Increasing evidence indicates that more extensive safe resections improve survival outcome for many patients with brain lesions. However, the attempt to completely resect lesions close to primary motor neurons may lead to neurological impairment, with reported rates of severe neurological deficits of up to 50%. The authors’ objective was to determine the feasibility and safety of low-threshold motor mapping and its efficacy for increasing the extent of lesion resection in the proximity of M1 and the CST in children and adolescents.

Methods. The authors analyzed 8 consecutive pediatric patients in whom they performed 9 resections for lesions within or close (≤10 mm) to M1 and/or the CST. Monopolar high-frequency motor mapping with train-of-five stimuli (pulse duration 500 μsec, interstimulus interval 4.0 msec, frequency 250 Hz) was used. The motor threshold was defined as the minimal stimulation intensity that elicited motor evoked potentials (MEPs) from target muscles (amplitude > 30 μV). Resection was performed toward M1 and the CST at sites negative to 1- to 3-mA high-frequency train-of-five stimulation.

Results. The M1 was identified through high-frequency train-of-five via application of varying low intensities. The lowest motor thresholds after final resection ranged from 1 to 9 mA in 8 cases and up to 18 mA in 1 case, indicating proximity to motor neurons. Intraoperative electroencephalography documented an absence of seizures during all surgeries. Two transient neurological deficits were observed, but there were no permanent deficits. Postoperative imaging revealed complete resection in 8 patients and a very small remnant (<0.175 cm³) in 1 patient.

Conclusions. High-frequency train-of-five with a minimal threshold of 1–3 mA is a feasible and safe procedure for resections in the proximity of the CST. Thus, low-threshold motor mapping might help to expand the area for safe resection in pediatric patients with lesions located within the precentral gyrus and close to the CST, and may be regarded as a functional navigational tool. The additional use of continuous MEP monitoring serves as a safety feedback for the functional integrity of the CST, especially because the true excitability threshold in children is unknown.

Key Words • brain mapping • eloquent tumors • low-threshold mapping • motor cortex • motor evoked potential • pediatric neurosurgery • technique

Abbreviations used in this paper: CST = corticospinal tract; DCS = direct cortical stimulation; MEP = motor evoked potential; NIHSS = National Institutes of Health Stroke Scale; PNET = primitive neuroectodermal tumor; TES = transcortical electrical stimulation.

* Drs. Schucht and Seidel contributed equally to this work.

Intraoperative identification of motor function is of paramount importance when resecting tumors close to primary motor neurons. This is especially important in the pediatric population, where the primary motor cortex (M1) may undergo vast reorganization due to the extensive plasticity of immature brains after vascular lesions and tumors, which may result in aberrant morphology. Intraoperative cortical and subcortical bipolar or monopolar mapping is the gold standard for identification of assemblies of motor neurons during tumor resection in adults. Continuous intraoperative monitoring of motor evoked potentials (MEPs) enables real-time assessment of functional integrity of the primary motor system; alterations in MEP monitoring correlate with postoperative deficits. Both methods are valuable for preserving motor deficits.
Low-threshold motor mapping for pediatric brain surgery

...tor function and are widely used.2,6,8,17,18 Yet applying the classic Penfield stimulation has a higher intraoperative seizure rate than short-train stimulation.34 Furthermore, using monopolar short-train stimulation might be more accurate in predicting the distance to the corticospinal tract (CST) in evaluating thresholds of MEPs.12,13,26,30 This functional guidance is of crucial importance when approaching the CST deep within white matter in an anatomical structure disturbed by a tumor.35

In a recent report we described that the use of a lowest monopolar threshold of > 3 mA (high-frequency train-of-five) was not associated with a significant motor deficit in adult patients undergoing resection of tumors located in the precentral gyrus.34 For tumors located adjacent to the CST, the true safe mapping threshold may be even lower.35

In the pediatric population, mapping is used mainly for epilepsy surgery and is most often performed using the 50- to 60-Hz Penfield technique.3 However, especially in the pediatric population it may be beneficial for the surgeon to estimate the distance to the CST in threshold values to indicate when the surgeon is getting close to the CST. Furthermore, the excitability of the cortex and the CST in children is unknown.12,28

The objective of this study was to investigate the feasibility, safety, and efficacy of low-threshold monopolar high-frequency train-of-five mapping during surgery on intraaxial lesions located within or close to M1 and the CST in the pediatric population.

