N navigating transcranial magnetic stimulation mapping of the motor cortex for preoperative diagnostics in pediatric epilepsy

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OBJECTIVE Navigated transcranial magnetic stimulation (nTMS) is a noninvasive technique often used for localization of the functional motor cortex via induction of motor evoked potentials (MEPs) in neurosurgical patients. There has, however, been no published record of its application in pediatric epilepsy surgery. In this study, the authors aimed to investigate the feasibility of nTMS-based motor mapping in the preoperative diagnostic workup within a population of children with medically refractory epilepsy.

METHODS A single-institution database was screened for preoperative nTMS motor mappings obtained in pediatric patients (aged 0 to 18 years, 2012 to present) with medically refractory epilepsy. Patient clinical data, demographic information, and mapping results were extracted and used in statistical analyses.

RESULTS Sixteen patients met the inclusion criteria, 15 of whom underwent resection. The median age was 9 years (range 0–17 years). No adverse effects were recorded during mapping. Specifically, no epileptic seizures were provoked via nTMS. Recordings of valid MEPs induced by nTMS were obtained in 10 patients. In the remaining patients, no MEPs could be elicited. Failure to generate MEPs was associated significantly with younger patient age (r = 0.8020, p = 0.0001863). The most frequent seizure control outcome was Engel Epilepsy Surgery Outcome Scale class I (9 patients).

CONCLUSIONS Navigated TMS is a feasible, effective, and well-tolerated method for mapping the motor cortex of the upper and lower extremities in pediatric patients with epilepsy. Patient age modulates elicitability of MEPs, potentially reflecting various stages of myelination. Successful motor mapping has the potential to add to the existing presurgical diagnostic workup in this population, and further research is warranted.

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KEYWORDS pediatric epilepsy; transcranial magnetic stimulation; neurosurgery; motor mapping; brain stimulation

In neurosurgery, physicians are often faced with the challenge of balancing the removal of dysfunctional tissue with the prospect of causing postoperative functional deficits in the process. This becomes especially impactful in pediatric epilepsy surgery, where surgery may often serve a curative role and where patients generally have comparatively high life expectancy. Seizures arising in or near tissue essential for the execution of movement, the primary motor cortex, represents a convergence of these concerns in children.

Modern neurosurgery typically relies on the gold standard of direct cortical stimulation (DCS) for functional mapping. DCS has found widespread use and acceptance for the identification of Rolandic cortex during surgery. In this technique, electrodes are used to apply electrical current directly to the cortex. This stimulation generates motor evoked potentials (MEPs), which in turn allows for the identification of local eloquence. However, DCS is not without its risks; clinical data suggest that DCS may facilitate the occurrence of intraoperative seizures. The pediatric brain generally is more excitable than the adult one, which could plausibly translate to a higher DCS-related seizure rate in children. Furthermore, surgery is performed under anesthesia, which may heighten...
en the intensity of stimulation necessary to stimulate the motor cortex adequately. Therefore, stimulation should be performed with caution in this population already prone to seizures. Moreover, DCS is inherently invasive and cannot be used in preoperative planning.

In light of these limitations, navigated transcranial magnetic stimulation (nTMS) has become recognized as a noninvasive modality that offers the option to generate preoperative functional motor maps. This technique utilizes electromagnetic induction combined with MRI-based neuronavigation to cause local depolarization of neurons, which in turn elicits MEPs and characterizes motor eloquence of cortical anatomy. Multiple studies have found that nTMS motor maps offer high accuracy and correlate well with other noninvasive modalities such as functional MRI or magnetoencephalography. In addition, various patient benefits have been attributed to the inclusion of nTMS motor mapping into presurgical workflow, including lower risk for surgery-related paresis and smaller size of craniotomy in brain tumor surgery. For nTMS-based motor mappings, a consensus protocol ensuring safe and reliable application has emerged recently in which recommendations regarding imaging, stimulation protocol, and clinical data integration were made. While developed for the context of brain tumor surgery specifically, these guidelines are similarly accepted for nTMS motor mapping applications in other populations.

