Clinical Applications of Transcranial Magnetic Stimulation in Pediatric Neurology

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Abstract
Noninvasive brain stimulation is now an accepted technique that is used as a diagnostic aid and in the treatment of neuropsychiatric disorders in adults, and is being increasingly used in children. In this review, we will discuss the basic principles and safety of one noninvasive brain stimulation method, transcranial magnetic stimulation. Improvements in the spatial accuracy of transcranial magnetic stimulation are described in the context of image-guided transcranial magnetic stimulation. The article describes and provides examples of the current clinical applications of transcranial magnetic stimulation in children as an aid in the diagnosis and treatment of neuropsychiatric disorders and discusses future potential applications. Transcranial magnetic stimulation is a noninvasive tool that is safe for use in children and adolescents for functional mapping and treatment, and for many children it aids in the preoperative evaluation and the risk-benefit decision making.

Keywords
cranial magnetic stimulation, noninvasive brain stimulation, functional mapping, presurgical mapping, seizures, depression, children, plasticity, neuromodulation, rapid rate transcranial magnetic stimulation

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Transcranial magnetic stimulation is a noninvasive brain stimulation method that is based on the principle that a current passing through a coil placed on the scalp results in a magnetic field that passes through the scalp and skull and induces secondary currents in the underlying brain tissue (similar to the effects of direct cortical stimulation). The neurons in the path of this secondary current depolarize and fire synchronously. Although transcranial magnetic stimulation was initially developed as a noninvasive alternative to direct cortical stimulation for the purposes of functional brain mapping, its neuromodulatory properties have led to several therapeutic applications. Further, its noninvasive nature, ease of use, and excellent safety profile have facilitated the application of transcranial magnetic stimulation in children. Transcranial magnetic stimulation has been successfully applied in healthy children and in children with neuropsychiatric disorders to examine normal and altered neurophysiology, and its usefulness as a therapeutic tool has also been explored.1-6 Recent advances in positioning and localizing the effects of transcranial magnetic stimulation have improved the accuracy and ease of application, and enabled the integration of transcranial magnetic stimulation with other clinical neurodiagnostic procedures. This is especially beneficial in pediatric neurology, as children who usually cannot lie still or perform tasks on command (a prerequisite for other functional neuroimaging procedures such as functional magnetic resonance imaging [MRI] and magnetoencephalography) can be tested using transcranial magnetic stimulation. The focus of this article is to review the literature and provide examples of the functional mapping with transcranial magnetic stimulation exemplifying its clinical utility, and discuss its use in investigating the pathophysiology and the treatment of epilepsy and other neurologic disorders in the pediatric population.

Transcranial Magnetic Stimulation Instrumentation
A typical transcranial magnetic stimulation stimulator consists of a power supply that charges a capacitor to a high voltage,
and a thyristor switch that discharges the capacitor (Figure 1A), which generates a current pulse, that is, a primary electric field with a very short rise time (microseconds) in the transcranial magnetic stimulation coil (Figure 1B). The stimulator has an adjustable dial to regulate the amount of current produced. The early magnetic stimulators used a circular transcranial magnetic stimulation coil that had a large area of effect but did not produce focal stimulation. Now, the circular coils are primarily used for peripheral nerve stimulation. Adding another loop to make a figure-8 shape (Figure 1C) has greatly improved the focality of the transcranial magnetic stimulation coil and made it more suitable for brain stimulation. In this design, the coil loops carry currents in opposite directions, but at the point where the 2 loops are in close proximity, the induced electric field is twice as strong (see Figure 1C). The current pulse creates a time-varying magnetic field orthogonal to the coil that passes through the scalp and skull without any attenuation (Figure 1D). This magnetic field interacts with the neuronal tissue underneath the coil and induces a secondary electric field (Figure 1E). The secondary electric field generated in the tissue is proportional to the strength of the magnetic field and its rate of change, as well as the distance from the surface of the coil, as the primary electric field drops off rapidly with distance (Figure 1E). The exact mechanism by which the secondary electric field activates neurons is not known, but there is evidence that the electric field depolarizes the cortical columns and axons that are aligned along its direction, which in turn generates an action potential (ie, activation of neurons; Figure 1E). At the present time, it is not known if the depolarization of these structures occurs independently or sequentially. The action potential generated propagates in both the orthodromic (propagation of action potential along the axon) and antidromic (propagation of action potential toward the cell body) directions. The distinctive feature of transcranial magnetic stimulation is that its rapidly changing magnetic field activates neurons, in contrast to slowly changing or static magnetic fields (such as MRI) that do not cause neuronal excitation.

**Figure 1.** Basics of transcranial magnetic stimulation. (A) Basic circuitry of a transcranial magnetic stimulation system. A typical transcranial magnetic stimulation stimulator consists of an alternating current power supply, a large capacitor, a switching mechanism, and an inductor (ie, the transcranial magnetic stimulation coil). (B) The biphasic transcranial magnetic stimulation pulse has a very short duration of 230 μs with a sharp rise time. (C) Figure-8 coil geometry produces a more focused induced E-field along the center column than along the periphery. (D) The primary electric field in the transcranial magnetic stimulation coil results in a magnetic field in the orthogonal direction (dashed orange lines) that passes through the scalp and skull without any attenuation. (E) The secondary E-field induced by transcranial magnetic stimulation is modeled from the scalp surface into the brain tissue. Note that the E-field is maximal at the scalp, and it decreases as the square of the distance until it is almost negligible at depths of 5 cm. The probable sites of transcranial magnetic stimulation interaction with the brain are the cortical columns (1) and axonal stimulation (2). (F) Transcranial magnetic stimulation applied to the primary motor cortex results in an involuntary contraction in muscles that can be measured by surface electrodes. (G) The transcranial magnetic stimulation–induced motor evoked response as measured by surface electrodes.
Commonly, the transcranial magnetic stimulation coil is positioned on the scalp and held in place by hand or with a passive holding device. Robotic controlled positioning and holding devices that are more accurate and reproducible are also being developed. A typical figure-8 coil (Figure 1C) is 70 mm in diameter and can stimulate about 1 to 2 cm² of cortex beneath its central junction, although the extent of the stimulated area is proportional to the primary current flowing through the coil as well as the depth of the area being stimulated. As the primary electric field drops off rapidly with distance, the electric field at cortical locations at depths of 25 mm is only ~30% of the field at the surface of the coil. Therefore, brain areas that are located more than 40 mm below the scalp (eg, insula, cingulate cortex, basal ganglia, and mesial temporal lobes) cannot be effectively stimulated using the standard transcranial magnetic stimulation coil. Newer coil designs that can penetrate more deeply, such as H-coils, are being developed to overcome this drawback.

