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Transcranial Magnetic Stimulation in Child Neurology: Current and Future Directions

Richard E. Frye, MD, PhD, Alexander Rotenberg, MD, PhD, Molliann Ousley, and Alvaro Pascual-Leone, MD, PhD

Transcranial magnetic stimulation (TMS) is a method for focal brain stimulation based on the principle of electromagnetic induction, where small intracranial electric currents are generated by a powerful, rapidly changing extracranial magnetic field. Over the past 2 decades TMS has shown promise in the diagnosis, monitoring, and treatment of neurological and psychiatric disease in adults, but has been used on a more limited basis in children. We reviewed the literature to identify potential diagnostic and therapeutic applications of TMS in child neurology and also its safety in pediatrics. Although TMS has not been

associated with any serious side effects in children and appears to be well tolerated, general safety guidelines should be established. The potential for applications of TMS in child neurology and psychiatry is significant. Given its excellent safety profile and possible therapeutic effect, this technique should develop as an important tool in pediatric neurology over the next decade.

Keywords: transcranial magnetic stimulation; corticospinal pathway maturation; cortical reorganization; corticospinal abnormalities; cortical excitability; cortical plasticity

Transcranial magnetic stimulation (TMS) is a 2-decade-old method for focal noninvasive brain stimulation that is based on the principles of electromagnetic induction, where small intracranial electrical currents are generated in the cerebral cortex by a powerful fluctuating extracranial magnetic field (see references 1 and 2 for a comprehensive review). In adult trials, TMS shows promise as a novel nonpharmacologic diagnostic and therapeutic technique with applications in neurology, psychiatry, and rehabilitation medicine. Yet, applications of TMS in the pediatric population have been slow to develop.

Preliminary success of this technique as a therapeutic tool for adult neurologic diseases such as stroke,³⁻⁵ major

depression,⁶ and epilepsy⁷⁻⁹ should prompt similar development of this technique in the pediatric setting. Additionally, TMS can provide insight into normal and aberrant developmental neurology and neurophysiology in children. Recent reviews of the safety of TMS in adults and children suggest that there is minimal risk associated with this technique.¹⁰⁻¹² The appendix lists all original studies that have included children in the study population. In this manuscript we review the current applications of TMS in the pediatric setting and provide a description of how TMS could be expanded to provide further benefit as a diagnostic and therapeutic technique in pediatrics.

Prior to reviewing the pertinent literature, we provide a short primer on TMS. We describe the basic design of the TMS device. This is followed by a description of the 3 common stimulation techniques and relevant TMS-derived neurophysiological measurements. The review of the TMS studies in pediatrics is then divided into 3 sections focused on (1) diagnostic applications, (2) therapeutic application, and (3) TMS safety in children.

The TMS Technique

The 3 essential components of a TMS device are storage capacitors, a stimulating coil, and a timing mechanism.^{13,14}

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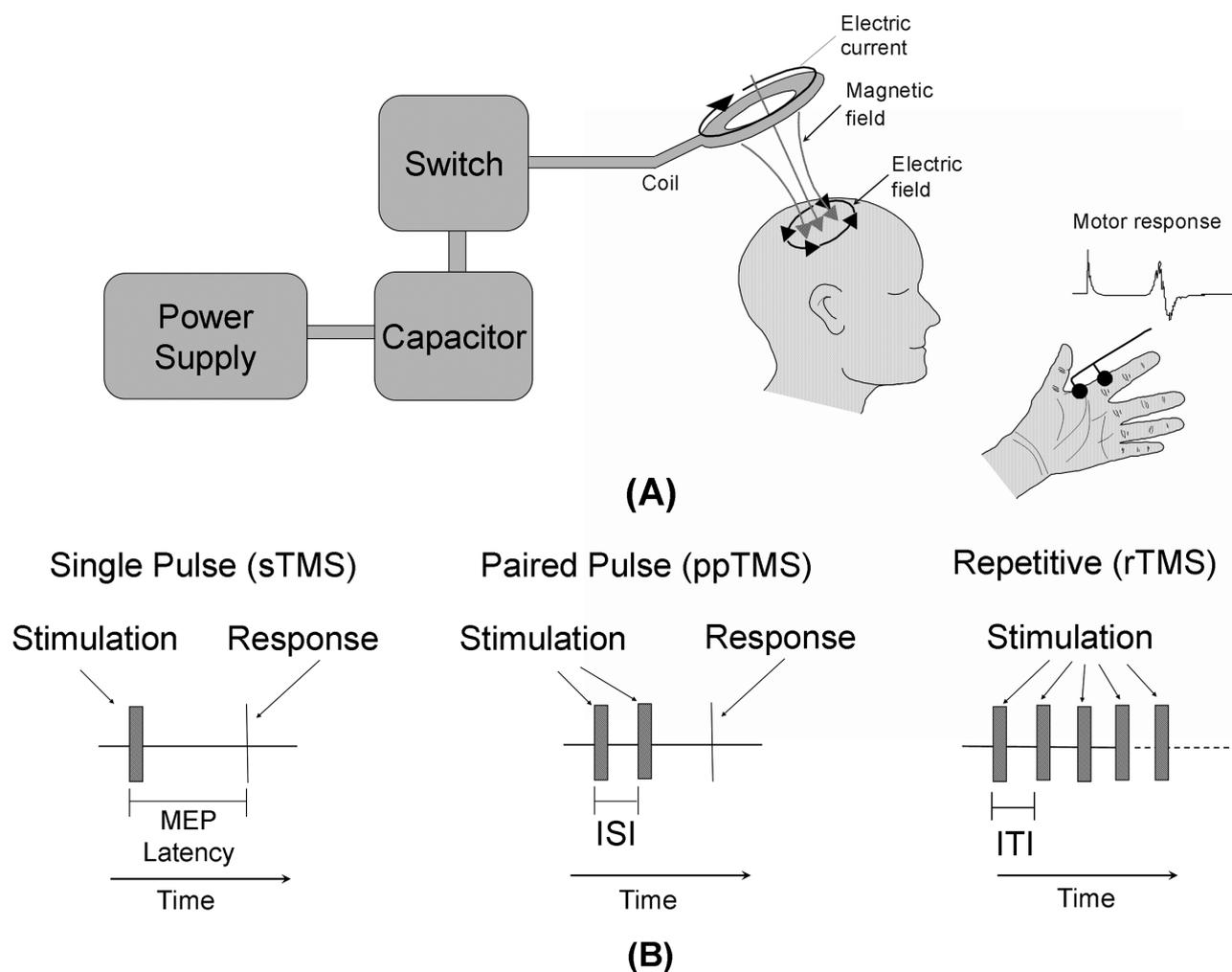


Figure 1. TMS device and applications. (A) A block diagram depicting the transcranial magnetic stimulator (TMS) circuit is depicted on the left. The power supply charges the capacitor. An operator or computer then signals for the charge stored in the capacitor to be released into the stimulation coil through a thyristor switch. The current flowing through the stimulating coil (here depicted as a circular coil) produces a perpendicular magnetic field which transverse the skull and induces electrical currents within the cortex underlying the coil. A detectable muscle contraction, typically in a contralateral limb, results if the stimulation coil is placed over the motor cortex. This motor response is quantitatively measured as the motor evoked potential (MEP). (B) Three diagrams depicting various TMS protocols. Single-pulse TMS (sTMS) provides a single stimulation to the cortex. If the coil is positioned over the motor cortex, a motor response is elicited. Paired-pulse TMS (ppTMS) stimulates the motor cortex with 2 pulses separated by a short interstimulus interval (ISI). The resulting motor response is compared to the motor response elicited by signal-pulse TMS. Repetitive TMS (rTMS) uses a train of pulses separated by a regular intertrain interval (ITI) for a specific period of time. The duration of the intertrain interval determines the stimulation frequency.

