS data were correlated with the intraoperative monitoring (IOM). Twenty-four hours to 96 h and after at least 3 months, follow-ups with neurological, electrophysiological examinations and TMS stimulation were performed.

Results Twenty-five patients with tumors in or near by the primary motor cortex region were included in the study. Twenty-one patients completed preoperative and first postoperative TMS and the neurological examination. Eight of 21 patients showed slight worsening of primary motor cortex function, 8 patients had an unchanged state, and 4 patients showed an improvement early after surgery. The changes of the electrophysiological examination like significant delay of the latency and/or reduced amplitudes matched well with the postoperative neurological outcome: if patients showed a worsening of the SEP's and MEP's, the postoperative results revealed deterioration.

Conclusion A preoperatively performed TMS using the MAGVENTURE® MagPro R30 and the LOCALITE® TMS Navigator could be established in our clinical daily practice and allowed a safe and reliable mapping of the primary motor cortex in order to minimize the risk of postoperative neurological deficits and improve the neurological outcome of the patients.

Keywords Transcranial magnetic stimulation · Brain tumor surgery · Primary motor cortex · Intraoperative monitoring · Brain mapping

Introduction

Prior to neurosurgery of brain tumors, different preoperative imaging technologies have proved useful for the planning and simulation of surgery, with the goal of improving the quality of the operation and neurological outcome of patients. Neuroradiological imaging, such as magnetic resonance imaging (MRI) with and without contrast enhancement, contributes major information on location, size, and possible dignity. Additionally, functional MRI is a useful technique to localize eloquent brain areas such as motor and language relevant cortices, and diffusion tensor imaging (DTI) can show their connections anatomically[4, 15]. Including this information in intraoperative neuronavigation, planning and simulation of the operative procedure help the performance of safe operative removal and optimizing resection, especially in gliomas and infiltrative growing metastasis [14]. Other methods that can be used preoperatively are electrophysiological examinations, such as evoked potentials, which can also be used intraoperatively. Motor-evoked potentials (MEP) are derived from muscles following a central stimulus, and sensory-evoked potentials (SEP) are the central electrical responses recorded from

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the nervous system followed by a peripheral stimulus. In addition to preoperative investigations, intraoperative monitoring (IOM), such as direct stimulation of the primary motor cortex during surgery in the central region and the use of the SEP phase reversal, became the gold standard [6, 24]. However, both procedures can only be used during surgery and do not influence the preoperative planning and setup.

Today's transcranial magnetic brain stimulation (TMS), developed by Antony M. Barker and Paul Merton, is an important noninvasive procedure for the stimulation of the cerebral cortex. An electromagnetic field is induced by placing the stimulation coil on the skull [3, 17]. The consequence is the generation of action potentials of axons, which run parallel to the electric field. So far, TMS has been used in different areas, for example, neurophysiological research, neurological diagnostic, and even as a therapeutic tool, for example, in the treatment of depression [1, 5]. Several studies on preoperative diagnostics of brain tumors affecting the primary motor cortex have been conducted. Krieg et al. showed that improved preoperative planning results in a smaller craniotomy [11]. Additionally, an improved postoperative outcome was associated with fewer neurological deficits [20].

Based on these studies, we aim to establish pre- and postsurgical TMS in our clinical daily practice. In contrast to the other publications, we use the navigational system of LOCALITE® and the TMS of MAGVENTURE® in combination with intraoperative navigation and neurophysiological monitoring with SEP. Our goal was to show equal results with a different technique. Furthermore, we wanted to show a correlation between the preoperative investigations, IOM, and postoperative outcome to offer a reliable tool for performing surgery and minimizing the risk of postoperative neurological deficits with the setup created.

Patients and methods

Patients

Thirty patients with tumors in or near the primary motor cortex region were examined and the prospective study was performed from May 2015 until May 2017. Finally, 25 patients were primary included. Demographic, histological, and stimulation data of the patients included are summarized in Table 1. Eight out of 25 patients were diagnosed with glioblastoma, 4 with meningioma, 12 with metastases, and 1 with a necrosis caused by radiotherapy.

The study design was approved by our local ethics committee (Ethic Committee at the Medical Faculty University Leipzig Az.: 118-15-09032015) adhering to the declaration of Helsinki and all patients gave written consent on participation in the study. The mean age was 60, 28±13, 54 years (range 30–84 years) with 15 male (60%) and 10 female (40%) patients. We included patients with a tumor in or near the primary motor cortex (distance primary motor cortex to tumor 18.2 mm ± 13.9 mm). In the MRI transferred to the TMS, we measured the distance of the primary motor cortex to the edge of the tumor for each patient. The Karnofsky performance scale index, which allows a classification of patients to their functional impairment, was set with a limit of 70% (with 100% indicating no deficit). Patients with a lower Karnofsky performance scale index, other neurologic and psychiatric diseases, and abuse of drugs and alcohol were excluded. Additionally, patients with epileptic seizures, implanted heart assist devices, other medical stimulators, or pregnancy could not be included in the study. The criteria of inclusion and exclusion are summarized in Table 2.

General study workflow

The study workflow is pictured in Fig. 1.

Preoperative phase The preoperative diagnostics included a neurological examination and preoperative SEPs. Localization of the primary motor cortex is mandatory to perform TMS. This was achieved with a frameless stereotactic positioning system from LOCALITE®. The definition of the target site was based on anatomic landmarks for the primary motor cortex and tumor location. The entry-target grid set was matched on the T1-weighted MRI (slices of 1 mm) with contrast agent. Before performing the TMS, the minimal stimulation intensity necessary to evoke a motor potential had to be determined. Testing is usually started with low intensities, such as 30% of the maximum stimulation strength, raising the intensity until a clear MEP and motor response was generated. Single pulses were applied with a MagPro R30, 230V with a CB60 figure-eight coil (MAGVENTURE®). The primary stimulation goal was to include at least 100 stimulation points. In order to include a stimulation point within the final presentation of the primary motor cortex mapping, a clear evoked potential had to be derived and a neurological feedback, such as a finger movement, had to be seen. Finally, the data were transferred into the navigational system (LOCALITE®).