### Neurophysiological Effects of Transcranial Magnetic Stimulation

Transcranial magnetic stimulation pulses applied to a cortical region can result in an excitatory or an inhibitory effect depending on the location, types of neurons stimulated, and the parameters of stimulation. For example, stimulation of the primary motor cortex results in involuntary contraction of muscles and can be seen on an electromyogram as a motor evoked potential (Figure 1F and G). By injecting random or “out-of-phase” firing and desynchronizing ongoing activity, transcranial magnetic stimulation can also result in a disruption of the region’s typical spontaneous activity. By doing so, a single-pulse or repetitive transcranial magnetic stimulation can transiently disrupt normal brain activity and result in a “virtual lesion.” These excitatory and virtual lesion effects of transcranial magnetic stimulation form the basis of paradigms used in functional mapping of motor and language systems. The observation that repetitive transcranial magnetic stimulation altered cortical excitability beyond the duration of its application led to exploring its utility as a therapeutic tool.

As a general rule, high-intensity, rapid-rate transcranial magnetic stimulation (rates >1 Hz) is hypothesized to result in a long-term potentiation-like phenomenon and is therefore used to facilitate or upregulate regions or networks that have decreased activity, whereas low intensity, slow transcranial magnetic stimulation (≤1 Hz) is thought to decrease activity of a brain region or a network by mediating long-term depression and therefore can be applied to inhibit or downregulate an overactive region or network. Lastly, a paired pulse paradigm explores the effects of the first transcranial magnetic stimulation pulse on the response elicited by a second pulse applied within a few milliseconds and is most commonly used to examine the phenomena of intracortical inhibition and intracortical facilitation.

### MRI-Guided Application of Transcranial Magnetic Stimulation

Initially, cortical regions were targeted by positioning the transcranial magnetic stimulation coil on the scalp on the basis of the 10-20 EEG system. However, the current standard is the image-guided application of transcranial magnetic stimulation, also termed navigated transcranial magnetic stimulation. Transcranial magnetic stimulation targeting is most effective when subject-specific anatomic and functional maps (functional MRI, positron emission tomography, magnetoencephalography, etc) are used to guide the transcranial magnetic stimulation coil placement (Figure 2A). The coil can then be positioned using either passive holding devices or robotic systems. Several commercial transcranial magnetic stimulation systems readily implement the MRI-based coil positioning using optical positioning systems (eg, infrared cameras) that also provide real-time visualization of the transcranial magnetic stimulation coil’s placement relative to its target region. A typical setup of a navigated transcranial magnetic stimulation system for a clinical study in a pediatric patient is shown in Figure 2A. In addition, most navigated transcranial magnetic stimulation systems provide real-time feedback on the magnitude and direction of the electric field (E-field) at the site of stimulation as well as the depth of stimulation (Figure 2B) and provide visual representations of the results where the transcranial magnetic stimulation findings are overlaid onto the MRI (Figure 2C).

### Clinical Applications of Transcranial Magnetic Stimulation

The unique ability of transcranial magnetic stimulation to noninvasively induce evoked responses and virtual lesions, and its neuromodulatory potential, has spurred its clinical applications. The first clinical transcranial magnetic stimulation application explored was the safety and the efficacy of repetitive transcranial magnetic stimulation in treating major depressive disorder. A figure-8 transcranial magnetic stimulation system was cleared by the US Food and Drug Administration (FDA) for the treatment of major depressive disorder in adults in 2008. The demonstration of the feasibility and accuracy of navigated transcranial magnetic stimulation in presurgical mapping of the motor and language systems soon followed, and its use in both children and adults was approved by the FDA in 2009 and 2012, respectively. In 2013, an H-coil-based transcranial magnetic stimulation system also gained FDA approval for use in treatment of depressive episodes in adults with major depressive disorder. See Table 1 for details of transcranial magnetic stimulation systems approved by the FDA and their indications; the American Medical Association recommendations for current procedural terminology codes are listed in Table 2.
Presurgical Motor and Expressive Language Mapping With Transcranial Magnetic Stimulation

As mentioned earlier, transcranial magnetic stimulation applied to the scalp over the primary motor cortex (usually hand and/or leg area) results in a motor evoked potential in the contralateral muscles that can be recorded using surface electromyogram. Single pulses of transcranial magnetic stimulation can be applied sequentially to neighboring cortical areas and the motor evoked potential from each site of stimulation recorded, thus generating a “motor map,” or the spatial extent of the motor cortex, which is then projected onto the MRI. A routine clinical motor mapping session in a cooperative adolescent or older child can be performed in under 30 minutes, including determination of the resting motor threshold (described below).

Table 1. Transcranial Magnetic Stimulation Systems Approved by the FDA and Their Clinical Indications.

