E lectrical cortical and subcortical stimulation is the gold standard for localization of motor function, and this validated intraoperative technique helps to preserve the eloquent structures of the primary motor cortex and CST.\textsuperscript{3,14,15,26,31,36,54} Intermittent subcortical mapping of the CST with a handheld probe is used to localize motor tracts in deep white matter structures.\textsuperscript{1,2,12} Continuous monitoring of MEPs by DCS with a strip electrode enables real-time assessment of the functional integrity of the CST.\textsuperscript{30,40} The predictive value of signal alterations of MEP monitoring for motor deficits has been shown in several studies.\textsuperscript{11,20–22,30,31,48}

Both methods are widely used and have improved...
the safety of motor eloquent tumor surgeries.1,8,11,13,14,20,21, 30,39,40,48 These techniques not only help to preserve motor function, but they also indirectly increase the success rate of radical tumor resection by clarifying whether a region that is presumed preoperatively to be eloquent is confirmed intraoperatively to be eloquent. The concept of presumed eloquence as a modifiable risk factor predicting disease progression and death has been shown recently.8

Although mapping and monitoring are used to provide a warning sign for motor system damage during tumor removal and are likely to have different strengths and weaknesses, they are not often used simultaneously. Many centers prefer one technique1,2,14,22,27,31,53 and those that have used both have rarely compared the clinical value of the two methods directly.10,20,33,35,37,40 Thus, it remains unclear whether a change in the DCS monitoring signal or a certain subcortical motor MT provides the first warning sign that the CST is close to the operational site and at risk of mechanical injury. Likewise, the lowest mapping MT at which the CST is still considered to be a safe distance from the site of dissection remains unclear. This lowest MT would be the clinically most relevant with regard to maximizing tumor resection; however, it must also be safe in terms of avoiding motor deficits.

In this study of a cohort of 100 consecutive patients who underwent excision of tumors with presumed subcortical (CST) motor eloquence, we investigated the relation between mapping and monitoring warning signs indicating a close but still safe distance from the CST. Direct cortical stimulation monitoring signal configuration and lowest mapping MTs were correlated to the motor function outcome at the 3-month follow-up. We also sought to determine whether a subcortical mapping MT exists where signal alterations in DCS-MEP monitoring start to occur.

**Methods**

**Patient Population and Preoperative Testing**

The authors analyzed data obtained in a series of 100 consecutive patients with intrinsic brain tumors (n = 76), metastatic lesions (n = 17), and cavernous malformations (n = 7) close (≤ 10 mm) to the CST, as shown on preoperative DTI fiber tracking. The tumor surgeries were performed from March 2009 until October 2011. We included only patients in whom the craniotomy and tumor approach allowed placement of a strip electrode on the precentral gyrus for DCS monitoring. All patients underwent extensive preoperative imaging including DTI fiber tracking and 3D T1-weighted gradient-echo sequence magnetized prepared rapid gradient echo (MP-RAGE) performed with a 3-T MAGNETOM TRIO Tim System MRI unit (Siemens). Tumors involving the gray matter of the precentral gyrus were excluded from the analysis because placing a strip electrode for DCS would have interfered with the surgical approach and especially the incision. Therefore, data in this subgroup were analyzed in a separate study.42 Infratentorial tumors were excluded as well. Patients with newly diagnosed brain tumors and patients with a first tumor recurrence were included. Preoperative clinical evaluation was done according to MRCS (grade range M1–M5), NIHSS (National Institutes of Health Stroke Scale), and Karnofsky Performance Scale. All patients signed an informed consent form for the surgery and the procedure. This analysis was approved by the local institutional ethics review board (Cantonal Ethic Commission [Kantonale Ethikkommission], Bern University Hospital, Bern, Switzerland).

**Preoperative Data**

There were 53 male and 47 female patients whose mean age (± SD) was 50 years ± 17 years. Seventy-nine patients presented with a newly diagnosed cerebral tumor and 21 suffered from tumor recurrence. The chief complaint leading to diagnosis was epileptic seizure in 50 patients, progressive motor weakness in 21, mental status changes in 11, and headache in 10. In 8 patients tumor progression was diagnosed in the MRI follow-up study. The preoperative Karnofsky Performance Scale score was 90% in 68 patients, 80% in 27, and 70% in 5 patients. In 56 patients preoperative motor status was normal and in 33 patients it was slightly impaired (Grade M4+). In 10 patients motor impairment ranged from Grade M4 to Grade M3, and one patient presented with Grade M2 impairment.