Despite the growing nTMS usage in brain tumor surgery, few reports exist regarding motor mapping within the framework of pediatric epilepsy surgery. While the safety of nTMS has been documented extensively, a history of epilepsy is still considered a relative contraindication, due to rare reports of accidental nTMS-provoked seizures. The impact and validity of reports such as these are debated. Nonetheless, studies involving the use of nTMS in patients with epilepsy are rare. Three cases of focal epilepsy were analyzed in a previously published study which compared cortical representations of specific muscle groups as identified by both nTMS and intraoperative DCS. The authors reported that nTMS-based mapping of the primary motor cortex in adult patients with epilepsy was reliable. Another study explored nonnavigated TMS motor mapping in 8 patients with epilepsy, without the intent of using the collected data for surgery. Studies addressing nTMS motor mapping for pediatric patients with epilepsy specifically are currently not published.

In this study, we examined the use of preoperative nTMS motor mappings in a group of pediatric patients with medically refractory epilepsy. Patient demographics and the clinical and mapping parameters are described. Additional factors such as complications related to, and tolerability of, stimulation are reported. We aimed to evaluate the applicability of nTMS in pediatric epilepsy surgery and to identify possible predictors of nTMS motor mapping success.

Methods

Ethics

This study was approved by the University of California, San Francisco, IRB. All research was conducted according to the Declaration of Helsinki. Written informed consent was obtained from the legal guardians of all patients.

Study Design and Workflow

The data analyzed in this study were taken from the local institutional database of UCSF. Data analysis was performed retrospectively. The decision regarding potential patient inclusion in this study was made by a pediatric neurosurgeon (K.I.A.). Inclusion criteria included having a diagnosis of medically refractory epilepsy, consideration for operative management of epilepsy, age less than 18 years, and the informed consent of a legal guardian. Patients were excluded if they had general nTMS contraindications such as implanted metal close to the skull or the presence of a cardiac pacemaker, dangerous seizure semiology (e.g., a propensity for respiratory arrest), poor seizure control, or continuous seizure manifestation.

Both the referral and a premapping patient assessment for potential nTMS contraindications were undertaken by the principal investigator (P.E.T.). The respective informed consent of a legal guardian was acquired before the mapping. During this step, the mapping process and any details of interest were explained and provided to both the legal guardian and (if possible) the patient. Any remaining questions were addressed. Clinical data were collected. Subsequently, nTMS-based motor mapping was performed as detailed below.

Magnetic Resonance Imaging

Since MRI is required for nTMS neuronavigation, every patient underwent high-resolution MRI. The sequences included both a T1-weighted, 3D spoiled gradient-recalled echo sequence steady-state sequence with TR 34 msec, TE 3–8 msec and 30° flip angle, and a T2-weighted, 3D fast spin-echo sequence with TR 3000 msec and TE 105 msec. Scans included the nasion and both cruses of helix to serve as anatomical landmarks for nTMS coregistration.

Clinical Data Collection

Recorded patient data included date of birth, sex, type of epilepsy, focus location, current antiepileptic drug (AED) regimen, complications, and postsurgical seizure control outcomes (determined by the International League Against Epilepsy [ILAE] and Engel classification systems).

Motor Mapping Procedure

Navigated TMS–based motor mapping was performed in accordance with previously published workshop guidelines. Mappings were performed using an E-field guided nTMS system (Nexstim eXimia NBS version 4.3, Nexstim Plc).

Recorded muscles were selected individually according to suspected seizure focus and clinical manifestation. Muscles included the adductor digitii minimi, the abductor pollicis brevis, the orbicularis oculi (OO), the tibialis anterior, the flexor carpi radialis, and the biceps brachii. MEPs were measured through surface electromyography (EMG) electrodes (Neuroline 720, Ambu). A valid MEP
was defined as a repeatable suprathreshold muscular response of plausible morphology and latency. The amplitude threshold for MEPs was defined as 50 μV. The valid latency interval was defined as 10 to 45 msec depending on the recorded extremity.