<table>
<thead>
<tr>
<th>TMS system name</th>
<th>FDA-approved clinical indication</th>
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<tbody>
<tr>
<td>Neurionetics/Neurostar (<a href="http://www.neurostar.com">www.neurostar.com</a>)</td>
<td>Major depressive disorder</td>
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<tr>
<td>Nexstim NBS system (<a href="http://www.nexstim.com">www.nexstim.com</a>)</td>
<td>Presurgical motor and language mapping</td>
</tr>
<tr>
<td>Brainsway system (<a href="http://www.brainsway.com">www.brainsway.com</a>)</td>
<td>H-coil for major depressive disorder</td>
</tr>
<tr>
<td>Magstim (<a href="http://www.magstim.com">www.magstim.com</a>)</td>
<td>Major depressive disorder</td>
</tr>
<tr>
<td>eNeura/Cerena/SpringTMS (<a href="http://www.eneura.com">www.eneura.com</a>)</td>
<td>Migraine with aura</td>
</tr>
<tr>
<td>Nexstim NBT system (<a href="http://www.nexstim.com">www.nexstim.com</a>)</td>
<td>Major depressive disorder (approved for marketing in Europe only)</td>
</tr>
<tr>
<td>Magventure (<a href="http://www.magventure.com">www.magventure.com</a>)</td>
<td>Major depressive disorder (approved for marketing in Europe only)</td>
</tr>
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</table>

Abbreviations: FDA, US Food and Drug Administration; TMS, transcranial magnetic stimulation.
and generating motor maps for the muscles of the upper and lower extremities in both hemispheres. This procedure can take longer in 4- to 5-year-old children who find it harder to maintain relaxed muscles and need frequent breaks. In children younger than 4 years, although it is usually not possible to estimate the motor threshold, the motor cortex can still be localized. We have successfully localized primary hand motor cortex in children as young as 17 months of age. In addition to its presurgical utility, transcranial magnetic stimulation–generated functional maps can also be used to study plasticity and reorganization of brain areas in response to disease, injury, or learning.

Cortical areas engaged during speech production are identified by the virtual lesion technique. The most common paradigms used in language mapping with transcranial magnetic stimulation are reading, object naming, and counting. Bursts of repetitive transcranial magnetic stimulation (usually 4-7 Hz for 1 second) time-locked to the stimulus are delivered to expressive and receptive language areas in both hemispheres as the patient performs the task. For each trial, the stimulus presented, the patient’s response, and the cortical location of transcranial magnetic stimulation are recorded. The patient’s responses during transcranial magnetic stimulation are compared with their baseline performance for errors and speech disruption. The brain areas where transcranial magnetic stimulation results in speech arrest, performance errors, and semantic errors are identified on the patient’s MRI. A typical transcranial magnetic stimulation language mapping session consists of establishing the baseline accuracy for naming (without transcranial magnetic stimulation), and naming when transcranial magnetic stimulation is delivered time-locked to stimulus onset. At our institution, we apply 5 Hz transcranial magnetic stimulation for 1 second and allow an intertrial interval of 3 to 4 seconds. The hemisphere to be stimulated first is chosen randomly, and transcranial magnetic stimulation is applied along the superior and middle temporal gyri beginning posteriorly from the parietotemporal junction and extending as anteriorly as the patient can tolerate. Next, transcranial magnetic stimulation is applied to the inferior and middle frontal gyri, covering the Broca area and premotor and mouth motor regions (Figures 3B and 4). Usually patients perform 50 to 100 trials of naming in each hemisphere. The transcranial magnetic stimulation intensity is set at 110% of the motor threshold initially, but reduced in increments of 5% if the patient experiences pain or excessive muscle stimulation that interferes with task performance. A routine clinical language mapping of both hemispheres can be completed in 1 hour in a cooperative child older than age 8 years. This procedure can take longer in younger children who cannot perform the naming task consistently and need frequent breaks. At our institution, the youngest patient who has undergone successful transcranial magnetic stimulation language mapping was a 6-year-old. Most common reasons for an incomplete study are pain at the site of stimulation, excessive stimulation of the temporalis muscle, and if the transcranial magnetic stimulation intensity has to be decreased to such an extent that the electric field at the site of stimulation falls below 50 V/m.

In the context of presurgical functional mapping, motor and expressive language maps generated noninvasively using transcranial magnetic stimulation are in good agreement with those generated by direct cortical stimulation in adult patients. The average distance between motor cortex identified by navigated transcranial magnetic stimulation and direct cortical stimulation is 6 mm, showing a good correlation between the 2 methods in adults. Further, the findings from transcranial magnetic stimulation motor mapping altered the surgical strategy in at least 25% of patients with brain tumors, strongly supporting its clinical utility. Most recently, evidence of improved postoperative outcome in patients who had undergone preoperative transcranial magnetic stimulation motor mapping is also emerging. Specifically, patients who underwent preoperative motor mapping with transcranial magnetic stimulation had smaller craniotomies and postoperatively had lower rates of residual tumor and fewer deficits. When compared to direct cortical stimulation, presurgical language mapping using navigated transcranial magnetic stimulation has high sensitivity (90%) and negative predictive value (99%). However, specificity of transcranial magnetic stimulation and its positive predictive value are low, indicating to the need for optimization of transcranial magnetic stimulation parameters. There are no studies that have examined the influence of preoperative language mapping on postoperative outcome. At the present time, there are very few reports of presurgical motor and language mapping studies using transcranial magnetic stimulation in children.

In addition to the spatial maps, another transcranial magnetic stimulation parameter that is clinically relevant is the measure of motor threshold. Motor threshold is an index of the overall cortical excitability of the motor cortex and is expressed as the lowest intensity of transcranial magnetic stimulation that elicits a motor evoked potential with ≥50 μV in amplitude in 50% of trials. Motor threshold can be assessed in a resting muscle or during contraction. The motor threshold is commonly used to normalize and compare the evoked responses across patients. Motor threshold has been shown to be a good index of normal electrophysiological maturation, as high values

### Table 2. AMA-Approved Current Procedural Terminology Codes for Transcranial Magnetic Stimulation Procedures.

<table>
<thead>
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<tr>
<td>90867—Therapeutic repetitive transcranial magnetic stimulation (TMS) treatment; initial, including cortical mapping, motor threshold determination, delivery and management</td>
<td></td>
</tr>
<tr>
<td>90868—Therapeutic repetitive transcranial magnetic stimulation (TMS) treatment; subsequent delivery and management, per session</td>
<td></td>
</tr>
<tr>
<td>90869—Therapeutic repetitive transcranial magnetic stimulation (TMS) treatment; subsequent motor threshold re-determination with delivery and management</td>
<td></td>
</tr>
<tr>
<td>0310T—Level III CPT code for investigational motor mapping extremities (noninvasive cortical stimulation)</td>
<td></td>
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</tbody>
</table>