**Intraoperative Monitoring and Mapping Techniques**

Anesthesia was induced with a bolus of propofol (1–2 mg/kg body weight), fentanyl (1–2 µg/kg body weight), and remifentanil (1–2 µg/kg body weight) and was maintained with propofol (100–200 µg/kg/min) and remifentanil (0.5 µg/kg/h). A short-acting relaxant (Esmeron 0.6 mg/kg body weight) was administered for intubation purpose only. Recovery from muscle relaxation was tested using the “train-of-four” technique involving percutaneous stimulation of the right median nerve (40 mA, 0.2 msec pulse duration).52

For intraoperative neurophysiological monitoring and mapping, we used the ISIS system (Inomed Co.) equipped with a constant-current stimulator (OSIRIS, maximal stimulator output of 220 mA; Inomed Co.). Muscle MEPs were recorded by pairs of needle electrodes inserted in standardized fashion in the contralateral target muscles for the face as well as the distal and proximal upper and lower limbs. After opening of the dura mater, the central sulcus was identified using the median nerve somatosensory evoked potentials phase-reversal technique. A strip electrode with 4 contacts (each 4 mm in diameter and with an interelectrode distance of 10 mm) was placed tangential to the assumed central sulcus, or if the craniotomy was not located over the precentral gyrus, the electrode was cautiously slid under the dura toward the assumed central sulcus.50 The placement of the strip electrode was verified and corrected with the help of the median somatosensory evoked potentials phase reversal. Then the contact of the electrode with the maximal positivity of the N25 peak corresponding to the position on the precentral gyrus was chosen for direct cortical motor stimulation.11,49,50 The position of the strip electrode was slightly adjusted until an MEP of all contralateral target muscles
was obtained with a threshold below 10 mA. Direct cortical stimulation via the strip electrode was performed with multiple trains consisting of 5 stimuli. Within one TOF stimuli, a pulse duration of 500 μsec and an interstimulus interval of 4.0 msec (frequency 250 Hz) were chosen. The MT was defined as the stimulation intensity that elicited MEPs from the target muscle at a minimum amplitude of 30 μV within 4 consecutive trains at a 0.5-Hz repetition rate.

For mapping purposes, a monopolar probe with a 1.6-mm electrode was used to deliver a monophasic current up to 22 mA. The reference electrode was placed at Fpz (frontopolar zone [midline]). Identical stimulation parameters, as described above for DCS, were applied. Anodal (positive-current) and cathodal (negative-current) stimulations were used for cortical and subcortical mapping, respectively.

Direct cortical stimulation–recorded MEPs were considered as stable, allowing ranges of (relative) thresholds ± 4 mA from baseline values. A sudden threshold increase greater than 4 mA in motor stimulation intensity that could not be explained by technical or anesthetic confounders was interpreted as a specific warning sign. An MEP loss was defined as no motor response even when using DCS intensity up to 20 mA. The surgeon was notified when motor stimulation intensity had to be increased greater than 4 mA or when a loss in MEPs occurred.

Subcortical monopolar TOF mapping via the hand-held probe was performed in deep white matter during dissection and tumor removal at the discretion of the surgeons. To identify the MT of every stimulation site, the stimulation current was systematically increased until an MEP response was elicited (maximum 22 mA), or it was started at 22 mA and then decreased until the MEP response was lost. Considering the fact that lower MTs correspond to a closer distance to the CST, quantitative values of the MT were used to functionally guide the surgeon. Approaching values below 10 mA, motor mapping was repeated every 2 mm of tumor resection with high temporal and spatial frequency. With real-time feedback from continuous DCS-MEPs via the strip electrode and simultaneous quantitative values from subcortical mapping, resection was continued. In cases of normal DCS-MEPs, tumor resection was continued until the mapping MT reached 5 mA. In cases in which the surgeon judged from the intraoperative setting that he would not be able to remove the tumor completely, we usually stopped resection around the 5-mA mapping MT level. However, when the surgeon believed he could achieve a gross-total removal or radiologically complete removal, resection was continued slowly, provided that the DCS-MEPs remained stable, and mapping was repeated every 1 mm of tumor resection. Resection was definitively stopped when the mapping MT reached 3 mA or below. If alterations in DCS-MEPs were noticed, resection was immediately suspended. In an attempt to avoid permanent postoperative motor deficit, removal of further tumor tissue was stopped when these DCS-MEP alterations persisted for more than 15 minutes despite suspension of tissue excision and despite removal of the retractor (rarely used), increasing cerebral perfusion pressure to normal, local application of nimodipine, normalizing anesthesia, and ruling out technical confounders.