Mapping was started by determining the cortical motor representation hotspot for the abductor pollicis brevis muscle. The hotspot was then used for determination of the resting motor threshold (rMT), defined as the stimulation intensity at which 50% of trials result in a valid MEP. After identification of rMT the mapping was performed using a stimulation intensity of 110% rMT. If no MEPs were obtainable at this initial value, stimulus intensity was increased stepwise by 10% rMT until satisfactory MEPs were present, no further raise in intensity was possible, or stimulation was no longer tolerable. If any stimulation-related discomfort was reported, the intensity was lowered to a level comfortable to the patient.

Initially, the entire hemisphere was mapped with stimuli being applied in a 1-cm raster. Perirolandic areas, regions to be resected, and any motor-positive site having emerged in the initial hemispheric mapping underwent a higher-resolution remap using at least 3 stimuli per site applied in a 5-mm raster. If no MEPs were elicitable, mappings were considered unsuccessful due to not yielding useful information.

Two attending physicians (K.I.A. and P.E.T.) were present for the entire procedure to ensure permanent monitoring of the patient and to note any potential complications. If any signs interpretable as symptoms or prodromi of seizures (i.e., aura, twitching, or increased spontaneous EMG activity) would have emerged, the procedure would have been aborted immediately, and an appropriate medical response would have been initiated. A variety of mapping factors were recorded, including intensity of individual stimuli, peeling depth on an MRI-based head model, maximum E-field values of stimuli, amplitude of MEPs for each recorded muscle, and latency of MEPs for each muscle.

Optimizations for Pediatric Patients

For successful application of nTMS to children, challenges arising from the young patient collective must be taken into account. Pediatric patients are prone to becoming restless and tend to have difficulties remaining still, both critical factors to ensuring high-quality EMG data. Thus, patient comfort was a high priority during the stimulation sessions. For the youngest patients, mapping during sleep was preferred. Physical contact with and a patient’s proximity to the caregiver (e.g., in a position on the parent’s lap) were encouraged. Electronic devices were used to direct the patient’s attention away from the mapping process. Timeouts were offered repeatedly, and patient responses during mapping were continuously assessed.

Statistical Analysis

Statistical analysis was performed in GraphPad Prism version 7.0 (www.graphpad.com) and RStudio version 1.2.5042 (www.rstudio.com). The level of statistical significance was set to 0.05 for all tests. For correlation of age and mapping success, as well as number of AEDs and mapping success, point-biserial correlation analyses were performed; mapping success was coded as a dichotomous variable and both age and number of AEDs as the respective continuous variable. Influence of sex on mapping success was analyzed via the two-sided chi-square test.

Results

Clinical Data

Sixteen patients were included in this study. Of these, 15 underwent surgery (1 patient declined). The median age was 9 years (range 0–17 years). Nine patients were male. The average mapping duration was 33 minutes (SD ± 11 minutes; range 19–56 minutes). At the time of nTMS motor mapping, 14 patients used at least one AED (Table 1). The median number of simultaneous AEDs was 2 (range 0–6). The most common single AED was lorazepam (7 patients). A higher number of AEDs correlated weakly, yet significantly with mapping success (r = 0.645, p = 0.007).

The patient cohort was subject to a variety of preexisting conditions. These included hemiparesis, attention deficit hyperactivity disorder, tuberous sclerosis, behavioral disorder, perinatal infarct, and a skull defect (Table 1). In our collective, we observed a wide distribution regarding anatomical locations of the epileptic foci. The most common focus location was right frontal (6 patients).

Postsurgical outcomes were classified via the ILAE and Engel classification systems (Table 1). The most frequent outcomes were Engel class I (9 patients) and ILAE class I (8 patients). There were no complications during or immediately after the nTMS mappings. One patient demonstrated a postoperative right foot drop. Motor mapping in this specific case had been restricted to upper-extremity musculature.