Intraoperative phase The MRI used for the intraoperative navigation also included the TMS stimulation points (Fig. 2). During surgery, additional direct primary motor cortex stimulation including the arm and the leg with a grid electrode, intraoperative SEPs, MEPs, and a SEP phase reversal to identify the precentral and the postcentral gyrus was performed using the IOM system ISIS (INOMED®). Early postoperative phase (48 to 96 h after surgery): a postoperative MRI (T1-weighted, 1-mm slices with contrast agent) was required for the TMS examination. The whole setup was complemented by a neurological and electrophysiological examination including TMS

Table 1 Demographic data, localization with distance to the primary motor cortex, histology of the tumor of the patients, and the extent of resection with n = percentage of the rest tumor included, the stimulation strength used during the different examinations, and the number of the stimulation points included (1 total resection glioblastoma, 2 partial resection glioblastoma, 3 total resection of a single metastases, 4 total resection of a single metastases by several intracerebral metastases, 5 partial resection of a single metastases, 6 total resection of a lymphoma/radial necrosis, 7 partial resection lymphoma/radial necrosis)

Pat	Age	Histology	Location	Extent of resection (*n*[%])	Preop stim. strength (%)	Preop In. points	Postop 1 stim. strength (%)	Postop 1 In. points	Postop 2 stim. strength (%)	Postop 2 In. points
1	75	Glioblastoma	Parietal left	2 (16)	80	107	85	0	n.a.	n.a.
2	61	Lymphoma	Right intraventricular	7	80	109	n.a	n.a.	n.a.	n.a.
3	52	Metastasis	Parietal left	4	100	116	100	140	n.a.	n.a.
4	53	Metastasis	Parietal left	4	60	103	60	101	65	109
5	67	Metastasis	Frontal right	4	80	126	80	106	70	95
6	55	Lymphoma	Frontal right	7	85	107	n.a.	n.a	n.a.	n.a.
7	61	Meningioma	Parietal left	1	70	110	70	110	70	110
8	60	Glioblastoma	Temporal right	2 (10)	80	93	100	0	100	60
9	62	Glioblastoma	Frontal right	2 (4)	55	110	55	79	55	106
10	67	Lymphoma	Frontal left	7	60	105	n.a.	n.a	n.a.	n.a.
11	55	Metastasis	Parietal right	4	80	109	90	33	n.a.	n.a.
12	66	Glioblastoma	Temporal left	2 (41)	75	113	80	104	60	150
13	33	Meningioma	Parietal left	1	64	101	64	180	64	161
14	70	Metastasis	Parietal left	3	51	88	65	79	n.a.	n.a.
15	78	Metastasis	Frontal left	3	95	n.a.	n.a.	n.a.	n.a.	n.a.
16	55	Metastasis	Frontal right	4	80	83	80	99	80	68
17	72	Metastasis	Parietal left	5	60	69	60	1	n.a.	n.a.
18	51	Metastasis	Parietal right	3	60	106	60	151	60	100
19	63	Glioblastoma	Frontotemporal right	2 (23)	70	109	70	108	n.a.	n.a.
20	36	Metastasis	Parietal right	3	65	116	65	140	n.a.	n.a.
21	68	Metastasis	Parietal left	4	55	103	55	101	n.a.	n.a.
22	84	Glioblastoma	Parietal left	2 (10)	75	204	75	151	n.a.	n.a.
23	50	Glioblastoma	Parietal right	1	70	107	70	123	70	104
24	58	Glioblastoma	Parietal left	2 (89)	70	110	70	110	70	110
25	76	Meningioma	Parietal right	1	70	93	70	105	n.a.	n.a.
26	65	Metastasis	Parietal right	3	65	110	65	90	65	107
27	74	Meningioma	Parietal left	1	75	104	85	30	85	107
28	72	Metastasis	Parietal right	4	75	109	75	33	75	103
29	30	Necrosis	Parietal right	6	60	114	60	104	n.a.	n.a.
30	55	Metastasis	Parietal right	4	85	108	n.a.	n.a.	n.a.	n.a.

Pat patient, *Preop* preoperative, *Postop 1* early postoperative, *Postop 2* late postoperative, *stim. Strength* stimulation strength, *In. Points* included points, *n.a.* not available

primary motor cortex mapping and SEP. In four patients, we missed to perform the postoperative SEP-examination. The stimulation parameters were identical to the first session. Stimulation was only increased in case no clear MEP or motor response could be evoked.

Late postoperative phase (at least 3 months after surgery) Fifteen of the 25 patients completed this follow-up. Another postoperative MRI and the TMS were combined with the second postoperative neurological and electrophysiological examination.

Results

Patient sample

A total of 30 patients with tumors of different dignities near or within the primary motor cortex were examined. In all patients with a meningioma, the tumor was resected completely. Out of the eight patients with a glioblastoma, one patient was resected completely. The other seven patients had a partial resection. In our study, we included 14 patients with metastases, 6 patients had just one metastasis, which was completely

Table 2 Inclusion and exclusion criteria

Inclusion	Exclusion
Tumor near the motor cortex	Epileptic seizures
Karnofsky > 70	Karnofsky < 70
Age > 18; < 85	Age < 18; > 85
Written consent on participation in the study	No written consent on participating in the study
	Participation in another clinical study
	Existence Medical-electronic devices (e.g., Pacemaker, cochlea implants)
	Other neurological and psychiatric disorders
	Pregnancy
	Alcohol and drug abuse
	Severe other diseases

resected in 5 of them. One patient had a partial resection. Eight patients suffered from several metastases, we removed the one near the primary motor cortex completely in all of them. Three patients had the diagnosis of a lymphoma; in two of them, the tumor was resected partial and one patient had a complete resection. We included one patient with a radial necrosis, which was resected completely. We analyzed the pre- and postoperative MRI of the patients with the glioblastoma, concerning the residual tumor in a volumetric analysis, which was measured with the BRAINLAB® software iPlan Net 3.0.0 Build 49 2009. The results are presented in Table 1. We divided the patients in two groups, the extent of resection less than 90% and more than 90%. We analyzed the dependence of the extent of resection with the neurological outcome; there was no difference between the two groups.