Postoperative Imaging

Independent senior radiologists from the neuroradiology department evaluated postoperative MRI, performed within 48 hours after surgery. The primary goal of surgery was radiologically complete resection of benign tumors and metastatic tumors, or gross-total resection of malignant tumors, defined as resection of all FLAIR signal areas in WHO Grade II gliomas and any T1-weighted contrast-enhancing tissue in WHO Grade III gliomas and WHO Grade IV glioblastomas. Additionally, early postoperative MRI perfusion- and diffusion-weighted images were included routinely to search for vascular injury and infarction.

Clinical Examination and Data Analysis

Postoperative clinical evaluation was performed using the same scales that were used preoperatively. The evaluation was repeated 1 day after surgery, on the day of discharge, and on the 3-month follow-up visit. Descriptive statistical analyses were performed for selected parameters including patient characteristics and MTs of MEP responses. For analysis of acquired neurophysiological data, NeuroExplorer of the ISIS (Inomed Co.) was used.

Although the cases presented in this paper were retrospectively analyzed, we applied the neurophysiological protocol and hypothesis as an institutional protocol in a prospective manner.

Results

Final Histopathology

The tumor entities according to final histopathological findings after surgery were distributed as follows: low-grade glioma (n = 18 [5 astrocytoma, 4 oligodendrogloma, 8 oligoastrocytoma, and 1 pilocytic astrocytoma]), anaplastic glioma (n = 19 [7 anaplastic astrocytoma, 3 anaplastic oligodendrogloma, 9 anaplastic oligoastrocytoma], glioblastoma (n = 35), ependymoma (n = 2), primitive neuroectodermal tumor (n = 2), metastasis (n = 17), and cavernoma (n = 7). Thus, 76% of the lesions were intrinsic brain tumors and 24% were metastatic or vascular lesions.

Extent of Resection and Reasons to Abort Further Removal

Postoperative MRI, performed within 48 hours after surgery, showed radiologically complete resection in 88% of the metastatic or vascular lesions and gross-total resection in 71% of the intrinsic brain tumors. Subtotal resection was achieved in the remaining 25 patients (25%).

In patients in whom subtotal resection was performed, we stopped the tumor removal because of preoperatively defined warning signs of intraoperative neurophysiological changes in 17 (68%) of 25 patients. In 7 of these 17 pa-
patients the resection was aborted due to unexpected occurrence of electrophysiological warning signs. Of these 7 patients, in 3 patients mapping revealed a site with an MT of 1 or 2 mA, in 2 patients persisting significant DCS alterations occurred, and in 2 patients a sudden DCS-MEP loss was observed. In the remaining 10 cases, the surgeon stopped the resection as planned according to our internal mapping limit when a mapping MT level of 3–5 mA was reached and DCS-MEPs did not show a significant change (> 4-mA stimulation threshold increase). In these cases, the surgeon judged from the intraoperative setting that he would not be able to remove the tumor completely without significant risk of damage to the CST. In 8 patients resection was stopped according to neuronavigation as preoperatively planned due to infiltration of other eloquent systems such as the basal ganglia, thalamus, optic radiation, or corpus callosum (planned subtotal resection in preoperatively judged gross-total resection–negligible tumors).

Postoperative Motor Deficits

New postoperative worsening in motor status 1 day after surgery was observed in 22 patients with intrinsic tumors and in 8 patients with metastatic or vascular lesions (total 30%). Of these, 25 presented with motor worsening of 1 point and 5 patients presented with a motor worsening of 2 or more points in MRCS grade. On day of discharge, the deficit had already reversed in 19 patients, but was still present in 11 patients (11% of all operated patients). Of these 11 patients, 2 (18%) had a relative worsening of motor status of 2 or more points in the MRCS grade. At the 3-month visit, 5% of patients (n = 5) presented with a persisting motor deficit. One of these 5 patients (20%) had relative worsening of motor status of 2 or more MRCS grades. The distribution of relative change in MRCS muscle strength grade at the 3 different time points is shown in Fig. 1.

Of the 24 patients in whom resection had to be aborted unexpectedly (those with MT 1–2 mA or severe irreversible DCS-MEP alterations or loss), 14 patients (58%) had a new motor deficit 1 day after surgery, 9 patients (38%) had a new deficit at discharge, and 5 patients (21%) had a persistent deficit at 3 months. Of the 35 patients in whom resection was stopped as planned according to our mapping criteria (MT 3–5 mA but no severe DCS-MEP changes), 9 patients (26%) had a new motor deficit the day after surgery, 1 patient (3%) had a new motor deficit at discharge, and no patient had a persisting deficit at 3 months.

