Original Article

Assessing Motor Function in Young Children With Transcranial Magnetic Stimulation

Shalini Narayana PhD\textsuperscript{a,b,c,*}, Roozbeh Rezaie PhD\textsuperscript{a,b}, Samuel S. McAfee BS\textsuperscript{b}, Asim F. Choudhri MD\textsuperscript{b,d,e}, Abbas Babajani-Feremi PhD\textsuperscript{a,b}, Stephen Fulton MD\textsuperscript{b,f}, Frederick A. Boop MD\textsuperscript{b,e}, James W. Wheless MD\textsuperscript{b,f}, Andrew C. Papanicolaou PhD\textsuperscript{a,b,c}

\textsuperscript{a}Division of Clinical Neurosciences, Department of Pediatrics, University of Tennessee Health Science Center, Memphis, Tennessee
\textsuperscript{b}Le Bonheur Neuroscience Institute, Le Bonheur Children’s Hospital, Memphis, Tennessee
\textsuperscript{c}Department of Neurobiology and Anatomy, University of Tennessee Health Science Center, Memphis, Tennessee
\textsuperscript{d}Department of Radiology, University of Tennessee Health Science Center, Memphis, Tennessee
\textsuperscript{e}Department of Neurosurgery, University of Tennessee Health Science Center, Memphis, Tennessee
\textsuperscript{f}Division of Pediatric Neurology, University of Tennessee Health Science Center, Memphis, Tennessee

Abstract

**OBJECTIVE:** Accurate noninvasive assessment of motor function using functional MRI (fMRI) and magnetoencephalography (MEG) is a challenge in patients who are very young or who are developmentally delayed. In such cases, passive mapping of the sensorimotor cortex is performed under sedation. We examined the feasibility of using transcranial magnetic stimulation (TMS) as a motor mapping tool in awake children younger than 3 years of age.

**METHODS:** Six children underwent motor mapping with TMS while awake as well as passive sensorimotor mapping under conscious sedation with MEG during tactile stimulation (n = 5) and fMRI during passive hand movements (n = 4). **RESULTS:** Stimulation of the motor cortex via TMS successfully elicited evoked responses in contralateral hand muscles in 5 patients. The location of primary motor cortex in the precentral gyrus identified by TMS corresponded with the postcentral location of the primary sensory cortex identified by MEG in 2 patients and to the sensorimotor cortex identified by fMRI in 3 children. In this cohort, we demonstrate that TMS can illuminate abnormalities in motor physiology including motor reorganization. We also demonstrate the feasibility of using TMS-derived contralateral silent periods to approximate the location of motor cortex in the absence of an evoked response. When compared to chronological age, performance functioning level appears to be better in predicting successful mapping outcome with TMS. **CONCLUSIONS:** Our findings indicate that awake TMS is a safe alternative to MEG and fMRI performed under sedation to localize the motor cortex and provides additional insight into the underlying pathophysiology and motor plasticity in toddlers.

Keywords: motor cortex, magnetoencephalography, MEG, transcranial magnetic stimulation, TMS, motor mapping, young children, functional MRI

Introduction

Assessing motor function is critical in neurological disorders such as epilepsy, tumor, and developmental disorders, particularly in the context of presurgical functional mapping and in the evaluation of disease and treatment-induced plasticity. Motor function routinely is assessed in the context of preoperative functional mapping in older children and adults via the use of functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG).\textsuperscript{1,6} Transcranial magnetic stimulation (TMS) increasingly is being used as an additional noninvasive tool to map the eloquent cortex.\textsuperscript{7,8} The recent advent of MRI-navigated TMS systems has markedly improved the accuracy of motor...
cortex localization and the ease of application. In addition, TMS has an excellent safety record in patients with neuropsychiatric disorders and children. Recent studies have demonstrated that TMS-derived motor maps are comparable with maps obtained during direct cortical stimulation and that patients mapped preoperatively with TMS appear to have significantly better postoperative functional outcome. Since its approval by the US Food and Drug Administration, mapping of motor and language functions via TMS has become an integral part of the presurgical functional mapping toolkit in older children and adults.