After being charged to approximately 5000 volts, the capacitors are discharged rapidly through a conductive coil over approximately 200 microseconds (Figure 1A).¹⁵ The current passing through the coil results in a fluctuating magnetic field which, in turn, induces a small intracranial electric current that focally stimulates the brain parenchyma. This is best evidenced by a motor response when the coil is placed over the primary motor cortex. Applied at appropriate intensity, stimulation of the primary motor cortex leads to gross movement and a measurable motor evoked potential in the hand

contralateral to the stimulated cortex (Figure 1A).¹ In this way, TMS represents a form of “electrode-less”, noninvasive cortical stimulation.¹⁶

Two types of TMS coils are typically used for human stimulation. A circular coil activates a large volume of brain tissue. A figure 8 coil is composed of 2 adjacent circular coils. The magnetic field of a figure 8 coil is focused at the point where the 2 circular coils meet, thereby providing stimulation to a focal area of brain tissue of approximately 1 cm³ in volume.

Three different TMS protocols are commonly used (Figure 1B)²:

- sTMS. Single-pulse TMS stimulates the brain with one magnetic pulse. Single-pulse TMS is typically utilized to study corticospinal tract characteristics, but also can be used to interrupt ongoing cognitive activity, especially if the chronometry of such activity is known.
- ppTMS. Paired-pulse TMS stimulates the motor cortex with 2 magnetic pulses that are separated by a variable interstimulus interval. The relative difference between the motor evoked potential amplitude following paired-pulse stimulation is compared to the motor evoked potential amplitude after single-pulse TMS. This ratio provides a measure of the cortical inhibitory-excitatory balance.
- rTMS. Repetitive TMS stimulates the brain with a series of magnetic pulses. Notably, in most subjects repetitive TMS has an inhibitory effect on the cortex if the time between the pulses is 1 second or more (ie, 1 Hz or low-frequency repetitive TMS), and repetitive TMS has an excitatory effect on the cortex if the frequency of stimulation is faster than 10 Hz and applied in bursts of 2 to 10 seconds with pauses of 20 to 30 seconds in between (ie, high-frequency repetitive TMS).²

The 3 aforementioned TMS techniques are commonly used to study 3 categories of neurophysiological measurements: (1) cortical excitability, (2) corticospinal pathway characteristics, and (3) interhemispheric dynamics.

Cortical excitability. This can be measured with 3 neurophysiological measurements: motor threshold, silent period, and the intracortical inhibitory-excitatory balance. *Motor threshold* is defined by the lowest strength single-pulse TMS pulse required to produce a criterion amplitude motor evoked potential (eg, 5 μ V peak-to-peak) on a prespecified fraction of trials (eg, 5 out of 10) with optimal placement of the coil over the contralateral motor cortex. Motor threshold is typically reported as a percentage of the maximum stimulator output rather than the absolute magnetic field strength. However, it should be noted that different stimulation devices may have different output strengths. Next, the *silent period* is the brief suppression of voluntary contraction in a contralateral target muscle following a single cortical stimulus to the motor cortex. The silent period includes cortical and spinal mechanisms, and appears to be supported in part by mechanisms independent of those generating the motor evoked potential that rely prominently on GABA-B neurotransmitter activity. Finally, *intracortical inhibitory-excitatory balance* is determined using paired-pulse TMS. The motor evoked potential amplitude elicited by a stimulation pulse that is preceded by a conditioning pulse is determined with various interstimulus intervals ranging from 1 to 500 milliseconds. Short interstimulus intervals result in intracortical inhibition, which is presumably mediated by GABA, and longer interstimulus intervals result in intracortical facilitation, which is presumably mediated primarily by glutamate.

Corticospinal pathway characteristics. These are determined by examining several neurophysiological measurements derived from the motor evoked potential, such as amplitude, duration, and onset latency. Since the motor evoked potential latency provides an index of the combined peripheral and central motor pathway latency, the peripheral pathway latency must be subtracted from the motor evoked potential latency in order to derive the central motor conduction time—a measure of corticospinal (ie, central nervous system) neural transmission speed. Peripheral pathway latency is estimated by either stimulating the proximal segment of the appropriate spinal roots by placing the TMS coil at the relevant spinal level or (more accurately) from the F-wave latency.

Interhemispheric dynamics. This can be measured by determining the ipsilateral silent period. This measurement uses single-pulse TMS to stimulate inhibitory transcallosal connections from the ipsilateral to the contralateral hemisphere, which, in turn, interrupts ongoing ipsilateral electromyographic activity.¹⁷ Alternatively, paired-pulse TMS can be used by applying one stimulus to one hemisphere with the second one at a variable interval to the other. The first stimulus results in a response in contralateral muscles, but also conditions, via callosal fibers, the response to the second stimulus. The interstimulus interval provides a measure of callosal conduction time.

Diagnostic Applications of TMS in Children

TMS has been used to study developmental neurophysiology and neurophysiologic abnormalities that result from neurological, psychiatric, and medical disease. This section is divided into 3 topics. First, normal developmental neurophysiology of the corticospinal motor tract as defined by TMS studies is reviewed. This information can help define basic developmental neurophysiological mechanisms and is the beginning of the development of a normative database of neurophysiological measurements that could be used as a diagnostic reference in the clinical setting. Second, we review studies that use TMS to investigate cortical motor map reorganization following congenital or postnatal central nervous system injury and following peripheral nerve injury as the result of limb amputation. Last, we review studies that have used TMS to investigate neurophysiological abnormalities in children with neurological, psychiatric, and medical diseases.

Motor Pathway Maturation in Neurologically Normal Children

The quality and speed of motor movements are known to improve during childhood.^{18,19} Poor quality and slow motor movements are associated with neurodevelopmental abnormalities as a consequence of such disorders as premature birth, learning disabilities, and neurobehavioral disorders. Abnormalities in the quality and speed of motor movements

are measured clinically by “soft neurological” signs. However, the developmental trajectory of these “soft neurological” signs is variable, resulting in a significant overlap between children with normal development and those at risk for abnormal development.^{18,19} The ability to measure motor maturation is important in light of the fact that abnormal early motor pathway maturation may be associated with impaired cognitive development later in childhood²⁰⁻²³ and adulthood.²⁴ As described below, TMS may provide a way in which motor maturation can be objectively and accurately measured and followed during childhood.

Objective measures of motor development as indexed by TMS measures could indeed define the significance of clinical correlates of motor development, such as “soft neurological” signs, and further define the normal trajectory of motor development. TMS studies have provided insight into normal neurophysiological changes that occur during motor system maturation, particularly with respect to the development of crossed and uncrossed corticospinal motor pathways. Table 1 outlines these studies and their findings. All studies listed in Table 1 have examined developmental changes in at least one neurophysiological measurement. The protocol used in each study is listed under each heading. Crossed and uncrossed refer to whether the motor evoked potential was recorded from the limb contralateral or ipsilateral to the hemisphere stimulated with the TMS coil, respectively. Relaxed and facilitated refer to whether the participants were required to actively contract the target muscle during TMS stimulation. The results are divided into 3 categories depending on whether there was a decrease, increase, or no change in the neurophysiological measurement value with age (as indicated with “From *age* to *age*”) or whether children demonstrated a different neurophysiological measurement value as compared to adults (as indicated with “*age* to *age* vs adult”).