Methods

Patient Population

Nine resections of brain lesions were performed close (≤ 10 mm) to M1 and the CST in 8 consecutive pediatric patients from October 2009 to October 2012. Patient characteristics are shown in Table 1. All patients underwent extensive imaging for preoperative assessment, including 3D T2-weighted sequences for identification of the precentral gyrus and diffusion tensor imaging, which served as the basis for fiber tracking of the CST (iPlan 3.0.2 software, VectorVision, Brainlab).

High-resolution T1-weighted gradient-echo sequence data sets (magnetization prepared rapid acquisition of gradient echo) were performed using a 3.0-T TRIO TIM MRT Magnetom Trio system (Siemens); 176 sagittal sections were analyzed (isovoxel resolution 1.0 mm, FOV 256 mm, matrix size 256, TR 1950 msec, TE 2.6 msec). Locations of the lesions and the proximity to motor eloquent areas are described in Table 2.

The patients’ parents signed informed consent for the surgery and the procedure. This study was approved by the local institutional ethics committee (Cantonal Ethnic Committee KEK, Bern University Hospital, Bern, Switzerland).

Neurophysiological Monitoring and Mapping Technique

In all cases the ISIS system (inomed) equipped with a constant-current stimulator (OSIRIS, inomed) was used for intraoperative neurophysiological mapping and monitoring. Motor evoked potentials were recorded by pairs of needle electrodes inserted into the contralateral facial muscles and proximal and distal upper and lower limbs. A bolus of propofol (2 mg/kg body weight for children older than 8 years and 4 mg/kg body weight for children 8 years or younger), fentanyl (1 µg/kg body weight), and remifentanil (1–2 µg/kg body weight) was used for induction of anesthesia, followed by propofol (9–15 mg/kg/hr) and remifentanil (0.5–0.9 µg/kg/min) for anesthesia maintenance. Esmeron was used for short-acting relaxation during intubation (0.5–1 mg/kg body weight). The “train-of-four” technique (involving percutaneous stimulation of the right median nerve at 40 mA, 0.2-msec pulse duration) was used to test recovery from muscle relaxation.28,40

The central sulcus was identified through the median nerve somatosensory evoked potential phase-reversal technique.4,27 To perform direct cortical stimulation (DCS) for MEP monitoring, a strip electrode with 4 contacts (each 4 mm in diameter and 10 mm apart) was placed on the presumed primary motor cortex.3,24,25 The MEPs were elicited by transcranial electrical stimulation (TES) if placement of a strip electrode was impossible due to the craniotomy site.5,39,40 A monopolar probe with a 1.6-mm electrode (monophasic current up to 22 mA) was used for mapping, with a reference electrode placed at Fpz. Stimulation was performed with multiple train-of-five stimuli, each with a pulse duration of 500 µsec and an interstimulus interval of 4.0 µsec.17,34,39,40 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 was regarded as the motor threshold.39,40 Anodal stimulation (positive current) and cathodal stimulation (negative current) were used for cortical and subcortical mapping, respectively.13,16,31

Neurophysiology-Guided Lesion Resection

Neuronavigation, based on preoperative images (Brainlab), was used for tailored craniotomy in all patients and for lesion localization in conjunction with sonography prior to opening of the dura mater (Table 2). The cortical peritumoral area presumed to contain primary motor tissue based on anatomy, neuronavigation, and phase-reversal findings was mapped for motor function in 2-mm intervals. If proximity to M1 was assumed, the motor threshold was identified by systematically increasing the stimulation current until an MEP response was elicited; if the starting site of resection was more distant from M1 or the CST, a threshold of 15 mA was used and was decreased until the MEP response was lost. Resection of the lesion was invariably started at the site of the highest motor threshold due to the fact that lower motor thresholds correlate with a closer location to eloquent tissue.12,23

As the resection approached the interface between the lesion and functionally eloquent tissue, mapping was repetitively performed to define a safe dissection plane. In accordance with a previously published internal protocol,24 we alternated tumor resection and motor mapping, repeating threshold assessment every 1–2 mm of tumor resection with the highest possible temporal and spatial frequency, especially when coming to motor thresholds less than 7 mA (motor threshold is defined as the minimal stimulation intensity that elicits MEPs from target muscles [amplitude...
Our strategy is to approach the lesions with very low current (3–6 mA) to avoid a false-positive MEP response resulting from current spread of higher stimulation intensities. This allows us to get as close as possible to the motor structure with consideration of the rule-of-thumb distance-to-current relationship (1 mm = 1 mA) that was previously observed.34 At a motor threshold of 3 mA, resection was cautiously continued only if MEPs were completely stable. For subcortical mapping, a motor threshold of 1 mA represented the ultimate sign to discontinue resection, even when DCS for MEP monitoring was completely stable.