**Abbreviation:** TMS, transcranial magnetic stimulation.
for motor threshold are seen in the very young, which steadily decrease and reach adult values around 13 years of age. Although it depends on many variables (including the technical setup, posture [ie, lying down or seated], pharmacological influence, age, and target muscle), and shows substantial intra- and interindividual variability, motor threshold is altered in a wide range of disease states. For example, motor threshold is increased in cerebral stroke, advanced motor neuron disease, or spinal cord injury. In contrast, motor threshold is decreased in conditions of a hyperexcitable corticospinal system, such as in the early stages of amyotrophic lateral sclerosis, or untreated idiopathic generalized epilepsy. A right-to-left comparison of motor threshold increases the sensitivity of detecting alterations in the motor system, for example, in cases of hemispheric lesions (as observed in Case 4, presented below). A clinically relevant state that influences motor threshold is medication. For instance, drugs that block the sodium channels in cortical neurons, such as antiepileptic drugs, result in marked increases in motor threshold. Thus, motor maps and motor threshold can potentially quantify neuronal dysfunction, disease progression, and drug treatment responsiveness in various neurologic and psychiatric disorders. In the context of clinical application, the advantages of transcranial magnetic stimulation are listed in Table 3 and compared with other functional mapping methods such as magnetoencephalography and functional MRI. We present below examples of the clinical utility of functional mapping in pediatric neurology practice.

**Presurgical Evaluation**

**Case 1**

In a 14-year-old previously healthy boy with a history of new-onset partial seizures, MRI revealed a mass in the left inferior frontal gyrus (Broca area) consistent with a glioma (Figure 3A). Because of the location of the mass, it was critical to localize the limb and face motor areas and expressive language functions in this patient. Transcranial magnetic stimulation was

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**Figure 3.** Presurgical functional mapping using transcranial magnetic stimulation: Case 1. (A) Motor mapping using transcranial magnetic stimulation in a 14-year-old patient with a glioma in the left opercular region (black arrow) revealed the cortical representation for the right hand and mouth in the precentral gyrus well away from the tumor. (B) However, expressive language was represented in cortical areas along the margin of the lesion. Yellow pegs represent brain areas where transcranial magnetic stimulation resulted in complete speech arrest, whereas orange pegs represent areas where transcranial magnetic stimulation resulted in performance errors during a naming task.

**Figure 4.** Presurgical functional mapping using transcranial magnetic stimulation: Case 2. Expressive language mapping in an 8-year-old girl with residual growth of a left temporal lobe ganglioglioma demonstrated the presence of eloquent cortex along the margins of the tumor. Transcranial magnetic stimulation–induced speech arrest (yellow pegs) and performance errors (orange pegs) were noted when transcranial magnetic stimulation was applied to cortex around the lesion.
Motor evoked potentials were elicited following single pulses of transcranial magnetic stimulation applied to the left primary hand motor cortex and resting motor threshold was determined to be 41% of machine output (equivalent to an E-field of 115 volts/meter). The extent of left primary hand motor cortex was mapped and projected onto the patient’s MRI (Figure 3A). In addition, the location of the left primary mouth cortex was identified by recording motor evoked potentials from the orbicularis oris muscle (Figure 3A). The hand and mouth motor cortices exhibited normal somatotopy and were found to be posterior to the lesion, separated by the precentral gyrus (Figure 3A). Expressive language areas were mapped with transcranial magnetic stimulation using an object-naming task. Speech disruptions in the form of speech arrest and performance errors such as delays and apraxia were noted when transcranial magnetic stimulation was applied along the margins of the mass (Figure 3B). The tumor was resected using microsurgical dissection techniques with the aid of stealth image guidance, intraoperative ultrasound, and intraoperative MRI. The pathology of the lesion was consistent with a low-grade glioma. Postoperatively, the patient had minimal speech impairment, and no motor difficulties.

**Case 2**

An 8-year-old girl with a past history of left temporal lobe ganglioglioma with residual tumor was admitted to the Le Bonheur Comprehensive Epilepsy Program, Le Bonheur Children’s Hospital, for presurgical evaluation. Expressive language mapping with transcranial magnetic stimulation in this patient demonstrated the presence of eloquent cortex along the margins of the tumor (Figure 4). Because of the close proximity and the extent of language cortex around the lesion, surgery was deferred and the patient was referred for chemotherapy and radiation therapy.

**Cortical Dysplasia**

**Case 3**

A 13-year-old girl was admitted to the Epilepsy Monitoring Unit of the Le Bonheur Comprehensive Epilepsy Program, Le Bonheur Children’s Hospital, for evaluation of new-onset partial seizures. Her MRI showed dysplastic appearance of the right parietal and frontal lobes and insula, with volume loss, polymicrogyria, and heterotopic gray matter along the posterior right lateral ventricle (Figure 5B). A vertical cleft extending from the posterior aspect of the right Sylvian fissure was also noted. Motor mapping with transcranial magnetic stimulation demonstrated normal location and extension of the hand and leg motor cortex in the left hemisphere (Figure 5A). The pathology of the lesion was consistent with a low-grade glioma. Postoperatively, the patient had minimal speech impairment, and no motor difficulties.