Crossed Corticospinal Pathway Development

TMS studies suggest that the crossed corticospinal pathways develop throughout childhood. Motor threshold appears to increase over the first 3 months of life²⁵ but then linearly decreases until adolescence, with the adult motor threshold reached in early adolescence.²⁵⁻³¹ This relationship has been confirmed in the upper and lower extremities²⁷ with muscles in both relaxed and facilitated state.²⁶ Crossed central motor conduction time when the target muscle is relaxed clearly decreases during childhood.^{25,27,28,32-36} Such developmental changes are found to continue into early adolescence if participant height is taken into account in the calculation of crossed central motor conduction time.^{27,35} If the study protocol uses motor facilitation, the developmental changes in crossed central motor conduction time end in early childhood.^{25,32-34,36} Crossed central motor conduction times in

both distal upper and lower extremities appear to have similar developmental patterns²⁷ but may be different in proximal as compared to distal muscles.³⁴ Motor evoked potential latency may decrease or increase during childhood depending on whether the stimulation protocol uses facilitation³⁷ or if this parameter is corrected for participant height.³⁸ Motor evoked potential amplitude has been reported to increase with age.^{27,28}

Uncrossed Corticospinal Pathway Development

Uncrossed corticospinal pathways may be extremely important during recovery from brain injury. These pathways may be clinically represented by developmental mirror movements and neurophysiologically represented by motor evoked potentials ipsilateral to the hemisphere stimulated with single-pulse TMS. One TMS study suggests that the uncrossed corticospinal pathway is faster than the normally predominant crossed corticospinal pathway before 6 months of age.²⁵ Another study detected the uncrossed corticospinal pathways in most children before 10 years of age and found it to be more prevalent in proximal as compared to distal muscles.³⁶

Development of Cortico-Cortical Connections

Cortico-cortical connections also undergo developmental change. Such change may account for the maturation of motor task performance that continues beyond childhood.^{32,33} Cortico-cortical and interhemispheric inhibition, as measured by the ipsilateral silent period, may be minimal at or before 5 years of age,²⁹ but increases with age,³⁹ reaching adult equivalent values in adolescence.⁴⁰ However, not all studies have been able to document cortico-cortical inhibition in childhood and early adolescence.²⁶ Developmental changes in the contralateral silent period duration,^{29,31} but not latency,^{26,33} have also been detected.

Intracortical Pathway Development

Developmental changes in intracortical inhibition have been measured using several protocols. The paired-pulse TMS method has been used to demonstrate a developmental increase in intracortical inhibition in one study³⁰ and no change in intracortical inhibition or facilitation in another study.³¹ Other studies have examined the developmental changes in a TMS-evoked electrophysiological cortical response that may represent inhibitory processes.⁴¹

Future Studies

Further studies must account for factors that result in measurement variation, such as participant height,²⁷ peripheral pathway latency,²⁷ amount of baseline muscle

Table 1. Developmental Changes by Age in TMS-Derived Neurophysiological Measurements

	Decrease	No Change	Increase
Motor Threshold			
Crossed, Relaxed			
Masur et al (1995) ²⁶	From 3 to 14 y		
Muller et al (1991) ²⁷	From 2 wk to 10 y		
Nezu et al (1997) ²⁸	From 1 y to adult		
Moll et al (1999) ³¹	From 8 to 16 y		
Crossed, Facilitated			
Eyre et al (2001) ²⁵	From 1 to 16 y		From neo to 3 mo
Heinen et al (1998) ²⁹	4 to 7 y vs adult		
Mall et al (2004) ³⁰	From 6 y to adult		
Masur et al (1995) ²⁶	From 3 to 14 y		
Moll et al (1999) ³¹	From 8 to 16 y		
Uncrossed, Facilitated			
Eyre et al (2001) ²⁵	From 1 to 16 y		From neo to 3 mo
Central Motor Conduction Time			
Crossed, Relaxed			
Fietzek et al (2000) ³²	From 2 mo to 10 y	From 10 y to 40 y	
Heinen et al (1998) ³³	6 to 9 y vs adult		
Nezu et al (1997) ²⁸	From 1 to 12 y	12 to 14 y vs adult	
Muller et al (1992) ³⁵	From 2 to 13 y ^a		
Muller et al (1991) ²⁷	From 2 wk to 10 y		
Muller et al (1991) ²⁷	From 2 wk to 13 y ^a		
Crossed, Facilitated			
Eyre et al (2001) ²⁵	From neo to 15 mo	From 15 mo to 16 y	
Fietzek et al (2000) ³²	From 2 mo to 5 y	From 5 to 40 y	
Heinen et al (1998) ³³		6 to 9 y vs adult	
Muller et al (1997) ³⁶		3 to 11 y vs adult	
Nezu et al (1999) ³⁴	From 2 to 10 y	10 to 13 y vs adult	
Uncrossed, Facilitated			
Eyre et al (2001) ²⁵	From neo to 16 y		
Motor Evoked Potential Latency			
Crossed, Relaxed			
Caramia et al (1993) ³⁷	From 2 to 12 y		
Nezu et al (1997) ²⁸		From 1 y to adult	
Crossed, Facilitated			
Caramia et al (1993) ³⁷			From 2 to 12 y
Koh and Eyre (1988) ³⁸	From preme to 8 y		From preme to 8 y ^a
Uncrossed, Facilitated			
Muller et al (1997) ³⁶	Absent after 10 y		Longer than crossed until 10 \
Motor Evoked Potential Duration			
Crossed, Relaxed			
Nezu et al (1997) ²⁸		From 1 y to adult	
Motor Evoked Potential Amplitude			
Crossed, Relaxed			
Muller et al (1991) ²⁷			From 2 wk to 10 y
Nezu et al (1997) ²⁸		From 1 to 10 y	From 10 y to adult
Silent Period			
Contralateral, Latency			
Heinen et al (1998) ³³		6 to 9 y vs adult	
Masur et al (1995) ²⁶		From 3 to 14 y	
Contralateral, Duration			
Heinen et al (1998) ³³			4 to 6 y vs adult
Moll et al (1999) ³¹			From 8 to 16 y

(continued)

Table 1. (continued)

	Decrease	No Change	Increase
Ipsilateral, Latency			
Garvey et al (2003) ³⁹	From 6 y to adult		
Heinen et al (1998) ²⁹	4 to 6 y vs adult		
Heinen et al (1999) ⁴⁰		10 to 15 y vs adult	
Masur et al (1995) ²⁶		From 3 to 14 y	
Ipsilateral, Duration			
Garvey et al (2003) ³⁹			From 6 y to adult
Intracortical Inhibition			
Bender et al (2005) ⁴¹			From 6 to 10 y
Mall et al (2004) ³⁰			From 6 y to adult
Moll et al (1999) ³¹		From 8 to 16 y	

NOTE: neo = neonate; preme = premature neonate.

a. Certain studies have corrected parameters for height of the participant.

contraction,³⁷ and skull and brain size.^{42,43} Given the many dynamic factors that occur during neural system maturation, such as synaptic pruning and development,²⁵ myelination of the corticospinal, intracortical, and transcortical pathways,⁴⁴ changes in axonal diameter and length,⁴⁵ and organization of pyramidal neuron-firing patterns,⁴⁶ the influence of developmental factors on corticospinal maturation may be better defined if future studies combine TMS with anatomic and functional measures of corticospinal pathway organization. In the future, anatomical neuroimaging will be essential for minimizing factors that contribute to measurement variation. For example, differences in skull and scalp thickness and cerebral spinal fluid volume that can critically influence the distribution of the induced intracerebral current could be taken into account.^{47,48} Clearly combining anatomic and functional information will help define normal development. Such information will greatly assist in developing normative developmental trajectories that may be useful for the early detection of developmental neurological abnormalities.