Postoperative MRI (< 72 hours) was performed in all cases and the images were evaluated by an independent senior neuroradiologist. Completeness of resection was judged visually based on the findings on residual enhancement on contrast-enhanced multiplanar T1 sequences (for malignant glioma), persistent hyperintense signal on 3-mm coronal FLAIR sequence (for low-grade glioma), or time-of-flight and 3-mm axial T2-weighted sequences (for vascular lesions). Neurological deficits were assessed at discharge or within 1 week after surgery. New postoperative neurological deficits that had vanished by the 3-month follow-up visit were regarded as transient, and persisting deficits were regarded as permanent.

**TABLE 1: Perioperative patient characteristics and histology**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex, Chief Complaint</th>
<th>Symptoms Prior to Op</th>
<th>NIHSS</th>
<th>MRC Grade at 1 Wk</th>
<th>MRC Grade at 3 Mos</th>
<th>NIHSS 3 Mos</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>16, M symptomatic epilepsy</td>
<td>none</td>
<td>0</td>
<td>M5</td>
<td>M5</td>
<td>0</td>
<td>pleomorphic xanthoastrocytoma (WHO II)</td>
</tr>
<tr>
<td>2</td>
<td>6, M symptomatic epilepsy</td>
<td>abducens palsy, gait disturbance, dysmetria of upper extremities</td>
<td>4</td>
<td>M5</td>
<td>M5</td>
<td>4</td>
<td>anaplastic oligodendroglioma (WHO III)</td>
</tr>
<tr>
<td>3</td>
<td>16, F symptomatic epilepsy</td>
<td>none</td>
<td>0</td>
<td>M5</td>
<td>M5</td>
<td>0</td>
<td>oligodendroglioma (WHO II)</td>
</tr>
<tr>
<td>4</td>
<td>17, F headache</td>
<td>none</td>
<td>0</td>
<td>M5</td>
<td>M5</td>
<td>0</td>
<td>pilomyxoid astrocytoma (WHO II)</td>
</tr>
<tr>
<td>5</td>
<td>2, M headache</td>
<td>gait disturbance, clumsiness &amp; weakness of hand</td>
<td>3</td>
<td>M4</td>
<td>M4</td>
<td>2</td>
<td>PNET</td>
</tr>
<tr>
<td>6</td>
<td>10, M symptomatic epilepsy</td>
<td>none</td>
<td>0</td>
<td>M5</td>
<td>M5</td>
<td>0</td>
<td>arteriovenous malformation</td>
</tr>
<tr>
<td>7</td>
<td>17, M symptomatic epilepsy</td>
<td>facial palsy, leg &amp; hand weakness</td>
<td>3</td>
<td>M4</td>
<td>M4</td>
<td>0</td>
<td>vascular malformation</td>
</tr>
<tr>
<td>8</td>
<td>9, M none</td>
<td>none</td>
<td>0</td>
<td>M5</td>
<td>M5</td>
<td>0</td>
<td>choroid plexus papilloma</td>
</tr>
</tbody>
</table>

* MRC = Medical Research Council.

**Results**

**Postoperative MRI (< 72 hours)** was performed in all cases after the lesions were mapped using independent senior neuroradiologist. Completeness of resection was judged visually based on the findings on residual enhancement on contrast-enhanced T1-weighted sequences (for malignant glial), persistent hyperintense signal on 3-mm coronal FLAIR sequence (for low-grade glioma), or time-of-flight and 3-mm axial T2-weighted sequences (for vascular lesions). Neurological deficits were assessed at discharge or within 1 week after surgery. New postoperative neurological deficits that had vanished by the 3-month follow-up visit were regarded as transient, and persisting deficits were regarded as permanent.