Several neurological disorders, such as tuberous sclerosis, perinatal stroke, megalencephaly, and epilepsy syndromes, including infantile spasms, Angelman syndrome, Rasmussen's encephalitis, and Dravet's syndrome are prevalent in children younger than 3 years of age and often are associated with motor symptoms. Additionally, pediatric intramedullary spinal cord tumors such as pilocytic astrocytoma, 75% of which occur in the first 2 years of life, usually present with motor weakness. Optimal treatment of these disorders requires better understanding of the disease pathophysiology and, if surgery is indicated, then accurate mapping of brain function is paramount. However, accurate assessment of motor functions is challenging in patients younger than 3 years of age, especially if there is associated developmental delay. This is especially true for MEG and fMRI, and in such cases imaging is attempted during sleep or sedation.

However, MEG and fMRI performed under these conditions suffer from 2 main drawbacks, namely indirect nature of motor mapping and risks associated with sedation. TMS has the advantage of mapping the motor cortex directly without requiring the patient's cooperation, making motor mapping feasible in patients who cannot perform tasks because of disease (in case of paresis or plegia) or behavior (such as autism or developmental delay). Furthermore, patients are not required to be still during data acquisition, thus precluding the need for sedation. Therefore, TMS can be used to assess the motor system in young children, including those with developmental delays, while avoiding the risks of sedation. We addressed the question as to whether reliable motor maps could be generated in very young patients with neurological disorders and we assessed the safety and tolerability of TMS in young children. We report here a series of 6 children younger than 3 years of age who underwent TMS motor mapping at our institution. The location of the motor cortex identified by TMS were verified against primary sensory cortex localized by MEG and sensorimotor cortex identified by passive digit movement during fMRI.

Methods

Patients

Six children younger than 3 years of age who underwent motor mapping with TMS between January 2013 and January 2014 were identified through a retrospective review of clinical evaluations performed at the Epilepsy Monitoring Unit of the Le Bonheur Comprehensive Epilepsy Program, Le Bonheur Children's Hospital. The institutional review boards at the University of Tennessee Health Science Center and the Le Bonheur Children's Hospital approved the retrospective chart review. In addition to undergoing motor mapping with TMS, patients also underwent continuous scalp video EEG monitoring, MEG for the localization of epileptiform discharges and somatosensory mapping, anatomical MRI, passive motor mapping with IMRI, and neuropsychological testing as part of the clinical evaluation. Relevant to this study, we are reporting the findings from the neuropsychological testing, and functional mapping with TMS, IMRI, and MEG. The children ranged from 17 to 35 months in age and included 4 males. The details of their diagnosis, motor signs, and medications are listed in Table 1. The results of neuropsychological assessment consisting of composite Mullen scale and gross and fine motor subscales were available on 5 patients.

Transcranial magnetic stimulation

Children were tested while they were seated on their parent's laps. The child was allowed to play with toys or watch TV during the study. Motor mapping was performed using an MRI-navigated TMS system (NBS system 4.0; Nexstim Inc, Atlanta, GA). The system uses a figure-eight coil with an outer winding of 70 mm that stimulates approximately 1-2 cm² of cortex beneath its central junction and had a maximum E-field of 172 Volts/meter at a distance of 25 mm from the coil surface. The depth of stimulation is determined in each instance by peeling the scalp and skull until the cortical surface is visualized. The strength of E-field at this targeting depth is calculated by taking into account the size and shape of the individual's head and the coil oriented parallel to the cortical columns.