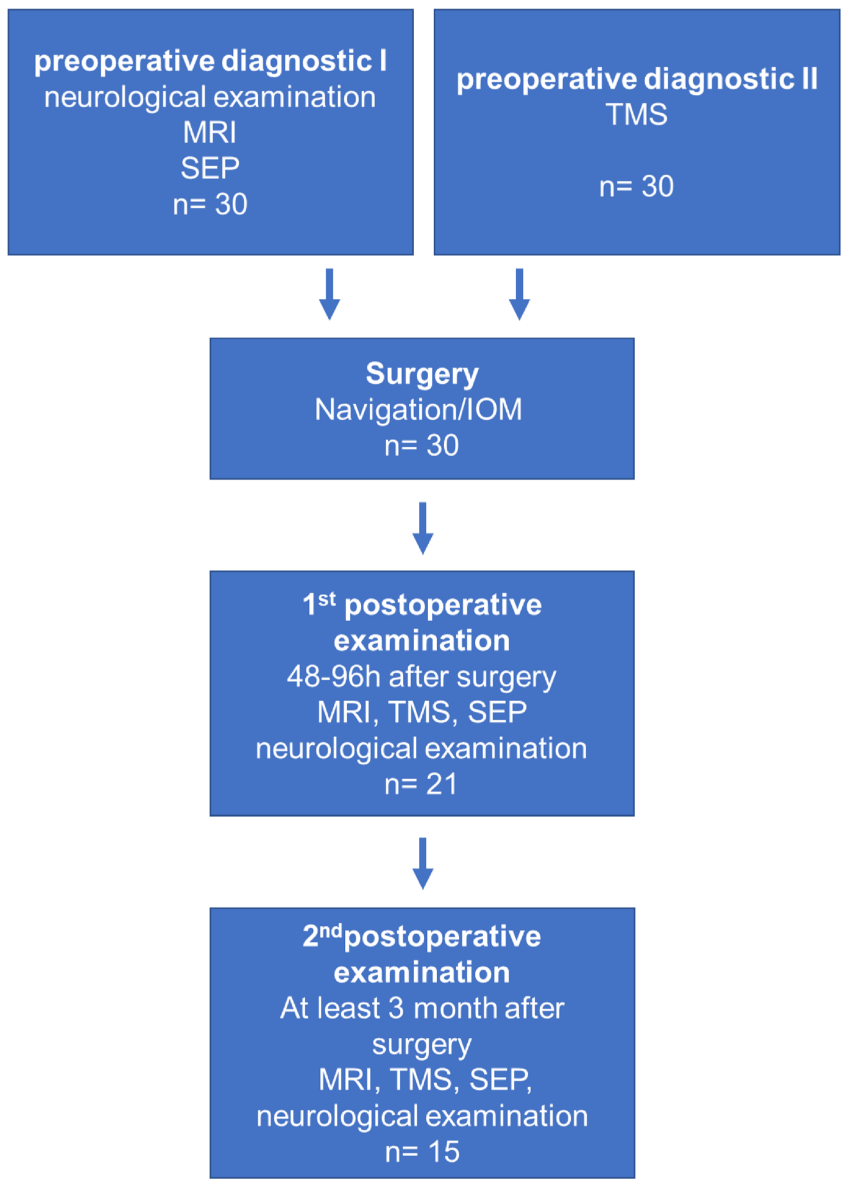

Fig. 1 General workflow of the study (*n*: number of patients; MRI: magnetic resonance imaging; SEP: sensory-evoked potentials; IOM: intraoperative monitoring with SEP, direct stimulation and phase reversal, TMS: transcranial magnetic stimulation mapping)

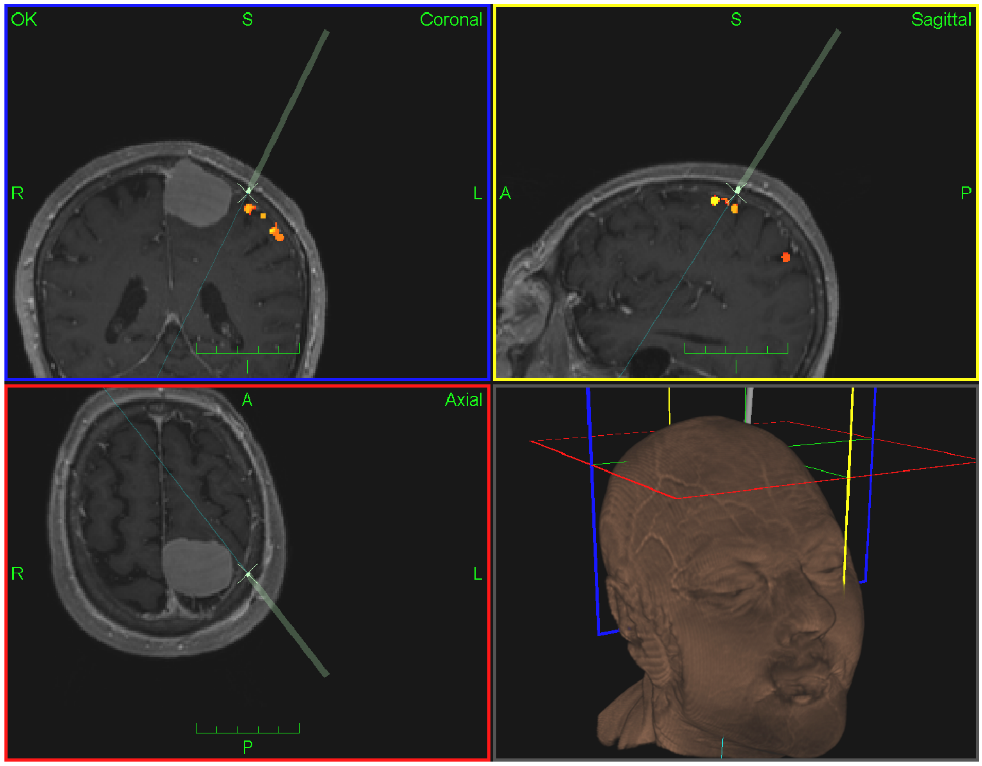

Fig. 2 Intraoperative navigation of the primary motor cortex of patient 27 (the meningeoma displaces the primary motor cortex to the front) in three common (axial, sagittal, coronar) views with the navigation of LOCALITE®