Mapping Results

The median peeling depth was 17 mm (range 6.4–22.2 mm). The median stimulation intensity over all stimuli was 60% of the maximum stimulator output (range 35%–100%). The median maximum E-field value was 136.5 V/m (range 59.4–536.2 V/m). The median number of pulses in each examination was 199.5 pulses (range 46–637).

Navigated TMS–based motor mapping was completed without adverse effects in all patients. Specifically, no seizures or prodromal seizure stages were provoked. Useful motor maps were achieved in 10 patients (Table 2 and Fig. 1); in the remaining 6 patients, MEPs could not be elicited. No map of the motor cortex could be generated in these cases. Notably, while the OO reacted to stimulation in 4 of 7 patients, latencies above 10 msec were not observed. Therefore, no OO MEP could be considered valid (see below).

Influence of Demographic Factors on Mapping Success

The mean age of patients whose mapping was successful was 12 ± 3.7 years, and the mean age of patients whose mapping was unsuccessful was 2.8 ± 2.5 years (Fig. 2). Point-biserial correlation analysis revealed a significant correlation between age and mapping success (r = 0.8020, 0.0001).
## TABLE 1. Patient overview

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Epilepsy Type</th>
<th>Other Diagnoses</th>
<th>Focus Location</th>
<th>AEDs at Mapping Date</th>
<th>Complications</th>
<th>Engel Class Outcome</th>
<th>ILAE Class Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>F</td>
<td>HCC</td>
<td>None</td>
<td>Lt frontal</td>
<td>Lacosamide</td>
<td>Postop rt foot drop</td>
<td>I</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>F</td>
<td>RE</td>
<td>None</td>
<td>Rt frontal</td>
<td>Oxcarbazepine, topiramate, lorazepam</td>
<td>None</td>
<td>I</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>F</td>
<td>RE partialis continua</td>
<td>POLG-1 mitochondrial disease</td>
<td>Rt frontal</td>
<td>Clonazepam, vigabatrin</td>
<td>None</td>
<td>IV</td>
<td>5*</td>
</tr>
<tr>
<td>4</td>
<td>17</td>
<td>M</td>
<td>RE</td>
<td>Hemiparesis, nephrolithiasis, hematuria, foot deformity</td>
<td>Lt paracentral</td>
<td>Clobazam</td>
<td>None</td>
<td>I</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>8</td>
<td>M</td>
<td>ADHD</td>
<td>None</td>
<td>Rt parietal</td>
<td>Clobazam, zonisamide, lorazepam, eslicarbazepine, lacosamide, donazepam</td>
<td>None</td>
<td>III</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>M</td>
<td>RE</td>
<td>Tuberous sclerosis</td>
<td>Rt posterior paracentral lobule, bilat frontal/temporal lobes</td>
<td>Levetiracetam, vigabatrin</td>
<td>None</td>
<td>II</td>
<td>3</td>
</tr>
<tr>
<td>7</td>
<td>5</td>
<td>F</td>
<td>RE</td>
<td>None</td>
<td>Rt frontal</td>
<td>Lamotrigine</td>
<td>None</td>
<td>I</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>13</td>
<td>M</td>
<td>RE</td>
<td>None</td>
<td>Lt frontoparietal</td>
<td>Lacosamide, levetiracetam, lorazepam, perampanel</td>
<td>None</td>
<td>II</td>
<td>4</td>
</tr>
<tr>
<td>9</td>
<td>16</td>
<td>M</td>
<td>RE</td>
<td>None</td>
<td>Rt frontal</td>
<td>Clobazam, divalproex, felbamate, lorazepam, oxcarbazepine</td>
<td>None</td>
<td>II</td>
<td>4</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
<td>F</td>
<td>HCC</td>
<td>None</td>
<td>Frontal insular</td>
<td>Carbamazepine, lamotrigine, lorazepam, clobazam, valproate</td>
<td>None</td>
<td>NA†</td>
<td>NA†</td>
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<tr>
<td>11</td>
<td>7</td>
<td>M</td>
<td>Focal epilepsy</td>
<td>Behavioral disorder</td>
<td>Rt frontal</td>
<td>Lorazepam</td>
<td>None</td>
<td>I</td>
<td>1</td>
</tr>
<tr>
<td>12</td>
<td>2</td>
<td>M</td>
<td>RE</td>
<td>None</td>
<td>Rt frontal</td>
<td>None</td>
<td>None</td>
<td>I</td>
<td>1</td>
</tr>
<tr>
<td>13</td>
<td>15</td>
<td>F</td>
<td>RE</td>
<td>Perinatal infarct</td>
<td>Lt parietal occipital</td>
<td>Carbamazepine, clobazam, diazepam, lorazepam</td>
<td>None</td>
<td>III</td>
<td>4</td>
</tr>
<tr>
<td>14</td>
<td>3</td>
<td>M</td>
<td>Focal partial epilepsy</td>
<td>Skull defect, behavioral disorder</td>
<td>Lt frontal</td>
<td>None</td>
<td>None</td>
<td>I</td>
<td>1</td>
</tr>
<tr>
<td>15</td>
<td>13</td>
<td>F</td>
<td>Focal epilepsy</td>
<td>Type II focal cortical dysplasia</td>
<td>Lt parietal</td>
<td>Clobazam, valproate, lacosamide</td>
<td>None</td>
<td>I</td>
<td>1</td>
</tr>
<tr>
<td>16</td>
<td>12</td>
<td>M</td>
<td>Focal epilepsy</td>
<td>Mesial temporal sclerosis</td>
<td>Rt temporal</td>
<td>Valproate, lacosamide</td>
<td>None</td>
<td>I</td>
<td>1</td>
</tr>
</tbody>
</table>