The high-resolution, T1-weighted MRI of each patient was coregistered to the patient's head by the use of anatomical landmarks and a surface-matching procedure implemented in the Nexstim NBS system. The motor-evoked response (MEP) elicited by TMS was recorded by surface electromyography (EMG) from bilateral adductor pollicis brevis, and brachioradialis muscles using disposable electrodes (Neuroline 720, Ambu Inc., Glen Burnie, MD) and sampled at 3 kHz and band-pass filtered from 10 to 500 Hz. The motor mapping procedure began with the application of TMS at an intensity set at 50% of the machine output to the most likely location of the primary motor cortex (the hand knob area). The intensity of TMS was increased in increments of 10% until an EMG response was observed or 100% of machine output was reached. The process was repeated while TMS was applied to neighboring cortex along the central sulcus, including pre- and postcentral gyri. The cortical locations where MEPs were observed on EMG were identified, and for each MEP, its peak-to-peak amplitude and latency (time from TMS stimulation to MEP onset) were calculated. Because the patients could not maintain relaxed muscles and had ongoing muscle contractions during TMS stimulation, we also examined the EMG recordings for any interruption of this voluntary activity after TMS, also termed the cortical silent period. Because the patients could not maintain a true baseline or a constant level of muscle contraction, motor threshold determination (resting or active) was not attempted. The TMS time locked EMG epochs were analyzed offline to determine MEP latency, peak-to-peak amplitude, and duration of cortical silent period.

Magnetoeencephalography

Patients underwent MEG with conscious sedation during tactile stimulation of the index fingers for localization of the primary somatosensory cortex. General anesthesia was induced by propofol injection and maintained with an infusion rate of 10 mg/kg/hr. Four hundred trials of pneumatically driven mechanical taps (25 lb/in²) were applied to the fingertip of the patient's index finger via a balloon diaphragm (1 cm in diameter). MEG data were collected using a whole-head neuromagnetometer (Magnes WH3600; 4-D Neuroimaging, San Diego, CA) equipped with 248 magnetometer sensors and housed in a magnetically shielded room. Trials of MEG event-related magnetic field segments in response to tactile stimulation were filtered off-line with a bandpass filter between 2 and 40 Hz and averaged. The brain activity sources were modeled as single equivalent current dipoles. Source solutions were considered satisfactory if they were associated with a correlation coefficient of at least 0.9 between the observed and the "best" predicted magnetic field distribution, and occurred early between 60 and 80 ms after stimulus onset to ensure activity sources represent primary
somatosensory cortical activity. The location of each estimated dipolar source was determined with reference to a Cartesian coordinate system based on 3 fiducial points on the head (the nasion and external meatus of each ear), and subsequently approximated by coregistering these points to the patient’s high-resolution anatomical MRI.

**Structural and functional MRI**

Structural and functional MR images were obtained on a 3 Tesla scanner (Signa HDxt; General Electric, Milwaukee, WI) with an 8-channel head coil. The patients were sedated using the same protocol as during MEG scanning. Axially acquired volumetric T1-weighted imaging was performed (fast spoiled gradient echo) with 0.8-mm slice thickness. Axial diffusion tensor imaging was performed with 25 directions of encoding, with a 3-mm slice thickness and 128 × 128 acquisition matrix. Block design blood-oxygen-level-dependent fMRI was acquired during a passive hand movement task where the MRI acquisition matrix. Block design blood-oxygen-level dependent-fMRI was acquired with a TR of 3 seconds. Five volumes were acquired for each 15-second paradigm iteration (passive hand movement and rest) for a total of 80 volumes during the 4-minute scan (2.55 mm × 2.55 mm × 3.5 mm voxels). Two scans were acquired, one for each hand. Instructions to the physician performing the passive movements were controlled using the Esys-fMRI system (InVivo Corp, Pewaukee, WI). Diffusion tensor imaging was performed for displacement of fibers by an intramedullary spinal cord neoplasm using previously described methods using vendor provided software (Functool; General Electric). The fMRI image preprocessing was performed to remove nonbrain tissues from the image, correct for motion, image intensity fluctuations and RF inhomogeneities, and register the brain to the anatomical MRI using image processing tools from the publicly available image analysis package FSL (www.fmrib.ox.ac.uk/fsl/).