Twenty-five patients were included in our study, because they completed the pre- and postoperative transcranial stimulation (Table 1). Five patients had to be excluded because of different reasons: one patient suffered a pulmonary embolism, two developed a postoperative seizure, and one had a swelling of the larynx and needed a tracheotomy. The fifth patient developed claustrophobia in the MRI and was unable to complete the postoperative MRI examination. Twenty-one out of 25 patients completed the early postoperative control including the TMS, the electrophysiological and neurological examination. Therefore, in addition to the five patients excluded because of a missing TMS, four additional patients were not analyzed in the electrophysiological evaluation.

Fifteen patients completed the whole study protocol including the first and second postoperative stimulation. The other patients were excluded mostly because of their worsened general condition. A total of 84% completed the setup, including two examinations, and 60% completed the whole experiment. Table 3 shows a summary of the discharged patients. We performed a sensitivity analysis of the dropout reasons of the discharged patients. In the five patients, who missed the completion of the perioperative setting, the highest probability for a dropout was a seizure after the surgery (area under the curve {AUC} 0, 7; asymptotic prob. 0, 16416). Ten patients were not able to perform the whole setting, the most probable factor for the dropout was the clinical worsening (AUC 0, 8; asymptotic prob. 0, 01255). The receiver operating characteristics (ROC) analysis was performed with Origin 2017®. The detailed data are shown in Table 4.

Perioperative TMS primary motor cortex mapping

The mapping of the primary motor cortex was performed in the preoperative setting. It took approximately 10 min for the prearrangement (preparing the dataset) and 25 min (24.9 ± 6 min) for the TMS (Tables 5 and 6). The muscles examined

Table 3 Discharged patients and dropout reasons

	Dropout reasons
Patient discharged postop I	
Patient 2	Clinical worsening
Patient 6	Claustrophobia MRI
Patient 10	Seizure after surgery
Patient 15	Edema of the larynx
Patient 30	Seizure after surgery
Patient discharges postop II	
Patient 3	Clinical worsening
Patient 11	Clinical worsening
Patient 14	Clinical worsening
Patient 17	Clinical worsening
Patient 19	Clinical worsening
Patient 20	Severe other diseases
Patient 21	Missing navigation data
Patient 22	Clinical worsening
Patient 25	Denial of the examination
Patient 29	Intracerebral abscess

postop I early postoperative, *postop II* late postoperarative

Table 4 Sensitivity analysis

Dropout reasons	AUC	Standard error	Asymptotic Prob
Postop I			
Clinical worsening	0.6	0.12479	0.48667
Claustrophobia MRI	0.6	0.12479	0.48667
Seizure after surgery	0.7	0.10469	0.16416
Edema of the larynx	0.6	0.12479	0.48667
Postop II			
Clinical worsening	0.8	0.08894	0.01255
Denial of the examination	0.6	0.11392	0.40538
Missing navigation data	0.55	0.11747	0.67739
Intracerebral abscess	0.55	0.11747	0.67739

AUC area under the curve

were the *M. abductor pollicis brevis* in 25 patients and the *M. tibialis* anterior in 4 patients. All datasets could be successfully transferred to the neuronavigational system and no data was lost. The range of the included stimulation points varied from 69 to 204 (mean 108 ± 23). We also compared the different stimulation strength throughout the setup. The mean stimulation strength was 69% ± 11%. The stimulation strength varied from 51 to 100%. We tried to keep the stimulation strength constant between examinations. Six patients required a higher strength of stimulation to produce a clear motor response (Table 1).

Presurgical TMS-mapping of the primary motor cortex was correlated with findings of the direct primary motor cortex stimulation during the surgical procedure (Fig. 2). The localization of the primary motor cortex by TMS corresponded well with intraoperative direct motor stimulation findings in all cases. The correlation was verified by matching the direct stimulation of the primary motor cortex with the indirect presentation of the TMS-mapping shown in the neuronavigational system. The direct stimulation was performed with a grid electrode. A match between the stimulation points was included and the direct stimulation was shown by placing the navigation pointer on the grid electrode. The semi-quantitative result was verified by a screen shot with the navigational system.

To compare the pre- and postoperative TMS primary motor cortex mapping, we used the area of primary motor cortex defined by the included stimulation points of both sessions. The MRI with the included TMS data of both examinations of the 25 patients was compared independently by three different examiners. The differences of the areas between the pre- and postoperative TMS stimulation were set as an increased (+), decreased (−), or equal field (0) (Table 5). A total of 18 examinations (72%) had an equal and seven (28%) had a different evaluation. The seven examinations with different results differed in their evaluation between equal or increased and equal or decreased. The majority vote was set as the result. Out of the 25 patients who completed the TMS part of the study, 12 showed a decreased area of the primary motor cortex, four showed an increased area, and nine showed an equal size. Another analysis was made to compare the electrophysiological results of the postoperative SEP and the TMS-mapping results. One patient who showed an improvement of the SEP had a reduced area in the TMS-mapping. Six of the 12 patients with stable electrophysiological results showed an equal region and six showed a reduced area. The patients with the worsening of the electrophysiological results had a high variation of TMS results. Three patients showed almost the same region, two patients showed a decreased area, and two patients had an increased area.