ADHD = attention deficit hyperactivity disorder; HCC = hypomyelination and congenital cataract; NA = not applicable; RE = refractory epilepsy.

* Patient died a few months after surgery due to underlying mitochondrial disease.
† Patient did not undergo surgery.
p = 0.0001863). The chi-square test did not show sex to be significantly connected to mapping success (p = 0.5153).

Discussion

General Discussion

Navigated TMS is a modality suited for presurgical, noninvasive localization of motor function. However, its use in this regard has for the most part been restricted to adult populations with intracranial tumors. Patient history of epilepsy is still considered a relative contraindication due to rare accounts of accidental seizure provocation via nTMS. In this study, we report the results of a single-institution cohort of 16 pediatric patients. In most patients (62.5%), nTMS was capable of mapping the primary motor cortex. To the best of our knowledge, there is currently no other series reported in the literature which has addressed nTMS motor mapping in this context. While our cohort is limited both in size and in underlying etiology, this series serves as preliminary evidence that nTMS motor mapping is feasible in pediatric patients with epilepsy without high rates of complications such as nTMS-related seizures. Further study of this subject may be useful to explore potential clinical benefits arising from the inclusion of nTMS motor mappings into the presurgical case workup.

Regarding the practical usage of the acquired data, one may imagine a variety of ways in which nTMS-derived mapping data may augment clinical management. Depending on the individual patient, the surgeon may choose to use the data only in terms of visually inspecting the identified motor-positive sites. Other workflows, however, have demonstrated that the data can successfully be fused to other preoperative imaging, including diffusion tensor imaging, which in turn enables MRI-based tracking of the corticospinal tract. The entire data complex may then be imported to the intraoperative neuronavigation system as an immediate reference informing the surgical procedure.