A general linear model was used to determine voxel-wise differences in activation patterns during task and rest conditions and statistical parametric image of z scores (SPI{z}) were generated and thresholded for a z score > 2.3 and a cluster significance threshold of $P = 0.05$ (corrected for multiple comparisons).

**Results**

**Motor symptoms and signs**

Patient 1 had left-sided atrophy of shoulder girdle, absent deep tendon reflexes, diminished tone, and paresis of the left upper extremity, loss of mass of intrinsic hand muscles, and normal tone, strength, and normal reflexes in the right extremities. Patients 2, 3, and 6 had normal muscle tone, bulk and strength, and normal deep tendon reflexes. Patients 4 and 5 had weakness with exaggerated deep tendon reflexes and extensor plantar response in the right extremities and normal tone and strength, normal reflexes, and flexor plantar response in the left extremities.

**TMS**

All patients tolerated the TMS procedure and no adverse effects were recorded during the procedure, specifically, no seizures were observed during the TMS procedure. The details of the TMS parameters, including the number of TMS pulses delivered, percentage of the machine output, the equivalent E-Field, and depth of stimulation for each patient are listed in Table 2. MEPs were elicited by stimulating along the precentral gyrus and the primary hand motor cortex was

---

**TABLE 1.** Demographics, Diagnosis, and Medication Information of Patients Undergoing TMS Motor Mapping

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age, mo</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Medications</th>
<th>TMS Motor Mapping</th>
<th>MEG Sensory Mapping</th>
<th>IMRI Passive Sensorimotor Mapping</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30</td>
<td>M</td>
<td>Cervicomedullary tumor with weakness in left arm and leg</td>
<td>Prednisone 0.44 mg/kg/day</td>
<td>✓</td>
<td>✓</td>
<td>NP</td>
</tr>
<tr>
<td>2</td>
<td>35</td>
<td>F</td>
<td>Intractable, symptomatic, generalized atonic seizures, secondary to hypothalamic hamartoma</td>
<td>Prednisone 0.44 mg/kg/day</td>
<td>✓</td>
<td>✓</td>
<td>NP</td>
</tr>
<tr>
<td>3</td>
<td>23</td>
<td>M</td>
<td>TSC2 with intractable myoclonic, partial, and atonic seizures</td>
<td>Valproic acid 36 mg/kg/day Zonisamide 10 mg/kg/day Levetiracetam 80 mg/kg/day Oxyccarbazine 24 mg/kg/day Ruflinate 32 mg/kg/day Clozabam 1.2 mg/kg/day no AEDs</td>
<td>✓</td>
<td>NL</td>
<td>✓</td>
</tr>
<tr>
<td>4</td>
<td>21</td>
<td>F</td>
<td>Right hemiplegic cerebral palsy with developmental delay, post-left hemispherectomy</td>
<td>Valproic acid 27 mg/kg/day Topiramate 2.3 mg/kg/day</td>
<td>✓</td>
<td>✓</td>
<td>NL</td>
</tr>
<tr>
<td>5</td>
<td>17</td>
<td>M</td>
<td>Intractable, symptomatic generalized myoclonic-tonic seizure; Encephalopathy characterized by right hemiplegic cerebral palsy with developmental delay</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>20</td>
<td>M</td>
<td>Intractable, symptomatic partial seizures of left frontal lobe origin; Tuberous sclerosis complex with small cardiac rhabdomyoma; Encephalopathy characterized by global development delay</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations:
- AED — Antiepileptic drug
- F — Female
- fMRI — Functional magnetic resonance imaging
- M — Male
- MEG — Magnetoencephalography
- NL — Not localized
- NP — Not performed
- TMS — Transcranial magnetic stimulation