Cortical Reorganization

Central Injury

Although it is believed that early brain injury, in general, is associated with better recovery than brain injury later in childhood, recovery from early brain injury is still very variable, and the mechanisms of recovery are still poorly understood. Ipsilateral corticospinal projections are believed to play a significant role in recovery from lesions affecting the motor system. As briefly discussed above, ipsilateral corticospinal projections may be prominent very early in life and can be neurophysiologically detected into

adolescence.²⁵ The exact pathway through which ipsilateral corticospinal neurons project to the affected limb following recovery from brain injury is not well understood. Normal ipsilateral corticospinal, corticoreticulospinal, or corticopropriospinal tract projections could play a role during recovery from unilateral brain injury. However, ipsilateral fetal corticospinal projections that normally regress at, or before, infancy could persist and aid in recovery. In addition, at the spinal level, contralateral axons could sprout terminal connections to the α -motorneurons of muscles in the affected limb.

In order to characterize the corticospinal projections from the ipsilateral hemisphere, investigators have compared motor evoked potential characteristics from analogous ipsilateral and contralateral muscles during single-pulse TMS. Some investigators have compared the ipsilateral cortical silent period durations and latencies,⁴⁹ or motor evoked potential amplitude, duration, and latency^{25,50-52} in combination with, or instead of, cross-correlation analysis.^{50,51,53,54} The distribution and overlap of ipsilateral and contralateral cortical motor maps in the ipsilateral hemisphere have also been studied.⁵⁵ In addition, single-pulse TMS has been combined with functional neuroimaging to clarify cortical activation patterns elicited by motor movement in individuals with congenital, perinatal, or neonatal unilateral brain injury.^{52,56}

A review of the TMS studies evaluating children with developmental and acquired hemiplegia and diplegia reveals several patterns of neural reorganization. Overall, TMS studies demonstrate at least 4 neurophysiological patterns of cortical reorganization in children with hemiplegia and at least 2 neurophysiological patterns of cortical reorganization in children with diplegia.

Hemiplegia. Following unilateral brain injury, 4 neurophysiological patterns of neural reorganization can be defined by

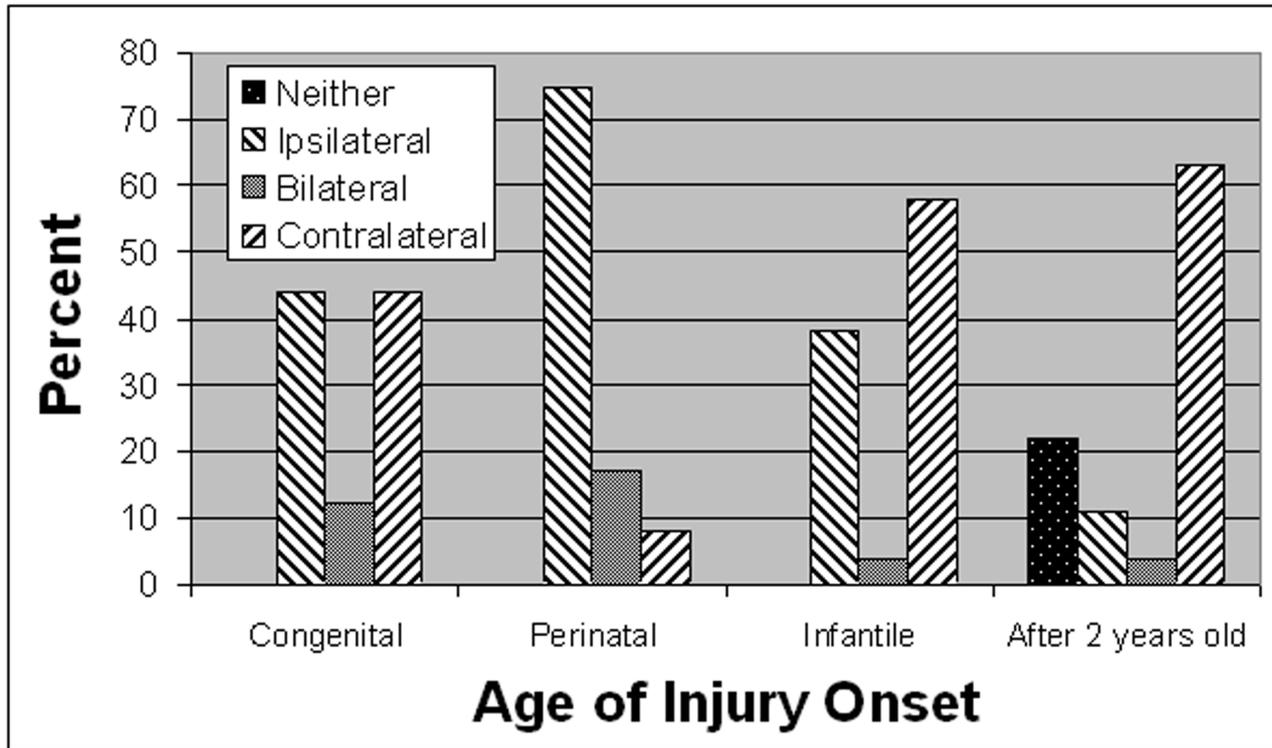


Figure 2. Reorganization patterns following recovery in acquired hemiplegia organized by age at which the cortical damage occurred. Note that the ipsilateral hemisphere is more often involved in motor control of the affected limb before 2 years of age, suggesting a greater preservation of the capacity for successful motor remapping for brain injury occurring early in life. The hemisphere of origin of the corticospinal projections to the affected limbs as determined by single-pulse TMS is shown. This figure was produced by reviewing all available studies in which the results of single-pulse TMS stimulation for individual cases of acquired hemiplegia were available.

whether application of single-pulse TMS to one, both, or neither hemisphere can evoke a motor evoked potential in the affected limb. These patterns may correlate with age and severity of the injury (see Figure 2). For example, unilateral brain injury after 2 years of age, when severe, may be associated with an inability to elicit a motor evoked potential in the affected limb by application of single-pulse TMS to either hemisphere. This suggests that no functional corticospinal pathways project to the affected limb from either hemisphere and probably indicates a poor recovery potential.^{50,51} This pattern of recovery does not appear if the injury occurs in or before infancy. Many children with injury in or before infancy were found to have unilateral lateralization of the motor system with the corticospinal pathway originating from the hemisphere ipsilateral to the affected limb. In these children, a motor evoked potential in the affected limb could be elicited only with application of single-pulse TMS to the ipsilateral hemisphere. This pattern appeared to be more common in children with hemiplegia acquired before birth (ie, congenital hemiplegia or hemiplegia associated with cortical dysplasia or perinatal hypoxia).^{50,51,53,54} For a minority of children with

hemiplegia acquired during the perinatal period and a few children with hemiplegia acquired after the neonatal period, a motor evoked potential in the affected limb could be elicited by application of single-pulse TMS to either hemisphere, suggesting bilateral corticospinal pathway projections to the affected limb.^{50,51,56} However, for many children with more mild hemiplegia, especially those who acquired hemiplegia in or after the infantile period, a motor evoked potential in the affected limb could be elicited only by application of single-pulse TMS to the contralateral hemisphere, suggesting that the corticospinal pathway found in normal children predominates.⁴⁹

The patterns described above are based on motor evoked potentials recorded from distal upper extremity muscles. Slightly different patterns of reorganization have been reported for proximal upper extremity muscles.⁵⁵ These impressive preliminary findings suggest that further studies have an excellent opportunity to define patterns of reorganization in congenital and early acquired hemiplegia. The limited sample sizes in many of these studies restrict the ability to generalize these findings.