Table 5 TMS results: comparison between the different expansions of the stimulation points included between preoperative and postoperative TMS. The evaluation was performed by three different examiners from our neurosurgery department. (+: increased area; −: decreased area; 0: equal results; 1: first examiner; 2: second examiner; 3: third examiner)

Pat	Age	Histology	Location	1	2	3
1	75	Glioblastoma	Parietal left	−	−	−
3	52	Metastasis	Parietal left	+	+	+
4	53	Metastasis	Parietal left	−	−	−
5	67	Metastasis	Frontal right	−	−	0
7	61	Meningioma	Parietal left	0	0	0
8	60	Glioblastoma	Temporal right	−	−	−
9	62	Glioblastoma	Frontal right	−	−	0
11	55	Metastasis	Parietal right	0	0	0
12	66	Glioblastoma	Temporal left	−	−	−
13	33	Meningioma	Parietal left	0	+	0
14	70	Metastasis	Parietal left	0	0	0
16	55	Metastasis	Frontal right	+	0	0
17	72	Metastasis	Parietal left	−	−	−
18	51	Metastasis	Parietal right	+	+	+
19	63	Glioblastoma	Frontotemporal right	−	−	−
20	36	Metastasis	Parietal right	+	+	0
21	68	Metastasis	Parietal left	0	0	−
22	84	Glioblastoma	Parietal left	0	0	0
23	50	Glioblastoma	Parietal right	−	−	−
24	58	Glioblastoma	Parietal left	+	+	+
25	76	Meningioma	Parietal right	0	0	0
26	65	Metastasis	Parietal right	−	0	−
27	74	Meningioma	Parietal left	−	−	−
28	72	Metastasis	Parietal right	−	−	−
29	30	Necrosis	Parietal right	0	0	0

Neurophysiology and neurological outcome

A clear correspondence between the intraoperative findings (IOM, TMS), postoperative neurological and electrophysiological examination could be demonstrated (Table 2). Representative MEPs and the TMS mapping of one patient,

Table 6 Representation of the neurological and electrophysiological findings of the patients included separated after the clinical outcome before and directly after surgery

Pat	Age	Histo	Location	Neurological status preop	Preop SEP	IOM SEP	Neurological status postop	Postop SEP
Improvement of the neurological outcome								
5	67	Met	Fro R	L Arm 4/5	L Tib: ↓ L	Med + Tib: ↓ L	No deficit	R Tib: ↓ L
9	62	GBM	Fro R	Facial nerve L	Regular	No data	No deficit	No deficit
14	70	Met	Par L	R Arm 4/5	Med: ↓L Tib: n.r.	Med: ↓ L L Tib: ↓ L R Tib: n. r.	No deficit	L med: ↓ L Tib: n.r.
23	50	GBM	Par R	L Arm 4/5	Regular	Regular	No deficit	R Tib ↓L
Steady state of the neurological outcome								
11	55	Met	Par R	No deficit	Regular	Regular	No deficit	No deficit
12	66	GBM	Tem L	Aphasia	Regular	L Med: ↓ A R Tib: ↓ A	Aphasia	Tib: ↓ L
13	33	Men	Par L	No deficit	Regular	Regular	No deficit	No deficit
16	55	Met	Fro R	No deficit	Regular	Regular	No deficit	No deficit
19	63	GBM	Frotem R	L Arm 4/5	Tib: ↓L	Tib: ↓ L L Med ↓ A	L Arm 4/5	Tib: ↓ L L Med ↓ L
20	36	Met	Par R	No deficit	Tib: ↓ L	Tib: ↓ L	No deficit	R Tib: ↓ L
21	68	Met	Par L	Coordination R Arm	Tib: ↓L	Tib: ↓ L L Med: ↓ A	Coordination R Arm	Tib: ↓ L
24	58	GBM	Par L	Coordination R Arm	regular	R Med: ↓ A L L Med: ↓ L R Tib: n.r.	Coordination R Arm	R Tib: n.r.
Worsening of the neurological outcome								
7	61	Men	Par L	R Leg 4/5	Tib: ↓ L	L Med: ↓ L Tib: ↓ L R Tib: ↓A	R Leg 0/5	R Tib: n.r.
8	60	GBM	Tem R	Facial nerve L	Regular	L Tib: n.r.	L Arm 0/5 L Leg dist 0/5, prox 3/5	Tib: n.r.
17	72	Met	Par L	R Arm 4/5	Tib: ↓L	R Med: ↓ A R Tib: ↓ A	R Leg 3/5	R Tib: n.r. L Tib: ↓ L
18	51	Met	Par R	L Arm 4/5 L Leg 3–4/5	L Tib: ↓L	L Tib: ↓L	L Arm 3–4/5 L Leg prox 3/5; dist 0/5	L Tib: n.r.
22	84	GBM	Par L	R Leg 3/5	Regular	Tib: ↓L L Med: ↓L R Med: ↓ A	R Leg prox 3/5, dist 0/5	R Tib: n.r. L Med: ↓ A
25	76	Men	Par R	Coordination L Leg	Regular	Tib + Med: ↓ A	L Leg dist 2/5	L Tib: ↓L
27	74	Men	Par L	Impaired balance	Regular	Regular	R Arm 4/5, R Leg prox 3/5, dist 3–4/5	regular
28	72	Met	Par R	L Leg dist 1–2/5	No data	Tib + Med: ↓L	L Leg 0–1/5	L tib: ↓L
29	30	Nec	Par R	No deficit	Tib: ↓L	Tib: n.r.	Sensory deficit L Arm	Tib: n.r.

Pat patient, *Histo* histology, *preop* preoperative, *postop* postoperative, *SEP* somatosensory-evoked potentials, *IOM* intraoperative monitoring, *Met* metastasis, *GBM* glioblastoma, *Men* meningioma, *Nec* necrosis, *Par* parietal, *Fro* frontal, *Tem* temporal, *Frotem* frontotemporal, *L* left, *R* right, *Med* N. medianus both sides, *L Med* left N. medianus, *R Med* right N. medianus, *Tib N. tibialis* both sides, *LTib* left *N. tibialis*, *RTib* right *N. tibialis*, *↓L* delayed latency, *↓A* reduced amplitude, *prox* proximal, *dist* distal, *n.r.* no response

who suffered a worsening directly after the surgery but recovered after 4 months, are shown in Fig. 3.

The changes in the SEP almost completely matched the postoperative neurological outcome. Therefore, if patients showed a change in the SEPs, the postoperative results revealed a worsening of the neurological outcome, such as sensory and motor deficits, while preserved SEPs were correlated with an improvement of the clinical outcome. A significant change of SEPs was defined as an amplitude change over 50% or the loss of response.