---
localized successfully in 5 patients (patients 1-5; see Figs 1-4). TMS localized the motor cortex in only the left hemisphere in patient 3 (Fig 2B). In addition, in patients 4 and 5, we observed TMS applied to the primary motor cortex induced interruption of voluntary activity visible in the surface EMG, termed the contralateral cortical silent period (CSP) (see Fig 3). The “contralateral” refers to the muscle where the silent period was observed (contralateral to the stimulated M1). The details of the intensity of MEP (expressed as peak-to-peak amplitude), MEP onset time, and duration of CSP are listed for the 2 hand muscles in Table 3.

The TMS findings in patients 1 and 4 are noteworthy. Patient 1 presented with an intramedullary lesion consistent with a pilocytic astrocytoma and a very thin rim of brainstem parenchyma at the margins of the lesion (see Fig 1A). Diffusion tensor fiber tracking showed spaying of fibers within the brainstem that extended to the thin peripheral rim of parenchyma, without abrupt truncation of major fiber tracts (Fig 1B). In this patient, TMS demonstrated decreased MEP amplitude associated with a delayed conduction time (see Table 3 and Fig 1E). Motor plasticity was demonstrated with TMS in patient 4, who had undergone left-sided hemispherectomy (see Figs 3 and 4). In this patient, stimulation of right M1 elicited MEPs in bilateral hand muscles, representing ipsilateral motor innervation. The left hand muscles were normally represented in the right M1 located along the precentral gyrus in addition to areas in the right M1 where TMS resulted in MEPs in the ipsilateral hand muscles (see Figs 3 and 4).

Neuropsychological assessment

The neuropsychological assessment using Mullen scales indicated that patients (all except #1) were functioning at levels significantly below their same age peers with their gross motor skills at age equivalent range 6-21 months and fine motor skills at age equivalent range 4-16 months (listed in Table 3).

MEG and fMRI

All patients recovered from propofol sedation after MEG and fMRI procedures without complications. MEG successfully localized S1 in 3 patients and sedation artifacts made MEG data unreadable in 2 children (patients 4 and 5) (see Table 1, Fig 1D, Fig 2A, and Fig 4C). fMRI localized sensorimotor cortex in 3 of the 4 patients scanned (see Table 1, Fig 2B, Fig 4A,B). In one patient (patient 6) both TMS and fMRI were not successful in mapping the motor system, whereas MEG successfully mapped the somatosensory cortex.

Discussion

In this study, for the first time we demonstrated, using TMS, successful localization of the primary motor cortex in very young children with neurological disorders. All children were tested while awake, and no adverse effects were recorded. TMS elicited reliable MEPs and successfully localized the primary motor cortex in 5 of 6 children younger than 3 years of age. There has been one prior report of preoperative TMS motor mapping in a 3-year old child with rolandic ganglioglioma.22 The location of the primary motor cortex identified by TMS in 5 patients was consistent with the primary sensory cortex identified either by MEG (patients 1 and 2; see Figs 1 and 2) or the sensorimotor cortex localized by fMRI (patients 3-5, see Figs 2 and 4). We also demonstrate that CSP elicited by the TMS, can be used to assess the degree of inhibitory activity in the motor cortex as well as localize the motor cortex.