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**Table 3. Merits of Functional Mapping With Transcranial Magnetic Stimulation Compared With Magnetoencephalography and Functional Magnetic Resonance Imaging.**

<table>
<thead>
<tr>
<th></th>
<th>TMS</th>
<th>MEG</th>
<th>fMRI</th>
</tr>
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<tbody>
<tr>
<td><strong>Ease of use</strong></td>
<td>Excellent</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>Presence of metal in mouth/body</td>
<td>Does not cause artifact</td>
<td>Frequently causes artifact</td>
<td>Occasionally causes artifact</td>
</tr>
<tr>
<td>Presence of arteriovenous malformations</td>
<td>Does not cause artifact</td>
<td>Does not cause artifact</td>
<td>Occasionally causes artifact</td>
</tr>
<tr>
<td>Patient cooperation and task execution</td>
<td>Not necessary</td>
<td>Necessary</td>
<td>Necessary</td>
</tr>
<tr>
<td>Motor mapping in young children (&lt;4 y)</td>
<td>Motor function directly measured; does not require sedation</td>
<td>Motor function indirectly mapped via sensory mapping; requires sedation</td>
<td>Motor function passively mapped; requires sedation</td>
</tr>
<tr>
<td>Functional motor reorganization</td>
<td>Readily demonstrated</td>
<td>Not readily demonstrated</td>
<td>Not readily demonstrated</td>
</tr>
<tr>
<td>Overt speech during functional mapping</td>
<td>Does not cause artifact</td>
<td>Frequently causes artifact</td>
<td>Frequently causes artifact</td>
</tr>
<tr>
<td>Corticomotor conduction time</td>
<td>Readily measured</td>
<td>Requires complex data processing</td>
<td>Cannot be measured</td>
</tr>
<tr>
<td>Effects of neuropsychiatric disorders on cortical excitation and inhibition</td>
<td>Readily measured</td>
<td>Cannot be measured</td>
<td>Cannot be measured</td>
</tr>
<tr>
<td>Effects of medications on cortical excitation and inhibition</td>
<td>Readily measured</td>
<td>Cannot be measured</td>
<td>Cannot be measured</td>
</tr>
<tr>
<td>The extent of the motor representation of muscles</td>
<td>Readily measured</td>
<td>Cannot be measured</td>
<td>Can be measured</td>
</tr>
<tr>
<td>Claustrophobia</td>
<td>Not reported</td>
<td>Occurs in 1 in 150 patients</td>
<td>Occurs in 1 in 150 patients</td>
</tr>
<tr>
<td>Concordance with direct cortical stimulation: Motor</td>
<td>Mean distance: 6 mm(^{17})</td>
<td>Median distance: 12.1 mm(^{19})</td>
<td>Mean distance: 12.9 mm(^{20})</td>
</tr>
<tr>
<td>Concordance with direct cortical stimulation: Language</td>
<td>Sensitivity: 90%</td>
<td>Sensitivity: 87%(^{31})</td>
<td>Sensitivity: 59%-100%</td>
</tr>
<tr>
<td></td>
<td>Specificity: 98%(^{18})</td>
<td>Specificity: NR</td>
<td>Specificity: 0%-97%(^{32})</td>
</tr>
</tbody>
</table>

**Abbreviations:** fMRI, functional magnetic resonance imaging; MEG, magnetoencephalography; TMS, transcranial magnetic stimulation; NR, not reported.
muscles only during contraction and at a transcranial magnetic stimulation intensity of 90% machine output (equivalent to an E-field of 300 V/m). The location and extent of the primary hand motor cortex in the right hemisphere was enlarged antero-posteriorly extending from the premotor cortex and parietal cortex and was located over the area of polymicrogyria. Further, the location of the primary leg motor cortex was displaced laterally and localized within the aberrant hand motor cortex. The extent of aberrant right primary hand and leg motor cortices are shown in Figure 5B.

Cortical Reorganization

Case 4

Functional mapping with transcranial magnetic stimulation can also be useful to probe the status of motor reorganization following brain injury. In the example shown in Figure 6, motor mapping was performed on a 16-year-old female patient who had suffered a traumatic injury from a steering wheel in utero at 32 weeks’ gestation when her mother was in a motor vehicle accident. She was treated for left intracranial hematoma and left frontoparietal porencephalic cyst that resulted from this injury. At age 13 years, the patient underwent left-sided functional hemispherectomy to treat her refractory partial seizure disorder and has been seizure-free since. Motor mapping with transcranial magnetic stimulation demonstrated the motor reorganization: the right hemisphere stimulation resulted in MEPs in both the contralateral muscles, and also in the ipsilateral muscles of both her hand and legs. The locations of ipsilateral (shown as red pegs on patient’s MRI in Figure 6), bilateral (yellow pegs), and contralateral (orange pegs), innervation were localized within the primary motor cortex. Motor evoked responses in bilateral hand muscles were elicited with stimulation of the post central gyrus, indicating an expansion of the spatial extent of the motor map into primary sensory cortical area (Figure 6). Such expansion of motor function into sensory cortex is most likely in patients with epilepsy and these findings are indicative of a posttraumatic reorganization in the motor system.

Utility of Transcranial Magnetic Stimulation in the Diagnosis and Follow-Up of Neurologic Disorders

Epilepsy. Because the underlying pathophysiology in epilepsy syndromes is altered cortical excitability,33 transcranial magnetic stimulation is well suited to examine the changes in cortical excitation in patients with epilepsy and has been used to detect such changes prior to treatment, following antiepileptic drugs (AEDs), and as a treatment tool. The alterations in the cortical excitability in patients with epilepsy is variable, and, depending on the type of epilepsy syndrome, can manifest as either increases or decreases in transcranial magnetic stimulation measures of motor threshold, intracortical inhibition and facilitation. For example, when compared with healthy controls, drug-naïve, new-onset patients with juvenile myoclonic epilepsy exhibited significantly lower motor threshold, decreased intracortical inhibition, and increased intracortical
facilitation, indicating an underlying cortical hyperexcitability in these patients.\textsuperscript{34,35} Similarly, patients with drug-naïve new-onset temporal lobe epilepsy exhibit hyperexcitability in the hemisphere with the epileptogenic focus, but normal excitability in the unaffected hemisphere.\textsuperscript{34} In other seizure types, variable degrees of alterations in motor threshold, intracortical inhibition, and intracortical facilitation measures are reported. Irrespective of the baseline abnormalities in the cortical excitability in patients with epilepsy, cortical excitability measures with transcranial magnetic stimulation can be useful in monitoring the effects of pharmacologic treatments. Transcranial magnetic stimulation can also be used to assess the effect of nonpharmacologic treatments, including vagus nerve stimulation, brain stimulation, and surgery on cortical excitability in patients with epilepsy. Most studies have reported a reduction in cortical excitability following antiepileptic drugs, with excitability returning to normal or near-normal levels in patients who become seizure free.\textsuperscript{33}