**Statistical Analysis**

Descriptive statistical analyses were performed (mean, standard deviation, and percentage) for selected parameters, such as patient characteristics and outcome.
surgery were 1–3 mA (in 3 cases), 4–5 mA (in 3 cases), 6–10 mA (in 2 cases), and 11–20 mA (in 1 case). Motor mapping allowed for step-wise, macroscopic complete resection before the motor threshold of 3 mA was reached in 6 patients and was completed in 1 patient at 3 mA. In 2 patients we decided to continue the local resection beyond the 3-mA threshold due to the stability of DCS for MEP monitoring and the presumed immediate border of the lesion. Cautious resection, mapping, and monitoring were frequently alternated, and the resections were performed with unchanged MEPs at motor thresholds of 2 mA and 1 mA in Cases 5 and 8, respectively (Fig. 1).

### Postoperative Outcome

Postoperative MRI revealed complete resection in 6 patients. In 1 patient (Case 7) an unexpected remnant was discovered on postoperative MRI and was completely removed in an early reoperation 6 days after the initial surgery in accordance with our in-house internal protocol (unpublished data, Schucht et al., 2013). The patient in Case 5 had a minimal infiltration (<0.175 cm$^3$) of the sagittal sinus, which we deliberately did not resect. Due to this very small remnant with a volume smaller than 0.175 cm$^3$, the resection was regarded as a gross-total resection and not a complete resection (despite complete local resection adjacent to primary motor neurons). The rates of radiologically complete resection and gross-total resections in our patients were thus 87.5% and 100%, respectively. According to postoperative imaging, no lesion remained at the sites where the low motor threshold was applied (for example, adjacent to the CST and the precentral gyrus).

### Neurological Deficits and Seizures

The patient in Case 7 showed weakness of the contralateral upper and lower extremities prior to surgery and after the first surgery. The deficit remained unchanged after reoperation, improved by the time of discharge 4 days after reoperation, and was not detectable at the 3-month follow-up assessment. The patient in Case 4 sustained a sensory deficit of the contralateral forearm and hand, which improved by postsurgical Day 6 (discharge) and had vanished by the 3-month follow-up visit. Transient and permanent morbidity after surgery were therefore 22% (2 of 9 cases) and 0%, respectively. Intraoperative electroencephalography, performed in all patients during lesion resection and mapping, showed no epileptic activity. One patient had a focal seizure on the 7th day after
surgery, and another patient developed a generalized seizure 1 week after discharge. After receiving antiepileptic monotherapy, both patients remained seizure free at the time of follow-up.

Discussion

Identification of Motor Eloquent Areas by Electrophysiological Stimulation

Mass lesions may distort the normal cortical and subcortical anatomy, making it difficult to localize specific brain functions based on anatomy alone. Intraoperative neuronavigation clarifies anatomy within the brain, but it adds only limited information on the function of a given tissue. Furthermore, neuronavigation is subject to brain shifting, resulting in increasing inaccuracy during surgery. Reorganization of the primary motor and sensory cortices due to focal lesions may lead to aberrant cortical representation in the perirolandic cortical region and the adjacent tissue, especially in the pediatric population. Making meticulous mapping of the peritumoral cortex close to the presumed primary motor area mandatory. We regard motor mapping and monitoring as complementary in avoiding motor deficits. Motor mapping helps to localize the CST and M1 and to estimate the remaining distance to primary motor neurons, whereas monitoring reliably predicts motor function depending on signal alterations. In the current series motor mapping was used for functional guidance when approaching eloquent motor tissue, while unchanged MEP signals confirmed the functional integrity of the CST, which is of added value especially at low motor thresholds.

Methodology of Stimulation and Intraoperative Seizures

Monopolar high-frequency (200- to 300-Hz) train-of-five stimulation has been shown to be as reliable as Penfield’s classic bipolar 50- to 60-Hz technique for mapping and localizing the CST. In contrast to the 50- to 60-Hz stimulation that causes a tonic muscle response, the train-of-five technique elicits a single MEP and allows a more quantitative evaluation of MEP changes regarding amplitude, latency, and duration. Furthermore, outside the space between the 2 tips the stimulation field of the bipolar stimulation probe is more heterogeneous with regard to the lines of equal potential. In contrast, monopolar electrical field is more reliable in quantitatively predicting the distance from the CST by absolute stimulation current values. The classic 50- to 60-Hz motor stimulation technique has also repeatedly been associated with the occurrence of intraoperative seizures. A reported incidence of stimulation-induced epileptic seizures of up to 24% may be regarded as a drawback, even if irrigation with cold Ringer solution provides a quick remedy. By comparison, the use of monopolar high-frequency stimulation localizes the primary motor region with similar accuracy but with a significantly lower risk of inducing seizures in adults. The absence of seizures induced through high-frequency train-of-five in our pediatric series is in line with the report of Ng et al. who described the use of high-frequency train-of-five for pediatric epilepsy surgery.