TMS motor mapping studies in healthy children (as young as 0.2 years) have demonstrated that reproducible MEP can be elicited in 2-year-old children, whereas the electrophysiological maturation is evident around 5-7 years and completed by 13 years of age.23 As demonstrated here, it is possible to localize M1, measure conduction times, and investigate reorganization of the motor cortex with TMS in toddlers with neurological impairments. In the present study, the MEPs were elicited via high or the maximum intensity of TMS, pointing to increased activation thresholds in these children. As noted previously, greater intensities of TMS are required to stimulate the immature motor system of toddlers. In addition, all patients except patient 1 had brain lesions and were developmentally delayed, with Mullen composite scores significantly lower than same-aged peers. The patient in whom we were not able to map the motor cortex with TMS (patient 6) was not the youngest child tested. However, this patient was performing at the lowest level of fine motor functioning (equivalent to ~4 months). Thus, functional level of the patient may be more important than the chronological age in determining the success of cortical mapping with TMS. Another factor that can result in greater stimulation thresholds are antiepileptic drugs (AEDs). All patients except patient 4 were on AEDs that have varied mechanisms of action ranging from blocking or stabilizing sodium channels, GABA agonists, GABA analogue,
and inhibiting presynaptic calcium channels. Although MEPs were elicited at the lowest intensity in a patient who was not on any AEDs (75% of machine output in patient 4), we did not find any systematic relationship between the type of AED and TMS response.

TMS motor mapping was successfully performed in 5 of 6 patients despite the fact that they had an immature motor system and were on AEDs. Two main factors influencing successful TMS in these patients are the use of MRI-navigated TMS and real-time E-field modeling. When directly compared with non-navigated TMS, navigated TMS leads to more accurate targeting of cortical areas, which in turn results in more significant physiological and behavioral effects in both diagnostic and therapeutic TMS paradigms.25-27 In addition, we used real-time visualization of the location and orientation of the E-field to guide TMS coil positioning.17 The advent of more powerful TMS coils and coils that can target deeper structures may further facilitate the application of TMS in young children.

Additionally, we demonstrate that TMS also can be used to investigate alterations in motor physiology in neurological disorders. For instance, in the patient with intramedullary tumor, correlating with clinical symptoms of weakness and absent reflexes in the left upper extremity, we observed decreased amplitude of MEP and delayed corticomotor latency in the left hand muscles. These findings indicate that compression of motor tracts in the spinal cord resulting in a net decrease in the corticospinal output and prolonged central conduction time. Central conduction times have been shown to correlate with degree of cord compression and clinical signs of upper motor neuron involvement in patients with intramedullary lesions.28 While peripheral conduction is usually unaffected, the observed prolonged latency in MEG indicating damage to the sensory fibers in this patient is consistent with previous reports.29,30 Using TMS, we also demonstrated reorganization of the motor cortex in this age group. An important advantage of TMS is its capability to map motor

FIGURE 1.
MRI, TMS, and MEG findings in patient 1. (A) Mid-sagittal MRI showing an enhancing mass in the medulla oblongata with craniocaudal dimension. (B) Axial view of directionally encoded fractional anisotropy map showing splaying of fibers within the brainstem which extended to the thin peripheral rim of parenchyma, without abrupt truncation of major fiber tracts. (C) Axial view of left (red squares) and right (orange squares) M1 as determined by TMS. The dashed line indicates the sagittal section in (D). (D) Right S1 (yellow square) localized to the postcentral gyrus by MEG. (E) Motor-evoked responses in right (red) and left (orange) hand muscles after the stimulation of contralateral M1. Arrows 1 and 2 indicate normal latency of 17.7 ms to the right hand muscles and delayed latency of 26.4 ms to left hand muscles respectively. (F) Stimulation of ulnar nerves demonstrates normal latencies in both hand muscles, and equal latency of 4.7 ms from ulnar nerve to APB muscles is indicated by arrow 3. APB, adductor pollicis brevis; MEG, magnetoencephalography; MRI, magnetic resonance imaging; TMS, transcranial magnetic stimulation. (The color version of the figure is available in the online edition.)
reorganization after brain damage, which we demonstrated in a 21-month-old patient with hemimegalencephaly who had undergone a functional hemispherectomy. Such reorganization has been demonstrated previously in older patients with congenital hemiparesis.31,32