Other disorders. Childhood neuropsychiatric disorders whose pathophysiology includes abnormalities in cortical excitability such as attention-deficit hyperactivity disorder, autism spectrum disorder, and Tourette syndrome have been investigated using transcranial magnetic stimulation. Transcranial magnetic stimulation–evoked measures of intracortical inhibition correlate with the presence and severity of attention-deficit hyperactivity disorder in childhood, as well as with commonly observed delays in motor control.\textsuperscript{36} Cortical inhibition is also found to be significantly reduced in the high-functioning autism group compared with both those with Asperger disorder and healthy children.\textsuperscript{37} Similarly, patients with Tourette syndrome show reduced intracortical inhibition at rest and during the early phase of movement preparation, as well as altered motor evoked potential recruitment during early and later phases of movement.\textsuperscript{33} These findings suggest that reduced cortical inhibition could explain in part the difficulty that patients have in suppressing involuntary tics.

**Therapeutic Applications of Transcranial Magnetic Stimulation in Pediatric Neurology**

Epilepsy. The increased cortical excitability in patients with epilepsy can also be a target of therapeutic transcranial magnetic stimulation. Low-frequency repetitive transcranial magnetic stimulation decreases cortical excitability by mediating long-term depression and has an excellent safety profile. Therefore, it is attractive as a treatment alternative in patients with refractory epilepsy. More importantly, the inhibitory effects of transcranial magnetic stimulation are long lasting. Over the last 15 years, a handful of studies ranging from case reports to randomized, double blind, sham-controlled series have investigated the efficacy of low-frequency transcranial magnetic stimulation in treating refractory epilepsy. Although the individual studies produced mixed findings, a meta-analysis that included studies with 4 or more patients found overall a significant effect size of 0.34, and, more specifically, cortical dysplasia or neocortical epilepsy showed a higher effect size (0.71).\textsuperscript{35} Recently Sun and colleagues examined the effect of 0.5-Hz transcranial magnetic stimulation applied to the epileptiform focus on a large number of patients with refractory epilepsy (n = 60) randomized into a low-intensity transcranial magnetic stimulation (essentially a sham condition) group and a high-intensity transcranial magnetic stimulation (treatment) group.\textsuperscript{39} Immediately following a 2-week transcranial magnetic stimulation treatment, the mean seizure frequency was reduced by 80% in patients receiving the transcranial magnetic stimulation treatment (compared to 2.3% reduction in the sham group), and remained low for up to 8 weeks after the completion of treatment. The aforementioned studies suffer from 2 main limitations, namely, the lack of accurate localization of epileptogenic focus (as those were estimated on the basis of surface EEG) and precise targeting of the treatment site (scalp locations were identified using 10-20 EEG scalp coordinates). Even though epilepsy is about twice as common in children as in adults (about 700 per 100,000 in children under the age of 16 years compared to 330 per 100,000 in adults), and children with epilepsy are at increased risk for social and educational problems, most transcranial magnetic stimulation treatment studies
are on adults. Therefore, it is critical to include children in future studies, especially because low-frequency transcranial magnetic stimulation is safe and does not result in the systemic adverse effects common to pharmacotherapy. In order to further improve the efficacy of low-frequency transcranial magnetic stimulation in treating epilepsy, future studies should consider improving the accuracy of localization of epileptogenic focus using magnetoencephalography and optimizing transcranial magnetic stimulation targeting using image guidance.

**Stroke.** Similar to epilepsy, the therapeutic effects of transcranial magnetic stimulation have been examined in motor rehabilitation in stroke patients as the main treatment and as an adjuvant with physical rehabilitation. Attempts have been made to improve cortical excitability directly by applying facilitatory repetitive transcranial magnetic stimulation to the lesioned motor cortex or indirectly by applying inhibitory repetitive transcranial magnetic stimulation to the contralesional motor cortex. Most of these studies are in adults, and report significant improvement in motor function. The few studies that have enrolled children with stroke provide preliminary evidence of improved motor function in the short term and demonstrate the safety and feasibility of repetitive transcranial magnetic stimulation in children. Further studies are needed in children to investigate the optimal transcranial magnetic stimulation parameters, and the use of transcranial magnetic stimulation as an adjuvant to physical therapy.

**Therapeutic application of transcranial magnetic stimulation in other disorders.** Transcranial magnetic stimulation is approved by the FDA for use in the treatment of depression in adults, and investigations into its efficacy and safety in children are ongoing. Preliminary findings indicate that the therapeutic effect size and adverse effects of transcranial magnetic stimulation treatment for depression in children is similar to that observed in adults. Similarly, studies investigating the effectiveness and safety of repetitive transcranial magnetic stimulation in treating migraine, headache, and functional movement disorders in children are ongoing and show promise. Recently, therapeutic transcranial magnetic stimulation applied to the frontal cortex has been shown to improve error monitoring and correction functions in children with autism. Transcranial magnetic stimulation can also induce voltages in nearby wires and electronic devices, transcranial magnetic stimulation can be safely applied in patients with active brain implants as long as the electrodes and the subcutaneous wires are not directly under the stimulating coil. Similarly, in cases of electronic implants such as programmable shunts, transcranial magnetic stimulation should be avoided in the vicinity of the implants. Transcranial magnetic stimulation 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 transcranial magnetic stimulation unit near the components located in the neck, chest, or back. The absolute and relative contraindications for transcranial magnetic stimulation use are listed in Table 4.