Correlation Between Stimulation Intensity and Distance to Motor Sites

There is some debate about whether young patients require higher stimulation thresholds to elicit a motor response due to the immaturity of the motor system. This would increase the risk of injury to M1 or the CST when approaching these structures until the defined motor thresholds are reached. Assuming that a yet unknown correlation exists between stimulation intensity and distance to the motor site, we approached the CST by using decreasing motor thresholds and using the same final motor thresholds as for adults, that is, 1 mA for subcortical stimulation as a sign to stop the resection. Furthermore, during the entire surgery we performed continuous MEP monitoring to ensure that the functional integrity of the CST was preserved. This strategy permits a safety feedback because even in cases of a higher excitability threshold we would have stopped at the first occurrence of MEP changes. With this combined approach, we did not observe motor deficits in any of the patients in whom these low motor thresholds were reached. The correlation between intraoperative stimulation thresholds and the distance to motor sites observed in our series is similar to that observed in adults. However, only 2 of our patients were younger than 7 years, which limits our ability to generalize about the relationship between patient age and stimulation thresholds.

Study Limitations

The major limitation of our study is the small sample size. Another limitation is the heterogeneity of the lesions, which included both intra- and extraaxial lesions; however, the warning criteria were applied regardless of the pathology and localization of the lesion. Although the advantages of mapping techniques are more obvious for intrinsic tumors, localization of the CST may also play a role during the removal of other lesions such as metastases and vascular malformations. Knowing the proximity to the CST may influence resection strategy, speed of dissection, power of electrocoagulation, and the technique used for hemostasis. Low-threshold train-of-five mapping could be considered a functional navigation tool to indicate when dissection should slow down. Stability of DCS for MEP monitoring gives real-time feedback about the functional integrity of the CST and supports the surgeon during tumor removal at low motor thresholds, if intended. In summary, the warning criteria presented in the current study might be a valuable additional tool for guiding the surgeon based on motor function during surgery close to the CST.

Our preliminary findings in pediatric patients suggest that quantitative mapping thresholds for assessing the risk of direct damage to the motor cortex, which were established in the adult population, may also be applied in the pediatric population. Low-threshold high-frequency train-of-five mapping may be regarded as a functional navigation tool cautioning further resection when approaching lower thresholds. Although our 0% rate of permanent new motor deficits compares favorably to the literature, further investigation is needed to robustly evaluate a safe lowest threshold, especially in young children.
Low-threshold motor mapping for pediatric brain surgery

Conclusions

Monopolar high-frequency train-of-five stimulation for motor mapping is a feasible and safe technique in pediatric surgery for lesions within or close to the motor system. Low-threshold high-frequency train-of-five mapping permits expansion of the resection area with regard to motor deficits up to a minimal threshold of 1–3 mA, and may be regarded as a functional navigation tool in the pediatric population. The minimal safe motor threshold is lower than previously thought and should be further investigated. We strongly advocate using additional continuous MEP monitoring as a safety feedback for the functional integrity of the CST, especially because the true excitability threshold in children is unknown.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Schucht, Seidel, Raabe, Beck. Acquisition of data: all authors. Analysis and interpretation of data: Schucht, Seidel, Raabe, Beck. Drafting the article: Schucht, Seidel. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Schucht. Statistical analysis: Schucht, Seidel. Administrative/technical/material support: Schucht. Study supervision: Raabe, Beck.

References

ry evoked potentials helps identify motor cortex more quickly in the operating room. Brain Topogr 5:53–58, 1992

Manuscript submitted July 19, 2013. Accepted January 24, 2014.
Please include this information when citing this paper: published online March 21, 2014; DOI: 10.3171/2014.1.PEDS13369.
Address correspondence to: Philippe Schucht, M.D., Department of Neurosurgery, Freiburgstrasse 10, Bern University Hospital, 3010 Bern, Switzerland. email: philippe.schucht@insel.ch.