In our experience, the success rate of S1 mapping with MEG under sedation during tactile stimulation is low and is around 30%.15 This low success rate with tactile stimulation is most likely due to propofol-induced suppression of cortical activity. Additional factors that contribute to the low success rate of S1 mapping with MEG are the presence of vagus nerve stimulator, dental crowns, VP shunt, and even frequent epileptiform discharges in the vicinity of S1. In such cases, because none of these factors adversely affect TMS mapping, TMS is a viable alternative to MEG. Motor mapping is performed routinely in children older than 4 years using fMRI,1 and the sensorimotor system has been shown with passive range of motion in sedated children as young as 1 year of age.12 However, it is not clear whether the activation maps derived during passive hand movement in fMRI represent mainly a sensory component or whether it includes a motor component.11 In our fMRI studies, although the most significant activated voxels were in S1, the activation cluster extended over M1 and overlapped with M1 locations identified by TMS (as in patient 4, shown in Fig 3A,B), indicating that the fMRI activation represents both motor and sensory components. In the earlier passive fMRI study,12 the sensorimotor cortex could not be localized for the paretic limb. In our study, however, we were successful in mapping the paretic hand for example the left S1/M1 demonstrated in patient 5 who had right hemiparesis (Fig 4B). However, presence of pathology like arteriovenous malformations in the vicinity of the motor cortex can result in false negative results.34 Similarly, tumors like gliomas can cause abnormal increases or decreases in BOLD response, leading to inaccurate fMRI mapping. In such situations, TMS can be a safe alternative to fMRI.

Safety of TMS

The magnetic field generated by TMS pulse exerts attractive forces on ferromagnetic objects and therefore TMS is contraindicated in patients who have ferromagnetic objects in the head. This would include patients

FIGURE 2.
TMS findings in patients 2 and 3. (A) TMS and MEG findings in patient 2. Coronal view demonstrating left M1 identified by TMS (red squares) and left S1 identified by MEG (hashed yellow square) and axial view demonstrating right M1 identified by TMS (orange squares) and right S1 identified by MEG (solid yellow square). The central sulcus is delineated in white. (B) TMS and fMRI findings in patient 3. Location of left M1 (red squares) as determined by TMS. Left (blue) and right (green) S1/M1 localized by passive fMRI under sedation. Voxels with z score >3 are included in the fMRI clusters. MEG, magnetoencephalography; MRI, magnetic resonance imaging; TMS, transcranial magnetic stimulation. (The color version of the figure is available in the online edition.)
with cochlear implants and programmable shunts. TMS can be safely applied in patients who have an implanted vagus nerve stimulation device, spinal cord stimulators/pumps, and epidural electrodes as long as precautions are taken not to discharge the TMS unit near the electronic/battery component. TMS also can be safely applied in patients having titanium plates in the scalp. Overall TMS application has been shown to be safe, but it is also important to be cognizant of potential adverse effects of TMS. The most common side effects are mild and include local pain, headache, and discomfort. Motor mapping using single-pulse TMS is usually well tolerated and experienced by most participants, including children to be as painless. A rare but severe adverse effect with TMS is induction of seizures. Most reports of seizures associated with TMS are during repetitive stimulation, and there are only a couple of reports of seizures after single-pulse TMS.

Specifically, TMS has been shown to be very safe in children. Reviews of published literature on TMS studies in children provide evidence that single- and paired-pulse TMS is safe even in children with epilepsy or with conditions like cerebral palsy that are inherently associated with increased risk of seizures. The risk of TMS causing a seizure in individuals with epilepsy is 1.1% with single-pulse TMS and 0.8% with the paired-pulse paradigm. The lowering of antiepileptic drugs and the presence of medically intractable epilepsy increases the likelihood of a typical seizure occurring during TMS. However, in all reports of a seizure during TMS, the patients had their typical seizure followed by their typical recovery course. The potential for seizure induction is theoretically greater because children have a lower seizure threshold and the stimulus intensity required for TMS is greater. Despite these concerns to date there have been no reports of TMS causing seizures in infants and children. This holds true for children who may be considered at risk, newborns, and even preterms as well as children with epilepsy. Furthermore, children’s subjective experience of TMS places it in the middle of a spectrum of ordinary childhood experiences. Therefore, all available data so far indicate that the use of TMS in children is safe; however, it is recommended that safety precautions should be taken. All patients should wear earplugs to reduce the effect of TMS on hearing. The rate and intensity parameters of TMS should be within the NIH guidelines for safety.