Diplegia. Two neurophysiological patterns of neural reorganization in spastic diplegia can be defined by whether application of single-pulse TMS to either hemisphere elicits a motor evoked potential in both limbs or in only one limb. For example, a motor evoked potential could be elicited in either limb with application of single-pulse TMS to either hemisphere for children with symmetric diplegia.⁵⁷ This suggests that both hemispheres reorganized to provide ipsilateral and contralateral corticospinal projections (or never organized to project predominantly contralateral corticospinal projections). However, single-pulse TMS to either hemisphere could elicit a motor evoked potential in the more affected, but not the less affected, limb in children with asymmetric diplegia.⁵⁷ A motor evoked potential in the less affected limb could be elicited only with single-pulse TMS applied to the contralateral hemisphere. This suggests that the less damaged hemisphere reorganized to provide motor output to both the ipsilateral and contralateral limbs, while the more damaged hemisphere only provided projections to the more affected limb. Thus, it appears that reorganization in spastic diplegia may be dependent on the symmetry of the insult. Reorganization may also be dependent on prematurity. Motor maps of the optimal single-pulse TMS scalp site for eliciting a motor evoked potential in the lower extremities appeared to be significantly shifted laterally in premature, but not term, children with diplegia.⁵⁷ One study found that transcallosal inhibition may be absent in adolescents with diplegic cerebral palsy.⁴⁰

Peripheral Nerve Injury

Single-pulse TMS has revealed cortical motor remapping as a consequence of amputation and replantation. The motor map of the contralateral deltoid was shown to expand after arm amputation without replant.⁵⁸ In another study, the motor maps of the first dorsal interosseous were unchanged following hand replantation, but hand function was limited, and the biceps brachii motor map was larger and shifted toward the motor map of the replanted hand.⁵⁹

Future Studies

Although TMS is clearly useful for revealing changes in motor maps and corticospinal pathway reorganization following recovery from brain injury, the significance of the various patterns of reorganization and the particular association between these patterns and the etiology of the brain damage is not clear. Many studies contain small sample sizes or mixed etiologies (ie, genetic, congenital, and acquired brain lesions) or lesion type (ie, cortical and subcortical). In future studies, well-selected homogenous populations may help link patterns of reorganization with etiology. In addition, monitoring dynamic neurophysiological changes during recovery will be essential. For

example, acute neurophysiological changes in the motor evoked potential⁶⁰⁻⁶⁴ and subacute changes in the motor map⁶⁵ that follow stroke have prognostic correlation with ultimate functional recovery in adults.

Studies using TMS in children have uncovered important information regarding CNS reorganization following central and peripheral nervous system injury. In the future, studying well-defined populations with TMS combined with other neuroimaging tools will provide insight into the neuroplasticity involved in successful and suboptimal recovery from brain damage. As TMS becomes more widely utilized by adult and child neurologists, this tool may become essential for the prognostic assessment in congenital and acquired brain injury.

Diagnostic Application in Neurological Disease

TMS has been used to demonstrate neurophysiological changes as a consequence of neurologic and medical disorders of childhood. TMS is particularly useful for interrogating the integrity of the corticospinal tract and measuring cortical excitability. These studies foreshadow the utility of TMS in the diagnosis and management of neurological disorders in children. Table 2 outlines the abnormalities in common TMS-derived neurophysiological measurements for specific neurologic and medical disorders. Seven common TMS-derived neurophysiological measurements are presented in this table. Certain studies may have considered other neurophysiological measurements not specifically represented in this table. Symbols represent changes in the specific neurophysiological measurement value as compared to values derived from control participants or the normal population (see legend at bottom of table).

Corticospinal Tract

Complement to anatomic neuroimaging. Single-pulse TMS can detect corticospinal tract abnormalities not identified by anatomic neuroimaging. For example, single-pulse TMS was used to reveal subtle abnormalities in motor evoked potential duration variability in a boy with adrenoleukodystrophy and long-tract signs despite magnetic resonance imaging changes confined to the parieto-occipital white matter region.⁶⁶ Similarly, single-pulse TMS has been used to detect neurophysiologic corticospinal tract abnormalities in children with multiple sclerosis and transverse myelitis who demonstrate no significant involvement of the motor system on magnetic resonance imaging.^{67,68} Indeed, single-pulse TMS may be useful to confirm the diagnosis of multiple sclerosis and estimate disease progression in adolescents and adults.^{69,70}

Differentiating and diagnosing neurologic disorders. TMS may aid in narrowing the differential diagnosis of neurological

Table 2. Changes in TMS-Derived Neurophysiological Measurements in Disorders of Childhood

	MT	CMCT	MEP Latency	MEP Amp	SP	ICI	ICF
Neurologic Disorders							
Adrenoleukodystrophy							
Nezu et al (1996) ⁶⁶		↔	↔				
Autosomal dominant cerebellar ataxia							
Lanzillo et al (1994) ⁷⁴		↔		↓			
Childhood onset altering hemiplegia							
Nezu et al (1997) ⁹³			↑	↓			
Childhood onset hereditary extrapyramidal disease							
Muller et al (1992) ⁸²		↔	↔				
Congenital mirror movements							
Cincotta et al (1996) ⁹⁵					↓		
Maegaki et al (2002) ⁹⁰			↑				
Reitz et al (1998) ⁹⁴			↑				
Duchenne muscular dystrophy							
Di Lazzaro et al (1998) ¹¹⁶	↑	↔					
Early onset non-Friedreich's ataxia							
Mondelli et al (1995) ⁷⁵		↑ / ↔					
Early onset recessive ataxia							
Lanzillo et al (1994) ⁷⁴		↑		↓			
Familial childhood primary lateral sclerosis							
Gascon et al (1995) ⁸¹		↔	≠	≠			
Friedreich's ataxia							
Claus et al (1988) ⁷¹		↑					
Cruz Martinez et al (1992) ⁷²	↑	↑		↓			
Cruz Martinez et al (1997) ⁷³	↑	↑		↓			
Lanzillo et al (1994) ⁷⁴		↑		↓			
Mondelli et al (1995) ⁷⁵		↑		↓			
Santoro et al (2000) ⁷⁶		↑		↓			
Schwenkreis et al (2002) ⁷⁷	↔	↑			↔		
Hereditary motor and sensory neuropathy I & II without associated pyramidal features							
Claus et al (1990) ⁷⁸		↔					
Hereditary motor and sensory neuropathy I with associated pyramidal features							
Claus et al (1990) ⁷⁸		↑					
Hereditary motor and sensory neuropathy II with associated pyramidal features							
Claus et al (1990) ⁷⁸		↑ / ↔					
Hereditary spastic paraplegia							
Claus et al (1990) ⁷⁸		↔					
Hirayama disease							
Shizukawa et al (1994) ⁸⁵		↑					
Infantile onset Pelizaeus-Merzbacher							
Nezu et al (1996,1998) ^{80,87}			≠	≠			
Multiple sclerosis							
Dan et al (2000) ⁶⁷		↓	↑				
Rett syndrome							
Eyre et al (1990) ⁹⁶	↓		↓				
Heinen and Korinthenberg (1996) ⁹⁷		↓					
Heinen et al (1997) ⁹⁸		↓					
Nezu et al (1998) ⁹⁹		↓	↓	↔			
Spasticity							
Dachy and Dan (2002) ⁸⁸	↑						
Spinal muscular atrophy type II							
Imai et al (1995) ⁸³		↔		↓			
Transverse myelitis							
Noguchi et al (2000) ⁶⁸			↑	↓			
Wilson's disease							
Meyer et al (1991) ⁸⁶		↑		↓			