Safety of Single-Pulse Motor Mapping

While nTMS motor mappings have become increasingly common for application in adult patients with intracranial tumors, the modality is still used sparingly in both pediatric and epilepsy patient populations. One reason for the hesitant approach in this context is likely the continued

<table>
<thead>
<tr>
<th>Muscle</th>
<th>APB</th>
<th>ADM</th>
<th>FCR</th>
<th>BI</th>
<th>OO</th>
<th>TA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amplitude, μV</td>
<td>433.6 ± 627.3</td>
<td>156.9 ± 124.9</td>
<td>252.5 ± 230.3</td>
<td>153.5 ± 119.2</td>
<td>349.0 ± 276.8</td>
<td>171.4 ± 167.3</td>
</tr>
<tr>
<td>Latency, msec</td>
<td>23.0 ± 6.1</td>
<td>23.6 ± 6.6</td>
<td>16.5 ± 3.1</td>
<td>14.5 ± 2.6</td>
<td>4.3 ± 1.2</td>
<td>34.0 ± 3.5</td>
</tr>
<tr>
<td>No. of positive stimuli</td>
<td>223</td>
<td>129</td>
<td>94</td>
<td>47</td>
<td>0*</td>
<td>19</td>
</tr>
</tbody>
</table>

ADM = adductor digiti minimi; APB = abductor pollicis brevis; BI = biceps brachii; FCR = flexor carpi radialis; TA = tibialis anterior. Mean values are presented as the mean ± SD unless indicated otherwise.

* Due to probable artifacts via direct nerve stimulation (see Discussion), no OO MEP was considered valid.


FIG. 2. Display of the age of patients split by mapping success. Boxes indicate middle quartiles, the bold line indicates the median, and bars correspond to the range of values.
effect of published single-case reports detailing nTMS-induced epileptic seizures. A review on previous case reports has expressed doubts concerning the link between TMS and seizure incidence in individuals with epilepsy. It is worth noting that in our cohort, no seizure occurred during or immediately after our single-pulse motor mapping. Furthermore, we only included patients diagnosed with medically refractory epilepsy, which by itself would suggest a low seizure threshold. Taken together, our current experiences lead us to believe that the application of nTMS motor mapping in pediatric patients with epilepsy likely does not have a high rate of seizure provocations.

Feasibility and Success Predictors

In our cohort, we were unable to elicit valid MEPs in approximately 38% of our patients. While still successful in the majority of cases, a clear deviation from the much higher success rate of adult cohorts (reported at > 99%) is demonstrable. An interesting observation in this context was the connection of mapping success and age. Mapping success correlated significantly with higher age (r = 0.8020, p = 0.0001863).

This finding is not entirely surprising. In many pediatric patients, corticospinal myelination is still in development. Navigated TMS relies on electromagnetic induction in order to cause the depolarization of a target neuron—the rapid change in magnetic field density affects the distribution of electrical charges in an insulated conductor. Since electrical insulation is key for this process, an immature neuron lacking proper myelination may be less responsive to nTMS than a neuron that has undergone full myelination. A 2017 simulation study indicated that the threshold for successful TMS increases in neurons as the myelin sheath decreases. The reported results, however, were based on virtual models of neuronal populations and their translation to the in vivo setting should be considered carefully. A clearer parallel might be drawn to investigations of MEPs in patients with multiple sclerosis (MS), a disease characterized by progressive loss of neuron myelination. A 2009 study comparing MEPs of a non-MS control group with those of patients with MS found reduced MEP amplitude and heightened MEP latency in patients with MS. The youngest patient in our cohort in whom we achieved successful mapping was 4 years of age. Although our oldest patient in whom we were unable to achieve mapping was 7 years of age, this specific failure was attributable to behavioral problems that made it difficult for the patient to sit still, which made acquisition of reliable EMG results impossible. Taken together, we would argue that age (likely as a proxy of myelination) influences elicitation of MEPs in children. While this may complicate actual motor mapping via nTMS in younger pediatric patients, it also points to a potential use of nTMS in the noninvasive tracking of brain maturation.