Evaluation of Subcortical Mapping MT

The lowest intraoperatively acquired individual monopolar mapping MTs were found as follows: an MT of more than 20 mA was found in 12 patients, an MT of 11–20 mA in 13, an MT of 6–10 mA in 20, an MT of 4–5 mA in 30, and an MT of 1–3 mA in 25 patients.

Of the 30 patients with a lowest mapping threshold of 4–5 mA, 40% (n = 12) had a new motor deficit at the day after surgery, 10% (n = 3) had one at discharge, and 0% (n = 0) had a new deficit 3 months after surgery. Of the 25 patients with a lowest mapping threshold of 3 mA or less, 32% (n = 8) had a new motor deficit 1 day after surgery, 16% (n = 4) at discharge, and 8% (n = 2) had a new deficit 3 months after surgery (Fig. 2).

Analysis of DCS-MEP Monitoring Signal Alterations

Stable DCS-MEPs were observed in 70% of surgeries (70 patients). Of these 70 patients, 17% (n = 12) had a new motor deficit 1 day after surgery, 0% had a new motor deficit the day of discharge, and 0% had a new motor deficit 3 months postoperatively.

Eighteen percent of patients had unspecific alterations in DCS-MEPs, such as slight (< 4-mA) or reversible threshold increments, that were often associated with a change in the depth of anesthesia or blood pressure fluctuations. Of the 18 patients with these unspecific DCS-MEP changes, 39% (n = 7) had a new motor deficit 1 day after surgery, 11% (n = 2) had a new motor deficit at discharge, and 0% had a new motor deficit 3 months after surgery.

Significant alterations in DCS-MEPs (> 4-mA threshold increase) that occurred suddenly and persisted for more than 15 minutes but with no DCS-MEP loss were observed in 8 patients. Of the 8 patients with persist-
Safe subcortical motor mapping thresholds

ing significant DCS-MEP changes, 88% (n = 7) had a new motor deficit 1 day after surgery, 63% (n = 5) at discharge, and 25% (n = 2) at the 3-month follow-up visit.

A sudden loss of DCS-MEPs was observed in 4% of the cases. Of the 4 patients with sudden and persisting DCS-MEP loss, 100% had a new motor deficit 1 day after surgery, 100% at discharge, and 75% (n = 3) at 3 months after surgery (Fig. 3).

Correlation of DCS and Mapping Thresholds

Except for the 2 patients with vascular injury, no irreversible DCS-MEP alteration or loss occurred when subcortical MTs were above 8 mA. One patient (Case 67 [see Table 1]) exhibited a sudden irreversible increase in stimulation threshold (> 4 mA) when mapping MT was 8 mA. He suffered no permanent motor deficit. The other irreversible DCS-MEP changes occurred with mapping MTs of 4 mA (2 patients), 3 mA (2 patients), and 2 mA (2 patients). A DCS-MEP loss occurred with lowest documented mapping MTs of 6 mA, 4 mA, and 1 mA. Except for the 2 patients with vascular injuries, the relative rate of irreversible changes or loss of DCS-MEPs in the different mapping groups was 0% in the > 20-mA mapping MT group, 0% in the 11- to 20-mA group, 10% in the 6- to 10-mA group, 10% in the 4- to 5-mA group, and 20% in the 1- to 3-mA mapping MT group (Fig. 4). Using single quantitative values and excluding the patients with vascular lesions, only 2 irreversible DCS-MEP changes or loss occurred at a motor MT of more than 4 mA, and the remaining 8 of 10 occurred at an MT of 1–4 mA. This corresponds to a rate of 3.4% (2 of 58 patients) at a mapping MT of above 4 mA and 20% (8 of 40 patients) at a mapping MT of 1–4 mA (p < 0.05, Fisher exact test, two sided). Reversible changes were found in every mapping threshold category ranging from 10% to 25%. All cases involving irreversible alterations or loss of DCS-MEP signal and their motor deficits are listed in Table 1.

Positive and Negative Predictive Values of Mapping and DCS-MEP Monitoring

For consideration of different mapping MTs and DCS-MEP changes as warning criteria for permanent motor deficit, the sensitivity, specificity, positive and negative predictive values are shown in Table 2. Because we had a vascular injury rate of 2%, we have calculated these values with (mechanical and vascular injury) and without (mechanical injury only) the 2 cases of remote ischemic CST damage.