(continued)

Table 2. (continued)

	MT	CMCT	MEP Latency	MEP Amp	SP	ICI	ICF
Epilepsy							
Benign rolandic epilepsy							
Manganotti and Zanette (2000) ¹⁰⁹				↑			
Nezu et al (1997) ¹⁰²	↑	↔		↔			
Generalized epilepsy							
Brodthmann et al (1999) ¹¹²							↑
Ertas et al (2000) ¹¹⁵					↑		
Macdonell et al (2001) ¹¹³	↔				↑		
Tataroglu et al (2004) ¹⁰⁶					↑		
Myoclonic epilepsy							
Manganotti et al (2001) ¹¹⁰						↓	
Reutens et al (1993) ¹⁰⁵	↑	↔		↔			
Valzania et al (1999) ¹¹¹	↔	↔	↔			↓	↑
Partial epilepsy							
Cincotta et al (1998) ¹¹⁴					↑/↔		
Cantello et al (2000) ¹⁰⁴	↑				↔	↓	↑
Ertas et al (2000) ¹¹⁵					↑		
Inghilleri et al (1998) ¹⁰⁷	↑				↓	↓	
Michelucci et al (1996) ¹⁰³	↑	↔	↔	↔			
Shimizu et al (2001) ¹⁰⁸			↑	↑			
Tataroglu et al (2004) ¹⁰⁶	↑				↑		
Psychiatric Disorders							
Attention-deficit/hyperactivity disorder							
Garvey et al (2005) ¹²⁴	↔				↓		
Moll et al (2000) ¹²⁰	↔				↔	↓, ↑ ^a	↔
Moll et al (2001) ¹¹⁸	↔					↓, ↑ ^a	↔
Ucles et al (1996) ⁹¹			R > L				
Ucles et al (2000) ⁹²		↑					
Attention-deficit/hyperactivity disorder and Tourette syndrome/tics							
Moll et al (2001) ¹¹⁹	↔				↓	↓	
Moll et al (2001) ¹¹⁸					↓	↓	
Tourette syndrome/tics							
Moll et al (2001) ¹¹⁸	↔				↓	↔	↔
Moll et al (1999) ¹²³	↔				↓	↔	↔
Ziemann et al (1997) ¹²¹	↔				↓ ^b	↓ ^b	
Medical disorders							
Insulin-dependent diabetes							
D'Annunzio et al (1995) ⁸⁴		↑			↓		
Malnutrition							
Karak et al (1999) ¹⁰⁰	↑	↑		↓			
Tamer et al (1997) ¹⁰¹	↑	↑					
Phenylketonuria							
Roricht et al (1999) ¹¹⁷	↑			↓	↓		
Scoliosis							
Tabaraud et al (1993) ⁸⁹			↔				

NOTE: MT = motor threshold; CMCT = central motor conduction time; MEP = motor evoked potential; SP = silent period; ICI = intracortical inhibition; ICF = intracortical facilitation.

Symbols: ↔ no difference in the parameter value between normal and clinical group; ↑ a higher parameter value in the clinical group as compared to normal group; ↓ a lower parameter value in the clinical group as compared to normal group; ≠ the parameter could not be detected in the clinical group.

a. Effect when treated with 10 mg methylphenidate.

b. Effect greater in participants with active tics and those not taking neuroleptic medication.

symptoms by confirming the presence of corticospinal tract involvement in specific neurologic diseases. For example, single-pulse TMS may help in differentiating between ataxia syndromes that present in childhood. Corticospinal tract abnormalities were found in children with Friedreich's ataxia and early onset recessive ataxia, but were less marked in early

onset non-Friedreich's ataxia and not present in autosomal dominant cerebellar ataxia.⁷¹⁻⁷⁷ Single-pulse TMS has been useful in confirming and quantifying the presence of pyramidal signs in children with hereditary motor and sensory neuropathy types I and II^{78,79} and identifying the level of the lesion in infantile onset Pelizaeus-Merzbacher⁸⁰ and familial

childhood primary lateral sclerosis.⁸¹ Single-pulse TMS may also be useful in indicating the lack of corticospinal tract involvement in some pediatric neurological disorders, including childhood onset hereditary extrapyramidal disease,⁸² spinal muscular atrophy type II,⁸³ and hereditary spastic paraplegia,⁷⁸ thereby narrowing the differential diagnosis. Thus, the utility of single-pulse TMS in diagnosing and differentiating neurological disorders is promising in children. However, much of this evidence is based on a small number of patients in limited studies. Further studies should help demonstrate the utility of TMS in the differential diagnosis of specific pediatric neurologic disorders and establish sensitivity and specificity of this technique for differentiating specific neurologic disorders.

Indexing neurologic disease progression and treatment. TMS can aid in following the progression and resolution of neurologic disorders. Corticospinal tract changes appear to correlate with disease duration and progression in Friedreich's ataxia^{72,73,75,76} and may be associated with the degree of metabolic control and microangiopathic complications in patients with longstanding insulin-dependent diabetes.⁸⁴ Single-pulse TMS has been used to verify the efficacy of treatment. For example, single-pulse TMS was used to document improvement in corticospinal tract function after neck stabilization in Hirayama disease,⁸⁵ D-penicillamine treatment in Wilson's disease,⁸⁶ and the lack of neurophysiological changes despite symptomatic improvement with digitalis treatment in infantile onset Pelizaeus-Merzbacher.⁸⁷ Single-pulse TMS has been used to verify the efficacy of intrathecal baclofen in spasticity⁸⁸ and the integrity of the corticospinal tract following scoliosis surgery.⁸⁹ The resolution of corticospinal tract asymmetry in idiopathic congenital mirror movements⁹⁰ and corticospinal abnormalities in transverse myelitis⁶⁸ have also been documented with single-pulse TMS. Thus, TMS appears to be useful for monitoring the progression, resolution, and treatment of neurologic disease associated with corticospinal tract changes.

Insight into disease mechanism. Asymmetry in neurophysiological height-corrected motor evoked potential latency was detected using single-pulse TMS in untreated children with attention-deficit/hyperactivity disorder (ADHD), suggesting asymmetric hemispheric function, and single-pulse TMS detected prolonged central motor conduction time in children and adolescents with ADHD.^{91,92} Single-pulse TMS has been used to demonstrate that corticospinal tract abnormalities in childhood at the onset of alternating hemiplegia are reversible⁹³ and that neuronal mechanisms of congenital mirror movements are neurophysiologically different than normal developmental mirror movements.^{94,95} Single-pulse TMS studies have demonstrated unique changes in neurophysiological corticospinal tract measurements in Rett syndrome that are consistent with the disorder's

neuropathology.⁹⁶⁻⁹⁹ Single-pulse TMS studies have demonstrated corticospinal tract abnormalities in malnourished children, suggesting possible delay in white matter myelination in such children.^{100,101}

Cortical Excitability and Interhemispheric Dynamics

TMS studies suggest that measures of the cortical excitability can provide diagnostic information, aid in monitoring treatment efficiency, and provide insights into disease mechanism.