Another interesting correlation emerged between mapping success and the number of AEDs, with a higher number of AEDs seemingly facilitating MEP elicitation. We are hesitant to regard this result as a real reflection of an underlying cause, mainly for two reasons. First, AEDs heighten seizure threshold by lowering neuronal excitability. It has been shown that this effect is reflected in heightened rMT, which should correspond to a lower probability of mapping success with an increasing number of AEDs. Second, our AED data were skewed with respect to age, with younger patients generally being less medicated than older ones (Table 1). Older age was associated significantly with mapping success (see Results). We would therefore conjecture that the apparent facilitative effect of AED medication is likely driven by the underlying difference in age. Unfortunately, our small population size prevented us from employing statistical techniques to determine the relative contribution of these two variables; future studies with larger populations should focus on this question.

In terms of immediate clinical implications, it may be more helpful to state that in heightening seizure threshold, even extensive medication does not seem to have a prohibitively strong inhibitory effect on the generation of MEPs.

Mapping the OO

The OO reacted to stimulation in 4 of the 7 patients in whom it was recorded. However, latencies were consistently below 10 msec. Published literature indicates that the expected time frame for OO MEPs is approximately 10 msec to 11 msec, and that latencies below this threshold are increasingly likely to be artifacts due to direct nerve stimulation. Therefore, while mappings of the OO may hold promise for presurgical planning, attention to latencies in these recordings is paramount.

Limitations

First, our sample size was limited to 16 patients. This unfortunately prohibited more elaborate statistical analyses such as multivariate regression, with which the impact of individual factors such as age and AEDs could be regarded separately. Considering the advancements in epilepsy medication and correspondingly decreasing frequency of epilepsy surgery, this limitation is only resolvable through longer intervals of data collection or integration of multicenter data (to which the authors would be open). Studies such as the present one may serve as examples of successful nTMS application in pediatric epilepsy surgery and thereby benefit future data collection. Additionally, the strong statistical significance and biological plausibility of our age/mapping success analysis leave us confident in our finding.

Second, the wide range of different AEDs within our population unfortunately prohibits more differentiated findings regarding the influence of each substance on MEP amplitude and MEP latency. Analyses such as these would potentially be highly valuable, as they could further elucidate cellular mechanisms of nTMS. In the immediate clinical context, however, the likely more important finding is that MEPs and rMTs can still be obtained despite the presence of AEDs.

Third, our patient collective showed an unusual distribution of epilepsy etiology with a relatively large section of refractory epilepsy, which may be considered atypical. Since epilepsy can lead to neuroplastic changes, it is not implausible to assume that various subtypes of epilepsy may in turn lead to varying patterns and degrees of functional reorganization. While nTMS is a useful modality
in the investigation of some epilepsy-related neuroplasticity, varying etiologies other than refractory epilepsy may nonetheless pose varying challenges, such as increased susceptibility to nTMS-related seizures. This limitation should be kept in mind in potential follow-up studies.

Conclusions

The results of our single-center cohort of 16 pediatric patients with medically refractory epilepsy indicate that nTMS motor mapping is feasible and effective. There were no adverse effects during or immediately following our mappings; notably, no visible seizures were provoked. The overall success rate (based on successful elicitation of MEPs) was 62.5%. A soft lower age limit for successful acquisition of MEPs seems to exist, which may be linked to myelination. Other factors such as the presence of AEDs and patient sex seem to have no prohibitive effect on the generation of useful nTMS motor maps. Further studies within this field are needed to elucidate possible interactions between AEDs and MEPs, as well as to demonstrate the safety of the approach with larger sample sizes.

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References


Disclosures
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
Conception and design: Auguste, Tarapore. Acquisition of data: Schramm, Mehta, Tarapore. Analysis and interpretation of data: Schramm, Tarapore. Drafting the article: Schramm, Mehta. Critically revising the article: Schramm, Tarapore. Statistical analysis: Schramm. Administrative/technical/material support: Auguste. Study supervision: Auguste, Tarapore.

Supplemental Information
Previous Presentations
Portions of this work were presented orally at the WAFMR/WSPR Joint Virtual Western Medical Research Conference, January 29–30, 2021.

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