In a surgical setting in which an immediate intraoperative decision must be made whether to continue with tumor tissue removal, the negative predictive value for a motor deficit is most important. This was 100% when DCS-MEPs remained stable or showed only unspecific or reversible changes (that is, the warning criteria DCS-MEP loss or irreversible DCS-MEP alterations did not occur) even at very low mapping MTs of 1–3 mA. The positive predictive value was 42% when any irreversible significant change or signal loss in DCS-MEPs occurred. For DCS-MEP loss, the positive predictive value was 75%. When we exclude the 2 cases of vascular injury, which is a known confounder of mapping and will be diagnosed by DCS-MEP changes, the negative predictive value for a motor deficit was 100% for a mapping MT of ≤ 10 mA versus > 10 mA, 98% for a mapping MT of ≤ 5 mA versus > 5 mA, and 99% for a mapping MT of ≤ 3 mA versus > 3 mA.

Electrophysiological Findings and Causes of Permanent Deficits

Further examination of the 5 patients with permanent deficits at 3 months postoperatively showed that in 2 cases the postoperative infarction was the result of a perforating vessel injury, and in 3 patients it was the result of direct mechanical injury to the CST (Table 1). Thus, the high mapping MTs of 13 mA and 20 mA in Cases 13 and 46 indicated that the site of tumor removal was still rather distant from the CST, whereas the sudden and irreversible DCS-MEP alteration/loss indicated CST damage. Both findings and the diagnosis of an infarction established using postoperative diffusion-weighted imaging supported the diagnosis of a vessel injury causing a remote CST damage, which is a known limitation of both mapping and MEP monitoring.

In Cases 7 and 24, which were treated relatively early in the series, the lowest documented mapping MTs were 6 mA and 3 mA, respectively. However, this was not the mapping MT at the end of the operation, because
the surgeon continued to achieve a gross-total resection. At the time of the sudden DCS-MEP loss in Case 7 and sudden significant DCS-MEP threshold increase in Case 24, surgery was stopped immediately without performing another round of mapping. Therefore, the mapping MTs were probably lower than 6 mA and 3 mA, but the exact MTs remain unknown. These cases show that continuing the resection at these low MT levels carries a risk of injury, as current mapping technique must be repeated with a high spatial and temporal coverage, which is not always the case.

In Case 56, we performed mapping with high spatial and temporal coverage and continued with the resection of a cavernoma even when a mapping MT of 1 mA was reached. As this was a cavernoma, we believed that we could remove it completely, despite having reached a mapping MT of 1 mA. After resection of the final tumor pieces, DCS-MEPs disappeared suddenly. Thus, Cases 7, 24, and 56 involved direct injury of the CST as the cause of the permanent motor deficit.

**Discussion**

Complete removal or gross-total resection remains

<table>
<thead>
<tr>
<th>Case No.</th>
<th>HP Grade†</th>
<th>Admission MRCS Grade</th>
<th>Grade Changes in MRCS</th>
<th>Intraoperative Data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 Day Postop</td>
<td>Day of Discharge</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>M5</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>13</td>
<td>1</td>
<td>M5</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>16</td>
<td>1</td>
<td>M5</td>
<td>0</td>
<td>0</td>
</tr>
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<td>24</td>
<td>1</td>
<td>M4+</td>
<td>2</td>
<td>1</td>
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<tr>
<td>54</td>
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<td>M4+</td>
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<td>M4+</td>
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<tr>
<td>83</td>
<td>1</td>
<td>M5</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

* Neurophysiological findings obtained in all patients and relative postoperative motor outcomes (MRCS grade), as well as postoperative MRI results, are shown. Abbreviations: CR = complete resection; GTR = gross-total resection; HP = histopathology; STR = subtotal resection.
† Histopathology grades: 1 = intrinsic tumor; 2 = metastasis or cavernoma.
‡ DCS-MEP findings: 1 = no change; 2 = reversible changes; 3 = irreversible MT increment; 4 = MEP loss.
§ High-frequency TOF monopolar MT groups: 1 = 1–3 mA; 2 = 4–5 mA; 3 = 6–10 mA; 4 = 11–20 mA; 5 = > 20 mA.
¶ Extent of resection on early postoperative MRI.