Thirteen out of 21 patients (62%) who completed the whole experimental setup, including the early postoperative control, showed no significant change in the SEPs before and after surgery, seven patients (40%) showed a worsening, and one patient showed an improved electrophysiological result (Fig. 4a). Analysis of overall postoperative neurological

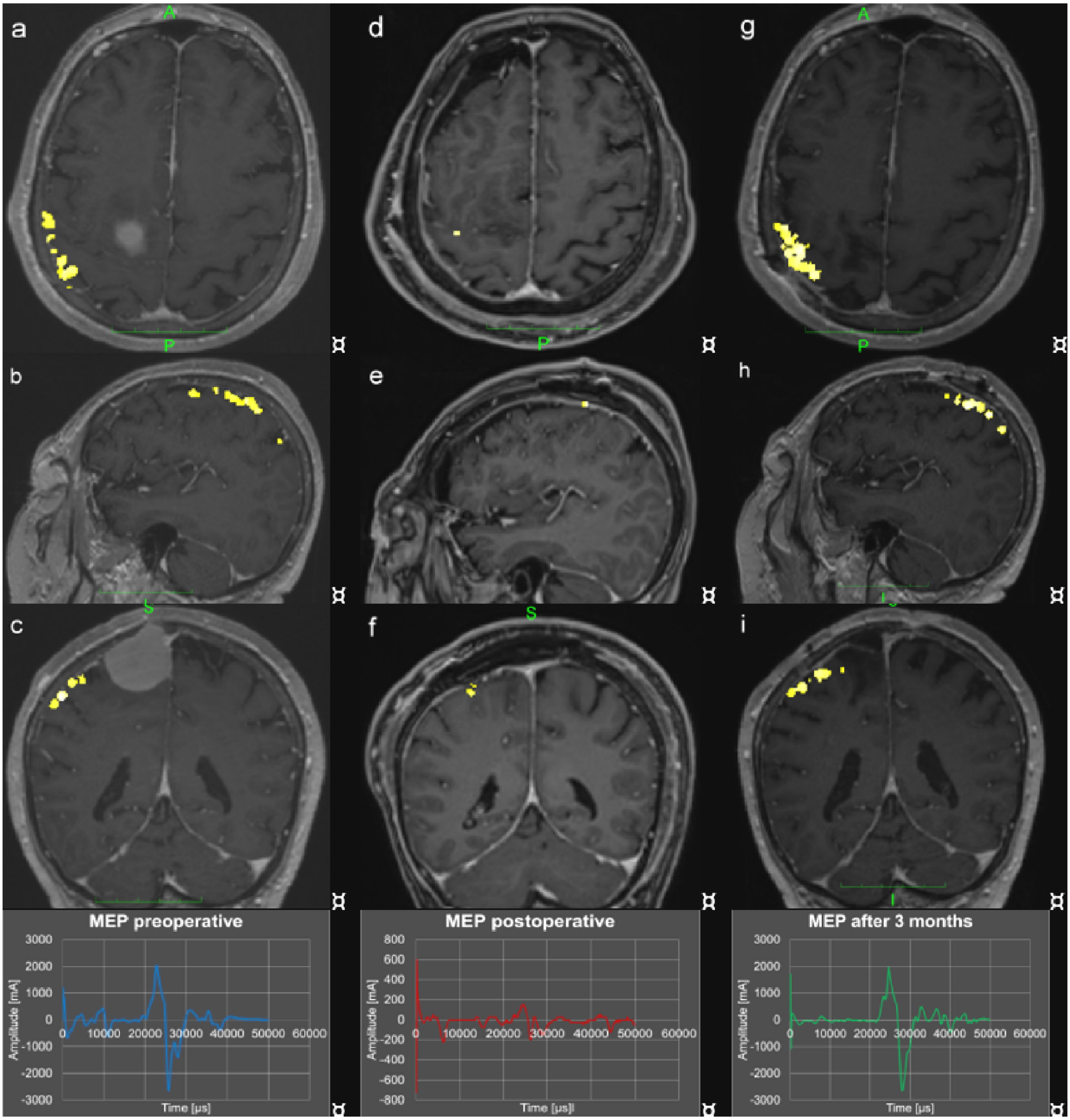

Fig. 3 TMS primary motor cortex mapping of patient 27 comparing representative curves of the motor-evoked potentials preoperative, postoperative, and after 3 months; graphic **a**, **b**, and **c** show the preoperative MRI with the stimulation points included in axial (**a**), sagittal (**b**), and coronar (**c**) view. Graphic **d**, **e**, and **f** show the same MRI slices in the early postoperative session and graphic **g**, **h**, and **i** show the late postoperative results. Below every row, representative MEP curves for each examination are shown

outcome out of the 21 patients who completed the first postoperative session revealed that four patients (19%) showed a neurological improvement, eight (38%) were stable, and nine presented a worsening (43%) of neurological status, including new sensory and motor deficits (Fig. 4b).

Of the 15 patients who completed the second follow-up, seven (46%) had a better neurological status, four (27%) showed a stable state, and four (27%) patients suffered from a worsening of the symptoms (Fig. 4c).