**Adverse effects of Transcranial Magnetic Stimulation**

**Local pain, headache, and discomfort.** Transcranial magnetic stimulation is usually well tolerated and experienced as painless by most participants, including children. At times, repetitive transcranial magnetic stimulation can be painful, especially when applied over prefrontal and temporal areas. Headache and neck pain are reported as the most common side effects of transcranial magnetic stimulation (40% of cases) applied to nonmotor areas. The cutaneous sensation is caused when repetitive transcranial magnetic stimulation stimulates scalp muscles, producing a twitch in the scalp and face muscles that can be uncomfortable or even painful in some. Some patients also complain of toothache following repetitive transcranial magnetic stimulation.

**Hearing loss.** Firing of the transcranial magnetic stimulation coil is accompanied by a click that results from rapid mechanical deformation of the wires in the coil. The loudness of the click may exceed 140 dB (at the highest intensities of transcranial magnetic stimulation). There have been reports of transient hearing loss in patients following repeated session of

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### Table 4. Absolute and Relative Contraindications for Transcranial Magnetic Stimulation Application.

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<tr>
<th>Contraindications for TMS</th>
<th>Absolute</th>
<th>Relative</th>
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<tbody>
<tr>
<td>Ferromagnetic material in the head</td>
<td>Cardiac pacemaker</td>
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<tr>
<td>Intracardiac lines</td>
<td>Implanted medication pumps</td>
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<tr>
<td>Increased intracranial pressure</td>
<td>Programmable ventriculoperitoneal shunts</td>
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<tr>
<td>Cochlear implant</td>
<td>Serious systemic illness</td>
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<td></td>
<td>Antipsychotic medications (clozapine, olanzapine, and quetiapine)</td>
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<td></td>
<td>Antianxiety medication (alprazolam)</td>
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<td></td>
<td>Antidepressant medications (bupropion, tricyclic antidepressants)</td>
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<tr>
<td></td>
<td>Medications treating obsessive compulsive disorder (clomipramine)</td>
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Abbreviation: TMS, transcranial magnetic stimulation.
transcranial magnetic stimulation (as in depression treatment). In order to minimize this risk, the patients should wear earplugs during the study.

**Seizure induction.** The most severe adverse effect with transcranial magnetic stimulation is induction of seizures. Seizures can be induced by repetitive transcranial magnetic stimulation when it is applied at high intensity, at higher rates, and with short intertrain intervals. Several cases of accidental seizure induced by repetitive transcranial magnetic stimulation have been reported, but most of these were prior to the establishment of safety guidelines. Since then, however, the incidence of seizure has decreased dramatically, and currently the risk of seizure is considered very low. Worldwide, of the 300,000 or more treatment or research sessions in the history of transcranial magnetic stimulation, approximately 20 transcranial magnetic stimulation–induced seizures have been reported.14 Several of these seizures were induced when transcranial magnetic stimulation parameters were outside the guidelines or patients were on medications known to reduce seizure threshold, and in some cases could represent nonepileptic events such as syncope.48 Thus, transcranial magnetic stimulation is very safe and the estimated risk of seizure under routine clinical use is approximately 1 in 30,000 treatments (0.003%) or 1 in 1000 patients (0.1%). In fact, the risk is less than or comparable to the risk of seizure associated with antidepressant medications.53 All transcranial magnetic stimulation seizures have occurred during stimulation, rather than later, and have been self-limiting with no long-term sequelae.

**Safety of transcranial magnetic stimulation in children.** Transcranial magnetic stimulation has been shown to be safe in children as well. Reviews of published literature on transcranial magnetic stimulation studies in children1,54 provide evidence that single and paired pulse transcranial magnetic stimulation is safe even in children with epilepsy, or with conditions such as cerebral palsy that are associated with increased risk of seizures. These reports suggest that there is “no discernable evidence” that single or paired pulse transcranial magnetic stimulation could cause harm to children. The potential for seizure induction is theoretically greater because children have a lower seizure threshold and the stimulus intensity required for transcranial magnetic stimulation is higher. Despite these concerns, to date there have been no reports of transcranial magnetic stimulation causing seizures in infants and children. This holds true for children who may be considered at risk, such as newborn and even preterm babies, as well as children with epilepsy.55 Furthermore, children’s subjective experience of transcranial magnetic stimulation places it in the middle of a spectrum of ordinary childhood experiences. Therefore, all available data so far indicate that the use of transcranial magnetic stimulation in children is safe.

**Safety of transcranial magnetic stimulation in persons with epilepsy.** The risk of seizure in patients with epilepsy is calculated to be 1.4% crude per-patient risk (4 of 280 patients) and no cases of status epilepticus were reported.57 Schroeder and colleagues58 have examined the safety of single pulse and paired pulse transcranial magnetic stimulation in patients with epilepsy by reviewing studies on a total of 837 individuals with epilepsy who have undergone transcranial magnetic stimulation. The authors conclude that despite the safety concerns, the risk of transcranial magnetic stimulation causing a seizure in individuals with epilepsy is small. Overall, the crude risk of having a transcranial magnetic stimulation–induced seizure is 1.1% (8 of 717 patients) with single pulse transcranial magnetic stimulation and 0.8% (1 of 120 patients) 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 transcranial magnetic stimulation. In all cases of a seizure during transcranial magnetic stimulation, the subject had their typical seizure followed by their typical recovery after the seizure. In most cases, it was not clear if the seizure was actually induced by transcranial magnetic stimulation or was merely a coincidence. Furthermore, there have been no clear long-term adverse consequences in any individuals with epilepsy who have experienced a transcranial magnetic stimulation–associated seizure. In fact, certain antiepileptic medications reduce the risk of seizures following transcranial magnetic stimulation. The risk of having a seizure during transcranial magnetic stimulation is reduced to 0.4% (2 in 500 cases) in patients who continue to take antiepileptic medications, and is zero (0 in 74 cases) in patients whose epilepsy is well controlled. The numerical risk assessment provided in this report enables physicians and researchers to more accurately inform their research subjects with epilepsy of the risk of seizure during transcranial magnetic stimulation. In another long-term follow-up study, the patients were followed up to 4 weeks after transcranial magnetic stimulation for their seizure frequency and no statistical difference in seizure frequencies between after and before transcranial magnetic stimulation (P > .05).59