**TABLE 2:** Calculated sensitivity, specificity, and positive and negative predictive values for different warning criteria, with and without the 2 vascular cases at the 3-month visit*

<table>
<thead>
<tr>
<th>Warning Criteria</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>MT ≤10 mA vs &gt;10 mA</td>
<td>60</td>
<td>24</td>
<td>4</td>
<td>92</td>
</tr>
<tr>
<td>MT ≤10 mA vs &gt;10 mA (excl VI)</td>
<td>100</td>
<td>24</td>
<td>4</td>
<td>100</td>
</tr>
<tr>
<td>MT ≤5 mA vs &gt;5 mA</td>
<td>40</td>
<td>44</td>
<td>4</td>
<td>93</td>
</tr>
<tr>
<td>MT ≤5 mA vs &gt;5 mA (excl VI)</td>
<td>67</td>
<td>44</td>
<td>4</td>
<td>98</td>
</tr>
<tr>
<td>MT ≤3 mA vs &gt;3 mA</td>
<td>40</td>
<td>76</td>
<td>8</td>
<td>96</td>
</tr>
<tr>
<td>MT ≤3 mA vs &gt;3 mA (excl VI)</td>
<td>67</td>
<td>76</td>
<td>8</td>
<td>99</td>
</tr>
<tr>
<td>DCS loss (Group 4) vs no loss</td>
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<td>99</td>
<td>75</td>
<td>98</td>
</tr>
<tr>
<td>DCS loss vs no loss (excl VI)</td>
<td>67</td>
<td>99</td>
<td>67</td>
<td>99</td>
</tr>
<tr>
<td>DCS loss or irreversible alt (Grade 3–4)† vs no change or unspecific changes only</td>
<td>100</td>
<td>93</td>
<td>42</td>
<td>100</td>
</tr>
<tr>
<td>DCS loss/irreversible alt (excl VI) vs no change or unspecific changes only</td>
<td>100</td>
<td>93</td>
<td>30</td>
<td>100</td>
</tr>
</tbody>
</table>

* alt = alteration; excl = excluding; NPV = negative predictive value; PPV = positive predictive value; VI = vascular injury.
† See Table 1 for definition of grades of DCS-MEP findings.
Safe subcortical motor mapping thresholds

the surgical goal in most intracranial tumors including gliomas, and there is increasing evidence that it prolongs overall and progression-free survival in patients with low-grade gliomas and glioblastomas.\(^{23-25,41,43,44,46}\) However, more than 50% of these tumors are judged to be “presumably eloquent” based on the preoperative images.\(^{8,9,45}\) Intraoperative mapping is used for the goal of maximizing tumor resection and minimizing neurological deficits.\(^{8,9}\) Thus, identification of mapping and monitoring red flags for impending mechanical damage of the CST remains a crucial topic.

In this context, we showed for the first time that mapping thresholds of 1–3 mA, which are lower than previously thought, might be safe provided that DCS-MEPs remain stable at the same time. Although irreversible changes in DCS-MEP signal occurred significantly more often when mapping reached MTs of 4 mA or less, none of the 32 patients with these mapping MTs and unchanged DCS-MEPs or only a reversible or minor (< 4-mA) DCS-MEP threshold increase had a permanent motor deficit.

**Interpretation of Findings**

The findings of the comparison between simultaneously performed mapping and monitoring and the motor outcome as described in the Results section allow the following interpretation: 1) Mapping MTs correlate with the risk of CST injury; 2) there is safe mapping corridor between the first (high) and critical (low) MTs; 3) the critical (low) mapping MTs are lower than previously thought; 4) DCS-MEP monitoring has the best positive and negative predictive value for a permanent deficit; 5) DCS-MEP changes often occur abruptly and can only be influenced in 60% of cases; 6) almost the entire predictive value of DCS-MEP monitoring hinges on the irreversibility of a major signal chance (> 4-mA MT increase or signal loss); 7) unfortunately, irreversibility is a post hoc definition; 8) considering that irreversible DCS-MEP changes and motor deficits occurred during tumor tissue removal at apparently safe mapping MTs in some patients (vascular injuries excluded), we believe that the most likely cause is an insufficient temporal and spatial mapping coverage of the surgical field.

**Differences Between the 2 Commonly Used CST Mapping Techniques**

In addition to the classical bipolar 50- to 60-Hz mapping, monopolar 200- to 300-Hz TOF stimulation was shown to be a reliable technique for localizing the CST.\(^{18,20,33,51}\) This high-frequency TOF stimulation allowed a more quantitative evaluation of MEP changes regarding amplitude, latency, and duration.\(^{1,19,42}\) In contrast to the TOF technique, the classic 50- to 60-Hz stimulation would not elicit a single MEP but rather cause a tonic muscle response.\(^{19}\) Moreover, radial spreading of the electrical field of the monopolar TOF probe allows the electrical current to enter perpendicularly into the axon, resulting in a more effective stimulation.\(^{31}\) The field of a bipolar stimulation probe is more heterogeneous with regard to the lines of equal potential, except for the space between the two tips. Thus, if the region of interest is not directly located be-