The four patients with the improved neurological status did not show a significant change of the SEPs. Instead, six of the nine patients who showed a worsening of the neurological outcome also showed a significant worsening in the electrophysiological examination, two showed a worsening of

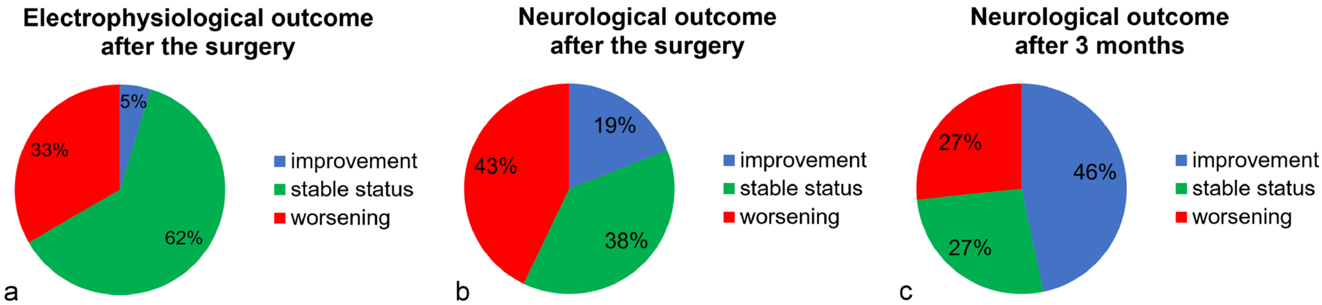

Fig. 4 Graphic with **a** electrophysiological outcome postoperative with patients included (*n* = 21); **b** neurological outcome after surgery with patients included (*n* = 21); and **c** neurological outcome after 3 months (*n* = 15)

symptoms, but an unchanged electrophysiological examination, and one showed an improved electrophysiological result. Seven of the eight patients with a stable neurological result showed a stable electrophysiological result, and one showed a worsening.

Discussion

Our prospective study was performed to implement TMS primary motor cortex mapping in our neurosurgical workflow of brain tumor surgery related to the primary motor cortex region. The navigational system of LOCALITE® and the TMS of MAGVENTURE® were used and combined with intraoperative neurophysiological monitoring.

Navigational system and TMS navigator

The choice of the LOCALITE® navigation system was made because this system is well established in our department. This system is also used for clinical research and implementation of enhanced ultrasound technology improving real-time imaging during brain tumor operations [2, 16, 18]. LOCALITE® uses the TMS stimulator of MAGVENTURE®, which is already being used by our neurological department and their aphasia and motor research programs [7, 8]. A disadvantage of this one-channel MEP setting, however, is that only one muscle can be examined at one time, whereas the NEXSTIM® system, which is used by other research teams, has six channels for the MEPs.

Analyzing only one upper limb muscle is insufficient for a precise mapping of the primary motor cortex, missing the representations of the face, arm, and leg. While just stimulating one muscle, the area of the positive motor area is quite small, but with the presentation of the stimulation points on the MRI, the gyrus precentralis can be tracked.

The preoperative monitoring by using TMS gives us a hint, where to detect the gyrus precentralis. Adding the intraoperative monitoring, with the stimulation of arm and leg, using the grid electrode, the exact dimension of the primary motor cortex can be clarified. We also started to use a direct monopolar hand-held electrode to stimulate the primary motor cortex directly in order to complement our intraoperative monitoring. In future studies, we plan to examine at least three muscles of the upper limb, including the *M. abductor pollicis brevis*, *M. brachioradialis*, or the *M. biceps brachii* and muscles of the lower limb, for example, *M. tibialis* anterior. Furthermore, we could expand the examination including face muscles. On the one hand, this will improve the accuracy of the preoperative localization of the primary motor cortex; on the other hand, this procedure will be much more time-consuming and might not be tolerated by patients with brain tumors. The stimulation of the lower limb was only performed in four patients with higher stimulation strength (10–25%), which the patients found uncomfortable.

In our study, we performed a line-navigated TMS (Ln-TMS). Our setting included the combination of the stimulation of a clear MEP signal and a motoric response of the limb. A stimulation point was only included in the navigational system if both measurements were definitely performed. In contrast to our study other research groups used the electric field navigated stimulation (En-TMS) in order to map the primary motor cortex.

En-TMS is a method where the electric field can be visualized and the position and the angulation of the coil can be optimized [10].

In this paper, the authors discussed the accuracy of the different stimulation methods [23].

With En-TMS, a significantly higher ratio of stimulation responses is described. In our study with the use of Ln-TMS, the possible spreading of the stimulation answers could be prevented by using the combination of the MEP and the limb reaction. Further, we tried to exclude false-positive stimulation points, which measured a hand movement, but not a clear motor-evoked potential. Here, no exact measurements were performed, but could be a part of another publication. Altogether with the combination of limb movement and clear motor-evoked potential, we tried to eliminate these points and optimize the mapping of the motor cortex in our pilot study.

Patient selection and epileptic seizures

Thirty patients in total seem to be a small number of included patients in 2 years. The study design excluded patients with epileptic seizures due to the risk of causing a seizure by performing the stimulation. This decision was made in agreement with the local ethical committee. We found different opinions about this fact in the literature. Warnings of induced seizures, especially in patients with tumors in the primary motor cortex, are given [22]. Otherwise, the groups of Krieg and Picht do not differentiate between patients with or without epileptic seizures [13, 19]. In their studies, the TMS procedure could not provoke a new seizure in any patient who had had a former epileptic seizure [25]. On the other hand, the most probable reason for the dropout directly after the surgery in our study was the development of new seizures. So, we proclaim that the dropout rate caused by seizures would be higher, if we had included patients with epileptic seizures in the first place. Regarding the high rate of patients, lost during follow-up, most patients were not able to perform the whole setting because of the conditional worsening. We should consider the natural development of the cancer disease, especially the brain tumors like metastasis and glioblastoma. At a certain point of these diseases, a worsening is inevitable.

Surgical planning

After performing the preoperative primary motor cortex mapping, the TMS results were shown to the operating surgeon. According to this data, the planning of the access was sometimes changed to guarantee a safe approach to minimize the risk of neurological deficits due to the surgical procedure. However, this is only an observation, not quantified research. In the future, we plan to add a questionnaire for the neurosurgeon in our study setting.

The exact location of the tumor and the possible displacement of the eloquent area, especially with the included meningioma cases, is an important point to discuss. If a meningioma displaces the primary motor cortex from the surface, the stimulation cannot be performed correctly. In our setting, four meningioma cases were included. Three tumors were located postcentral and one precentral, so the primary motor cortex was not shifted from the surface, it was only moved frontal or in one case parietal. In all cases, a mapping of the primary motor cortex was possible.

TMS, neurophysiology, and neurological outcome

In our study, we analyzed the SEP as the relevant electrophysiological examination, because this was the standard measurement performed before implanting the TMS in our surgical setup.