**FIGURE 3.**
TMS findings in patient 4. Left panel: TMS stimulation along the precentral gyrus resulted in MEPs (orange circle) and CSP (hashed orange circle) in the contralateral hand muscles. TMS stimulation also resulted in MEP in ipsilateral muscle (red circle). Central sulcus is shown in white. Right: Representative contralateral MEP (1), ipsilateral MEP (2) and CSP (3). CSP, cortical silent period; MEP, motor-evoked response; TMS, transcranial magnetic stimulation. (The color version of the figure is available in the online edition.)
should be continuously monitored visually and by EMG for signs of seizures or intracortical spread of excitation.

**Limitations**

This study does have some limitations. MEPs were elicited by applied TMS along the precentral gyrus, and because of the challenges of performing a systematic examination, complete motor mapping was not possible in these young children. However, eliciting MEPs from TMS stimulation confirmed the presence of motor area along the precentral gyrus. The 70-mm figure-eight coil used in this study stimulates a large area of cortex under the coil especially at 100% of machine output. Hence there is a possibility that MEP could result from stimulation of cortical area not directly beneath the coil center, leading to mislocalization. However, in addition to the strength of E-field, the orientation of the TMS coil is also an important factor in determining the effective E-field.17 In our patient cohort, even though attempts were made to optimally orient of the TMS coil to

**TABLE 3.** Summary of TMS and Neuropsychological Assessments

<table>
<thead>
<tr>
<th>Patient#</th>
<th>Left-hand Muscles</th>
<th>Right-hand Muscles</th>
<th>Neuropsychological Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MEP Amplitude, µV</td>
<td>MEP Onset, ms</td>
<td>CSP Duration, ms</td>
</tr>
<tr>
<td>1</td>
<td>79.4 (38.4)</td>
<td>26.4 (2.7)*</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>174 (99.2)</td>
<td>15.9 (3.5)</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Not elicited</td>
<td>Not elicited</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>225.8 (107)</td>
<td>19.8 (3.1)</td>
<td>25.6</td>
</tr>
<tr>
<td>5</td>
<td>178.5 (109)</td>
<td>19.3 (1.4)</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>Not elicited</td>
<td>Not elicited</td>
<td>-</td>
</tr>
</tbody>
</table>

Abbreviations:
- CSP = Contralateral silent period
- MEP = Motor-evoked potential
- NP = Not performed

When average values are listed, the standard deviations are in parentheses.

*P < 0.05.
stimulate the cortex directly underneath the coil center, not all stimulations were oriented optimally. However, in all our patients, at each stimulation site, MEPs were elicited from only one muscle group indicating that the stimulated area was most likely small. Nevertheless, care should be taken to keep the stimulation more focused, especially when performing pre-operative mapping prior to resection of a dysplasia or cortical neoplasm. A targeted stimulation is also important in examining motor plasticity in children with cerebral palsy.42

Conclusions

In summary we demonstrate the feasibility of using TMS to directly map the motor system, probe motor pathophysiology, and motor plasticity in young children without using conscious sedation. When applied within safety guidelines, TMS can be a safe and useful motor mapping tool in children. TMS can also be useful in mapping the motor system in children with low functional performance levels and on AEDs. Large-scale studies are required to further examine the effectiveness and safety of TMS and optimize the application of TMS in children with neurological disorders.

The authors thank Lilia Birg for help in collecting MEG data and Brian Potter, PhD, and Nancy Clanton, PhD, for the performing the neuropsychological assessments.

References