### Mapping as a Tool to Quantitatively Localize the CST

The influence of subcortical motor mapping on resection grade and motor outcome during eloquent tumor surgery has been demonstrated by many groups.\(^{1,8,14,16,39}\) Eliciting an MEP depends on the charge applied to the tissue, which itself depends on stimulation intensity and pulse duration.\(^{38,51}\) Moreover, the current density decreases with distance.\(^{18,20,28}\) Thus, mapping localizes the CST, but the size of the area with positive stimulation varies with the intensity of stimulation current. The higher the stimulation intensity, the larger are the areas where MEPs can be generated, and vice versa. This also implies that with a higher stimulation intensity a positive stimulation can be found at a greater distance from the CST. This “stimulation-intensity-to-CST-distance” relationship has been increasingly investigated to better guide the surgeon during tumor resection. Studies comparing a positive bipolar 50- to 60-Hz stimulation response with diffusion tensor–imaged fiber tracking of the CST\(^{1,4,5,16,53}\) were limited by intraoperative brain shift, with lack of navigation accuracy (L.H. Stieglitz et al., unpublished data, 2012) and tonic muscle responses caused by 50-Hz stimulation.\(^{39,42}\) and only allowing a semiquantitative evaluation.

More recently, the monopolar TOF technique was used for a quantitative analysis, assuming that the closest tumor resection border to the imaged CST on the postoperative MR image would correspond to the lowest intraoperative stimulation site.\(^{19}\) Kamada et al.\(^{38}\) found a convergent nonlinear correlation of distance and postulated 1.8 mA as the electrical threshold of direct CST contact during monopolar cathodal subcortical stimulation (train of 5 stimuli, pulse duration 0.2 msec). Nossek et al.\(^{33}\) compared the thresholds of subcortical monopolar mapping (train of 5–7 stimuli, pulse duration 0.5 msec, 300 Hz) to navigation with brain shift correction by intraparative ultrasonography. They showed a linear correlation between the distance to the CST and MTs, with a relationship of 0.97 mA for every 1 mm of brain tissue,\(^{33}\) which corresponds to our rule of thumb: 1 mA = 1 mm.\(^{42}\) This linear correlation between stimulus intensity (train of 5 stimuli, pulse duration 0.2 msec, 500 Hz) and distance was also recently postulated by Ohue and colleagues,\(^{35}\) who analyzed the distance of the postoperative resection cavity to the imaged CST on early postoperative DTI MRI. Quantitative stimulation value–based motor mapping might allow definition of a “functional distance” to indicate when resection should slow down and to define functional borders of high-risk resection.

### What is the Critical Mapping Threshold for the CST?

The recommendations for when to stop further removal of tumor tissue vary widely. They range from aborting resection when there is a positive motor response
regardless of applied stimulation frequency or current intensity\(^{9,27}\) to having an MT range between 7 and 5 mA (minimum lower limit 3 mA) as the definitive mapping stop sign for further safe tumor resection.\(^{18,20,33,37,40}\)

Our hypothesis of a probably safe MT of greater than 1 mA is based on the following observations.

Using only the data from the lowest mapping MT group (1–3 mA), there were 2 patients with deficits (8%) and 23 patients without deficits (92%). With only these 2 cases, a repeated mechanical injury of the CST due to systematic violation of the critical distance from the CST is unlikely. If the “true” critical distance were reached, there would be more patients with permanent deficits, especially with a mapping MT of only 2 mA (0 of 11 patients). One (25%) of 4 patients with a mapping MT of only 1 mA had a DCS-MEP loss and a permanent deficit. The other 3 patients showed stable DCS-MEPs and no deficit. Therefore, we think that the 1 mA could be postulated as the critical distance from the CST where deficits regularly occur. But how do we explain the other 2 cases with permanent motor deficits and a mapping MT of 3 and 6 mA? As we have described, the MTs in these patients were acquired before continuing with tumor resection. The most likely hypothesis is that the resection continued at an MT of 6 mA (Case 7, which was an early case) and at 3 mA (Case 24) was not performed carefully enough. Especially when continuing resection at an MT of 3–4 mA or below, mapping requires the interruption of the surgery at every 1 mm of tumor removal. With the contemporary mapping technique, this is not only time consuming, but it is also prone to inaccuracies due to limited spatial mapping coverage of the surgical field.