Epilepsy. TMS studies in children suggested that antiepileptic medications may elevate the motor threshold.¹⁰²⁻¹⁰⁵ At least one study demonstrated a higher motor threshold in partial epilepsy as compared to generalized epilepsy and control subjects.¹⁰⁶ The motor threshold was found to be elevated in the affected hemisphere as compared to the unaffected hemisphere of a child with progressive focal epilepsy.¹⁰⁷

Hemisphere excitability may depend on etiology since another study showed hyperexcitability in the affected hemisphere of a child with unilateral cortical dysplasia and intractable simple partial seizures, with this hyperexcitability reduced after multiple subpial transections.¹⁰⁸ Cortical hyperexcitability has been suggested in benign epilepsy with centrotemporal spikes¹⁰⁹ and progressive myoclonic epilepsy.¹¹⁰

Abnormal intracortical inhibition and/or facilitation have been consistently found in epilepsy. Intracortical inhibition was found to be reduced in progressive myoclonic epilepsy^{110,111} and the affected hemisphere in focal motor epilepsy.¹⁰⁷ Intracortical facilitation was found to be increased in progressive myoclonic epilepsy¹¹¹ and idiopathic generalized epilepsy.¹¹² One study suggests that the amount of intracortical inhibition reduction and intracortical facilitation enhancement may be proportional to subclinical seizure activity.¹⁰⁴

The silent period has been found to be prolonged in treated children with idiopathic generalized epilepsy¹¹³ and motor, but not nonmotor, cryptogenic partial epilepsy.¹¹⁴ This latter finding is asymmetric, showing greater prolongation in the limb contralateral to the normal hemisphere. Others have suggested that the silent period is reduced in the epileptic cortex.¹⁰⁷ Prolongation of the silent period has been suggested to be related to seizure control¹¹⁵ and/or antiepileptic treatment.¹⁰⁶

Thus, TMS has demonstrated that abnormalities in cortical excitability and interhemispheric dynamics are found in patients with epilepsy. Further studies are needed in order to determine how these parameters can be used to diagnose the type and severity of the epilepsy, guide the choice of the best antiepileptic agents, and monitor treatment efficacy.

Medical, neurologic, and psychiatric disease. Single-pulse TMS studies were the first to demonstrate cortical hyperexcitability in Rett syndrome.⁹⁶ Duchenne muscular dystrophy and well-controlled phenylketonuria patients have been found to be associated with an elevated motor threshold despite normal corticospinal tract parameters.^{116,117} Intracortical inhibition was found to be reduced in ADHD¹¹⁸⁻¹²⁰ and Tourette syndrome.¹²¹ Methylphenidate treatment was found to partially reverse intracortical inhibition abnormalities in children with ADHD,^{118,120} whereas such treatment has been found to enhance intracortical facilitation in normal adults.¹²² The cortical silent period was found to be reduced in controlled phenylketonuria patients,¹¹⁷ tic disorder,^{118,121,123} and ADHD.¹²⁴

Using TMS to Detect Subtle Neurophysiological Abnormalities

The versatility of TMS allows exploration of static and dynamic aspects of cortical and corticospinal tract function in specific neurologic and medical disorders. TMS can detect corticospinal tract abnormalities that anatomic neuroimaging does not reveal, allowing the involvement of white matter tracts and the progression and resolution of such involvement to be followed. Alternatively, the confirmation or exclusion of corticospinal tract involvement in several neurologic syndromes may aid in differential diagnosis. TMS has been used to identify abnormalities in cortical excitability in epilepsy, myoclonus, tic disorder, attention deficit disorder, Tourette syndrome, and Rett syndrome. In addition to providing insights into the neurological mechanisms underlying these disorders, TMS may also aid in monitoring the efficacy of therapy.

Therapeutic Applications

Therapeutic applications of TMS have been growing in adult neurology. Below we briefly review some of the applications of TMS in adults and outline how such techniques could be applied to the pediatric population.

Stroke Recovery

TMS may have therapeutic utility for augmenting stroke recovery in children. In adults, TMS has been used to augment rehabilitation of motor function. TMS directed to the motor cortex combined with peripheral nerve stimulation, the so-called "dual stimulation" paradigm, results in changes in cortical excitability and motor output maps in normal participants that last hours and days, respectively.^{3,4} Several clinical parameters were found to improve in patients with chronic hemiplegia using such a paradigm.⁵ The enhanced neuroplasticity of the young brain may potentiate any therapeutic effect of TMS. Future studies will need to address "dual stimulation" therapy in children.

TMS may also be applicable for guiding neuroplasticity after stroke in children. Neuroimaging studies indicate that the best functional recovery from hemiplegia following stroke in adults is associated with the development of alternative pathways from the affected hemisphere to the affected limb without connections from the unaffected hemisphere to the affected limb.^{64,125} Authors have suggested that the ipsilateral hemispheric projections during the acute and subacute poststroke period represent a transient stage of reorganization in normal recovery. However, optimal functional recovery appears to involve attenuation of temporary ipsilateral hemisphere function with concomitant reorganization of the affected hemisphere. Chronic continuation of ipsilateral hemisphere motor function could induce interhemispheric rivalry, thereby impeding optimal functional recovery.

TMS has been used to experimentally demonstrate hemispheric rivalry in normal subjects.¹²⁶ TMS has been used to treat nonmotor neurologic deficits that presumably result from hemispheric rivalry in adults with acquired unilateral brain lesions. For example, single-pulse TMS over the left frontal or parietal cortices improved tactile extinction in patients with right cortical damage.^{127,128} Naeser and Pascual-Leone applied low-frequency repetitive TMS to the right supplementary motor area of chronic Broca's aphasia patients based on functional neuroimaging data showing overactivity in this brain region.¹²⁹ This TMS treatment appeared to significantly improve confrontational naming with this effect sustained up to 8 months following the treatment.^{130,131} Presumably, TMS released the residual function of a unilateral damaged cortical area by dampening excessive interhemispheric inhibition.

It is not known how patterns of reorganization in the adult correlate with cortical reorganization in the child, but the evidence from adult studies provides guidance for studying and understanding brain reorganization after brain injury in children. Evidence suggests that TMS may be beneficial in guiding neuroplasticity in adults. Since neuroplasticity is believed to be more prominent in the pediatric brain, such therapies may be more successful in children.

Psychiatric Disorders

TMS has been applied to bipolar and chronic depression, anxiety, obsessive-compulsive disorder, and schizophrenia in adults using various protocols with a variety of successes.⁶ Although the TMS protocol and patient selection need to be more clearly defined, the data from many adult studies are promising. Data from the pediatric population are limited. Five of seven older adolescents with bipolar depression, unipolar depression, or schizophrenia responded to therapeutic TMS protocols.¹³² The ability of TMS to guide neuroplasticity is exciting in the area of psychiatry since TMS therapy could be used to modify abnormally functioning circuits before chronic changes are established.

Thus, preliminary applications of TMS in children and adolescents are encouraging, but larger case series and, eventually, controlled trials are needed.