SEPs were always measured preoperative and intraoperative. Additionally, MEPs could be used. This stimulation was performed with the ISIS (INOMED®). With the SEPs, just an indirect stimulation of the primary motor cortex can be shown.

The MEPs in the TMS study were performed with the MAGVENTURE® one-channel system, but could not be transferred, and more important, no valid measurements of the amplitudes could be documented. With the development of a new measurement tool, we are now able to take out the valid data and will include this data in further studies. This is an important step in order to implement this method in our clinic. A complete comparability between the TMS data generated by the MAGVENTURE® system and the intraoperative data, which is documented with the ISIS (INOMED®), is not possible. Previous studies have already demonstrated good correspondence of the TMS with the direct cortical stimulation [20]. Our study could confirm this with direct primary motor cortex stimulation and verification through the navigation, despite the fact of localizing the primary motor cortex region only by stimulation of one muscle. While placing the grid electrode and identify the sulcus centralis, the primary motor cortex can be presented. By using the navigational pointer and placing it on the grid electrode, the gyrus precentralis can be seen on the navigational system and matched also the stimulation points. Using just one muscle means a small marked area, but the gyrus can be tracked. The correlation between the preoperative TMS data and the direct stimulated gyrus was verified by the surgeon without any exact measurements. The overlap of both data was documented just with a screenshot. In order to define the difference between the preoperative and intraoperative data, an additional measurement tool needs to be developed, because it is not included in our current setting.

Further, a good correlation between the IOM and the postoperative neurological outcome could be detected. As demonstrated in our study, neurological improvements correlated with stable electrophysiological results.

On the other hand, six out of nine patients (67%) with a clinical worsening also showed a worsening of the SEP, and seven out of eight patients (87.5%) with a stable clinical state did not show any significant change in the electrophysiological examination. Furthermore, the patient with a worsening of the electrophysiological examination without a neurological correspondence could be an incorrect measurement, caused by, for example, a different examiner or different physical conditions of the patient (e.g., water deposits in the legs due to intensive care treatment). Fortunately, most of the patients with a worsening of the symptoms recovered, especially when the IOM did not show a complete loss of the amplitudes. Thus, this helps to complete the resection during the surgery, even with a decrease of the IOM curves. A reason for that transient deterioration of the neurological status could be the intraoperative manipulation and the edema around the tumor and not the destruction of the cells because of the tumor itself. These findings confirm intraoperative and postoperative findings of the group of Kombos and Krieg [9, 12].

Regarding analyzing the neurological outcome, neurological worsening of patients was reported in the literature in 11–13% after 3 months postoperatively using TMS and intraoperative neurological monitoring [21, 22]. The early neurological examination in our series showed a worsening of 43% and decreased to 29% after 3 months. However, these results should be interpreted carefully because of the low number of patients examined after 3 months in our series. In difference to other studies, we performed a long-time follow-up with a neurological examination to identify the final neurological outcome. With this additional step in our setup, we could measure the improvement of an early postoperative worsening. Regarding the seven patients with a partial resection of the glioblastoma, we performed a postoperative volumetric analysis of the residual tumor, where no dependence between the neurological outcome and the extent of resection was found. We cannot compare these data with a group of total resection, because we included only one patient with a total resection of a glioblastoma in our study. Altogether, with the use of TMS in our setting, we tried to minimize the risk of a neurological deficit by decreasing the extent of resection in the primary motor cortex. In the end, we cannot find a correlation between the extent of the residual tumor and the neurological outcome in our study due to the number of patients included. Furthermore with the LOCALITE® system, we are not able to perform the volumetric analysis, so we used this tool in our BRAINLAB® navigational system. In the future, this tool will be included in our LOCALITE® system.

Additionally, we performed the late postoperative TMS to display the neuronal plasticity. As shown in Fig. 3, we compared the stimulation points in the MRI at different stimulation times. For now, an exact measurement tool is missing, but will be developed by the LOCALITE®.

The analysis comparing preoperative and postoperative TMS results was made with three examiners with a subjective assessment of the primary motor cortex area defined by the stimulation points included. At this time, the area that was mapped cannot be quantified more precisely and, thus, compared objectively. We will try to use the tool invented by LOCALITE® in further studies.

Other criticisms could be the area defined by the stimulation points included and its variety of numbers. The TMS mapping was performed with minimal stimulation intensity necessary to present a motor-evoked potential with a clear neurological response. In some examinations, higher stimulation intensity, such as 100%, was necessary in order to have a clear response. This measurement can cause too large areas of the primary motor cortex, which is another safety aspect for the patient, when the surgeon is more careful, because an increased motor cortex area is shown. To perfectly identify the exact area, the grid electrode was used during surgery.

Another critical point is that not all our stimulation points included were represented on the primary motor cortex, which can be defined by anatomic landmarks in the MRI. One reason for this inaccuracy could be the stimulation of the premotor cortex, which could possibly lead to indirect stimulation responses. Including more points can lead to a more accurate definition of the motor cortex area and a better comparability. Further, the stimulation strength is a possible discussing point. Surgical manipulation and varying coil-cortex-distance (CCD) influences the TMS effect. This effect can lead decreased MEP data. By using the same stimulation intensity, we could show this effect. If no stimulation was possible, we used higher stimulation strength, such as mentioned in six patients in order to perform the postoperative TMS.

Other limitations of our prospective study are the lack of a control group and the small sample size. We are planning a prospective case-control study in the future.

Conclusion

The TMS, which was performed in difference to other research groups with TMS of MAGVENTURE®, allows a safe and reliable mapping of the primary motor cortex both pre- and postoperatively with good correspondence to intraoperative direct cortex stimulation. In summary, the combination of preoperative TMS mapping and intraoperative SEP contributes to an improvement of the localization of the primary motor cortex. In this pilot study, TMS is successfully integrated into our clinical and surgical workflow. Further research with a higher number of patients, a case-control design, and an extension to other eloquent brain areas, such as the language and visual cortex, is mandatory.

Compliance with ethical standards

Conflict of interest All authors 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.

Informed consent Informed consent was obtained from all participants of the study.

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

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