**Relation Between Motor Mapping Thresholds and MEP Monitoring Changes**

Some groups have already combined motor mapping with continuous monitoring of MEPs\(^{20,40}\) because stable MEPs in supratentorial surgery have been proven to predict good postoperative motor outcome.\(^{11,30}\) However, data from a direct comparison between mapping thresholds and DCS-MEP changes are scarce. Nossek et al.\(^{33}\) have found that MEP monitoring, compared with mapping alone, could not increase the predictive value for immediate postoperative motor deficit. Two recently published studies that discussed mapping thresholds used combined monitoring of DCS-MEP but there was no analysis of the additional value of DCS-MEP warning criteria.\(^{35,37}\) We provide data supporting the benefit of using simultaneous quantitative motor mapping and DCS-MEP monitoring during the final steps of resection with very low mapping MTs and for diagnosing remote vascular damage. The simultaneous use of mapping and monitoring in our cases may already have reduced the incidence of major DCS-MEP signal alterations compared with other studies. Although different definitions were used, our 12% rate of irreversible alteration and irreversible loss compares favorably with the range of 17%–35% reported by other groups.\(^{21,22,32}\)

**Limitations**

An important limitation of subcortical motor mapping is that direct vascular damage, critical end-artery blood supply (for example, in the lenticulostriate territory), and ischemia due to brain retraction are not detected. In cases of ischemia involving the CST, however, DCS-MEP monitoring will show alterations, eventually even resulting in a loss of MEPs.\(^{31,48}\) This makes the combined mapping-monitoring approach a valuable tool that provides supplementary information to the surgeon.

It is evident that in tumors involving the primary motor cortex no continuous MEP monitoring is possible, as placing a strip electrode on the precentral gyrus would interfere with the surgical approach. Therefore, tumor surgery in the gray matter was not analyzed in this series and data are presented in another study.\(^{32}\)

Surgery of brainstem tumors does not allow placement of a strip electrode on the precentral gyrus due to the remote site of craniotomy. In brainstem tumors, transtemporally elicited MEPs may be used, which contrasts with very proximal tumors adjacent to the CST, where transcranial MEPs may already stimulate CST fibers distal to the tumor.\(^{20,38}\)

It remains unknown whether edema in the white matter influences the “current-to-distance” relation of about 1 mA equaling 1 mm. The concept of approaching the CST by quantitative subcortical TOF mapping is limited if voltage-dependent stimulation is used. When applying this concept, it is important to rely on constant-current stimulation so that the effective current in the brain tissue will be stable regardless of tissue impedance.

In the current study, the warning criteria were applied regardless of the pathology of the tumor. Although the advantages of mapping techniques are more obvious in intrinsic tumors, localization of the CST may also play a role during the removal of other lesions such as metastatic lesions or vascular malformations. Knowing the proximity of the CST may influence the strategy of resection, speed of dissection, power of electrocoagulation, and technique of hemostasis in both entities. Low-threshold TOF mapping could be considered as a functional navigation tool to indicate when dissection should slow down. The stability of DCS-MEPs gives real-time feedback about the functional integrity of the CST and supports the surgeon during tumor removal at low MTs, if intended. In summary, the warning criteria presented here may be a valuable additional tool for guiding the surgeon based on motor function during surgery close to the CST. However, it is important to mention that our results represent preliminary data and that further investigations of larger case series are needed to provide a more robust evaluation of these warning criteria.

**Conclusions**

There is an overlapping hierarchy between motor mapping and monitoring as warning signs for CST damage. Mapping provides an early warning sign and localizes motor tracts, whereas monitoring permits a good prediction of unchanged motor function when no signal alterations occur. Monitoring changes may occur rather late compared with mapping findings (that is, below a mapping MT of 3–4 mA). However, the use of monitor-
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ing as a warning sign alone is limited, as the first sign of DCS-MEP signal change may occur abruptly and was reversible only in 60% of signal changes. Moreover, the predictive value of DCS-MEP hinges on the irreversibility of major signal changes, which remains unknown for the surgeon and which is a post hoc definition. Therefore, mapping should primarily guide the resection of tumors close to the CST, but it should be complemented by monitoring when resection is performed at low mapping MTs. We assume a monopolar mapping MT of around 1 mA (train of 5 stimuli, pulse duration 0.5 msec) or even less where irreversible DCS-MEP changes regularly occur. Therefore, we recommend stopping tumor resection no later than at an MT of 2 mA. Limited spatial and temporal coverage of the resection plane by mapping may contribute to false higher MTs that may in fact be lower. Only DCS-MEP monitoring can diagnose remote CST damage by a vascular injury.

Disclosure

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