Epilepsy

Early studies attempted to use TMS to induce seizures in epilepsy patients. These studies documented the poor efficacy of TMS as a tool for inducing such seizures.¹³³ This may have been due to a therapeutic effect of TMS on epilepsy. Indeed, low-frequency repetitive TMS may have a therapeutic effect on epileptic discharges and seizures. This has been demonstrated in animal models¹³⁴ and mesiotemporal epilepsy.¹³⁵ Uncontrolled human studies have reported improvement in progressive myoclonic epilepsy⁷ and intractable focal epilepsy^{8,9} following low-frequency repetitive TMS. High-frequency repetitive TMS may also have utility in modulating the activity of seizure foci. For example, focal hyperperfusion, as measured by single photon emission computed tomography, was reversed in 2 patients with epilepsy partialis continua with one application of high-frequency repetitive TMS.¹³⁶

Several controlled studies have examined the efficacy of low-frequency repetitive TMS on seizure control in adults. A controlled study demonstrated a nonsignificant decrease in seizure frequency in intractable focal epilepsy after 1 week of daily low-frequency repetitive TMS. Patients with neocortical foci had a greater response than patients with mesial temporal foci, suggesting that focal cortical abnormalities may be more responsive to TMS treatment.¹³⁷ Indeed, 2 of the most successful studies appear to suggest that targeting a cortical focus is efficacious. In an open study, Fregni et al.¹³⁸ targeted cortical malformations in 8 patients with refractory epilepsy in one session of low-frequency repetitive TMS. Compared to a 4-week baseline preceding the treatment, this treatment significantly reduced the number of epileptiform discharges as measured by electroencephalogram and the number of self-reported seizures. In a follow-up study Fregni et al.¹³⁹ applied 5 sessions of low-frequency repetitive TMS in a randomized double-blind sham-controlled fashion. The number of reported seizures in the treatment group was significantly lower up to 2 months following the treatment. Certain aspects of cognition also improved in the treatment group. However, Joo et al.¹⁴⁰ found that 2 different doses of low-frequency repetitive TMS applied to focal or multifocal epilepsy patients reduced the number of epileptiform discharges, but did not reduce the number of clinical seizures. These researchers did not find any difference in the reduction in the number of seizures or epileptiform discharges between the focal and multifocal groups.

Although the utility for TMS in seizure control is encouraging, further evidence of efficacy will be needed before this technology can be applied clinically. Differences in application protocols, seizure etiology, and the differential therapeutic effect of TMS on different seizure types require

specific attention. These studies verify the safety of TMS in epileptic patients. A mature therapy for focal epilepsies will indeed be highly beneficial in children. Thus, pediatric trials will hopefully begin soon.

Learning Disabilities

As mentioned above, TMS has been used to treat neurologic deficits that presumably result from hemispheric rivalry in adults with acquired unilateral brain lesions. Like the chronic Broca's aphasia patients described above, children with dyslexia and young children at risk for reading disorders show reverse lateralization of cortical activity, particularly in the temporoparietal area, during language processing.¹⁴¹ Although language training can ameliorate some of the abnormal cortical activity in the right temporoparietal area, lateralization of cortical activity usually remains abnormal.¹⁴² Application of low-frequency repetitive TMS to overactive cortical regions in dyslexic individuals could promote normal lateralization and release any inhibitory influence on the left underactive language areas from hemispheric rivalry mechanisms. Alternatively, since high-frequency repetitive TMS and single-pulse TMS can enhance cognitive performance,¹⁴³⁻¹⁴⁶ TMS protocols could be developed to enhance cognitive function for children with specific learning disabilities by exciting underactive neural pathways.

TMS Safety in Children

TMS has been reportedly used in over 800 normal children and over 300 neurologically abnormal children, including at least 25 children with epilepsy. Several authors have highlighted the absence of reported adverse effects in children.^{10,11} The 84 TMS studies in which the cortex of children was stimulated with TMS were reviewed: 15 mentioned that no side effects occurred, one mentioned that one patient had an adverse reaction to the protocol,¹³² and another study mentioned that the patient experienced transient dullness in the left upper limb.⁸⁵ The remainder of the studies did not comment on side effects.

The maximum charge density of TMS is markedly below the level at which neural damage can occur,¹⁴⁷ and no microscopic brain damage could be found after hundreds of TMS stimuli to rat, rabbit, or human brains.¹⁴⁸⁻¹⁵⁰ In adults, TMS safety studies have examined the electroencephalogram and cognitive, audiologic, and hormonal parameters,¹⁵¹⁻¹⁵³ and safety guidelines have been developed.¹⁵⁴ In children, no change in auditory function as assessed by brain stem auditory evoked potentials, otoacoustic emissions, acoustic reflex, and a pure tone audiometric and logaudiometric was found after TMS without ear protection.¹⁵⁵ Safety guidelines need to be developed for TMS use in children.

Summary

From the review of the current uses of TMS in children, we can see the great potential for TMS in the future for the pediatric population. TMS can (1) provide an index of maturation of the cortex and corticospinal pathway, (2) detect patterns of CNS reorganization following brain damage, (3) help diagnosis and follow neurological and medical diseases, (4) provide insight into disease mechanisms, and (5) monitor the efficacy of treatment. In addition, TMS is being developed as a nonpharmacologic therapeutic intervention for several neurologic and psychiatric conditions in adults, such as stroke,³⁻⁵ major depression,⁶ and epilepsy.⁷⁻⁹ TMS has been shown to directly modulate neuroplasticity in adults with effects that last minutes to days to months. Since the pediatric brain is thought to be significantly more plastic than the adult brain, TMS therapy could result in neuroplasticity changes that may be longer lasting. Clearly, the potential utility of this technique in pediatric neurology is significant, although attention to safety is critical. Hopefully, more studies will be designed to apply this technique to the pediatric population, especially with its excellent safety profile in this population.

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Appendix

Transcranial Magnetic Stimulation Studies Using Pediatric Participants

Study Topic	Reference Numbers
Normal central pathway development	
Central motor conduction time	25,27,28,32-36
Motor threshold	25-31
Motor evoked potential latency	28,36-38
Motor evoked potential duration	28
Motor evoked potential amplitude	27,28
Intracortical inhibition	30,31,41
Silent period	26,29,31,33,39,40
Motor pathways reorganization	
Diplegia	40,57
Hemiplegia	49-51,53-56
Replantation	58,59

Study Topic	Reference Numbers
Neurological disorders	
Adrenoleukodystrophy	66
Alternating hemiplegia	93
Ataxia	71-77
Congenital mirror movements	90,94,95
Duchenne muscular dystrophy	116
Extrapyramidal disease	82
Hereditary motor and sensory neuropathy	78,79
Hereditary spastic paraplegia	78
Hirayama disease	85
Multiple sclerosis	67
Pelizaeus-Merzbacher	80,87
Primary lateral sclerosis	81
Rett syndrome	96-99
Spasticity	88
Spinal muscular atrophy II	83
Transverse myelitis	68
Wilson's disease	86
Epilepsy	
Benign rolandic epilepsy	102,109
Generalized epilepsy	106,112,113,115
Myoclonic epilepsy	105,110,111
Partial epilepsy	103,104, 106-108, 114,115
Treatment	138
Psychiatric disorders	
Attention-deficit/hyperactivity disorder	91,92,118-120,124
Depression, schizophrenia	132
Tourette syndrome/tics	118-121,123
Medical disease	
Insulin-dependent diabetes	84
Malnutrition	100,101
Phenylketonuria	117
Scoliosis	89

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