**Safety of transcranial magnetic stimulation in patients with other neurologic and psychiatric disorders.** Application of both diagnostic and therapeutic transcranial magnetic stimulation has been shown to be safe in patients with neurologic and psychiatric illness, and the incidence rate of adverse effects is comparable to that seen in healthy volunteers. In treatment studies, specifically in depression, there are rare reports of patients suffering from a hypomanic episode. It is thought to be more due to the treatment intervention rather than transcranial magnetic stimulation per se. In the United States, since the market introduction of the NeuroStar TMS Therapy system (www.neurostar.com) in October 2008, 7 seizures have been reported out of 250,000 NeuroStar transcranial magnetic stimulation treatment sessions in more than 8000 patients.14 Consistent with previous observations, in 5 of the 7 seizures, patients had concurrent use of medications that are known to alter seizure threshold. In other neurologic and psychiatric disorders where transcranial magnetic stimulation is being investigated as a treatment tool,
the adverse effects are limited to seizures, local discomfort, and hearing loss. Recently, in a treatment study, patients on average received 6800 pulses of high-intensity 10 Hz repetitive transcranial magnetic stimulation daily over several days without any serious adverse effects. One patient in particular has received more than a million transcranial magnetic stimulation pulses delivered over 185 sessions in 2 years with no serious adverse effects.60

To date, we have performed motor and language mapping in 70 children with epilepsy and brain tumors. All patients tolerated the procedure and patients who did not have a history of seizure disorder did not experience any serious adverse effects including seizures. However, in one 6-year-old patient who had a history of startle-induced seizure had a typical seizure episode during motor mapping, most likely elicited by transcranial magnetic stimulation clicks. Nevertheless, motor mapping could be completed in this patient. Two patients with history of epilepsy had seizures during placement of electromyogram electrodes before administration of any transcranial magnetic stimulation and 1 patient with epilepsy had a seizure during a break in a language mapping session, several minutes after cessation of transcranial magnetic stimulation. Consistent with previous reports57 in our institution, patients with epilepsy experienced their typical seizure and recovery most often unrelat-ed to transcranial magnetic stimulation. Further, the risk of having a transcranial magnetic stimulation–induced seizure in patients who did not have seizure disorder was not any different from that for the general population. However, it is recommended that safety precautions be taken during a transcranial magnetic stimulation study in children. All patients should wear earplugs to reduce the effect of transcranial magnetic stimulation on hearing. The rate and intensity parameters of transcranial magnetic stimulation should be within the guidelines for safety.56 Patients should be continuously monitored visually and by electromyography for signs of seizures or intra-cortical spread of excitation.

Emerging Brain Stimulation Techniques in Children

**Theta-burst stimulation.** Theta-burst stimulation is a recently developed therapeutic transcranial magnetic stimulation pulse pattern designed to mimic the naturally occurring theta rhythm of the hippocampus that mediates synaptic plasticity.61,62 The most common theta-burst repetitive transcranial magnetic stimulation protocol is a series of 3-pulse, theta-rate bursts (30-50 Hz) delivered in 5-Hz trains (eg, a 3-pulse 50 Hz transcranial magnetic stimulation burst every 200 ms). The advantage of theta-burst stimulation over conventional repetitive transcranial magnetic stimulation is that it is effective at sub-threshold intensities, and by changing the pattern of application (continuous vs intermittent) it can mediate both excitatory and inhibitory neuronal plasticity. Furthermore, session durations for theta-burst stimulation are much shorter than traditional repetitive transcranial magnetic stimulation protocols, greatly reducing the time commitment for patients and therapists, and further reducing the adverse effects profile. Recently, the safety and tolerability of theta-burst stimulation in pediatric population has been demonstrated,63 with only mild adverse events reported in 5 of 40 children. Hence, theta-burst stimulation is a promising therapeutic tool, and its utility in treating neurologic and psychiatric disorders in the pediatric population merits further investigation.

**Transcranial direct current stimulation.** Transcranial direct current stimulation is a recently developed noninvasive brain stimulation technique where weak electrical currents are applied to the scalp in order to modulate brain function. Unlike transcranial magnetic stimulation, transcranial direct current stimulation is not focal stimulation. It has the advantages of being inexpensive, readily portable, and safe, with no reports of seizure or other serious adverse effects. Although several studies have demonstrated the utility of transcranial direct current stimulation in treating stroke, depression, anxiety, schizophrenia, and chronic pain in adults,64,65 currently there are no FDA-approved clinical indications for transcranial direct current stimulation. The application of transcranial direct current stimulation has been shown to be feasible and safe in children as well66; however, reports on its clinical efficacy in treating neuropsychiatric disorders in this age group are mixed and more large-scale randomized trials are needed.6

Conclusions

At present, transcranial magnetic stimulation is a safe and noninvasive means of localizing motor and language functions in the brain in the pediatric population. Use of MRI guidance and E-field mapping have improved the spatial resolution and the targeting accuracy of transcranial magnetic stimulation. In addition to its diagnostic utility, transcranial magnetic stimulation is also gaining prominence as a nonpharmacologic treatment tool for various childhood neuropsychiatric disorders. We believe that the critical information that transcranial magnetic stimulation provides, coupled with its ease of use, will result in increasing pediatric applications in the near future.

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Author Contributions

SN conceived the study, performed literature search, acquired and processed transcranial magnetic stimulation data, assimilated and interpreted all the data, and drafted this manuscript. AM, FAB, and JWW characterized the patients, and along with ACP aided in interpretation of the data and provided critical revision of the manuscript for important intellectual content.

Declaration of Conflicting Interests

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Ethical Approval
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