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NON-INVASIVE BRAIN STIMULATION IN CHILDREN: APPLICATIONS AND FUTURE DIRECTIONS

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Abstract

Transcranial magnetic stimulation (TMS) is a neurostimulation and neuromodulation technique that has provided over two decades of data in focal, non-invasive brain stimulation based on the principles of electromagnetic induction. Its minimal risk, excellent tolerability and increasingly sophisticated ability to interrogate neurophysiology and plasticity make it an enviable technology for use in pediatric research with future extension into therapeutic trials. While adult trials show promise in using TMS as a novel, non-invasive, non-pharmacologic diagnostic and therapeutic tool in a variety of nervous system disorders, its use in children is only just emerging. TMS represents an exciting advancement to better understand and improve outcomes from disorders of the developing brain.

Keywords

• Transcranial magnetic stimulation • Non-invasive brain stimulation • Neuromodulation • Neurostimulation • Child • Pediatrics • Safety • Therapeutic trials

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Abbreviations

CMCT - Central motor conduction time
CSP - Cortical silent period
DLPFC - Dorsolateral prefrontal cortex
ECT - Electroconvulsive therapy
EPC - Epilepsia partialis continua
ISI - Interstimulus interval
iSP - Ipsilateral silent period
LIHI - Long latency interhemispheric inhibition
MEP - Motor evoked potential
M1 - Primary motor cortex
MRI - Magnetic resonance imaging
MT - Motor threshold
PT - Phosphene threshold
RMT - Rest motor threshold
rTMS - Repetitive transcranial magnetic stimulation
SICI - Short interval intracortical inhibition
SMA - Supplementary motor area
TBS - Theta burst stimulation
TDCS - Transcranial direct current stimulation
TMS - Transcranial magnetic stimulation

Introduction

Modern non-invasive brain stimulation offers sophisticated measurement and modulation of human neurophysiology. Transcranial magnetic stimulation (TMS) has provided over two decades of data in focal, non-invasive brain stimulation based on the principles of electromagnetic induction. Its minimal risk, excellent tolerability and increasingly sophisticated ability to interrogate neurophysiology and plasticity make it an enviable technology for use in pediatric research with future extension into therapeutic trials. While adult trials show promise in using TMS as a non-invasive, non-pharmacologic diagnostic and therapeutic tool in a variety of nervous system disorders, its use in children is only just emerging. TMS represents an exciting advancement to better understand and improve outcomes from disorders of the developing brain.

As the majority of current non-invasive brain stimulation research in children involves TMS, this will be the focus of this review. Our aim is to provide an overview of current translational approaches - from adult to pediatric populations as well as from neurophysiological research to clinical applications and therapeutic trials. Such applications will be discussed across clinically relevant neurological states including developmental neurophysiology, perinatal stroke and cerebral palsy, epilepsy, neuropsychiatric disease, headache, and metabolic disease. A brief overview of emerging brain stimulation methods such as transcranial direct current stimulation (TDCS) is discussed.

Principles of TMS

Transcranial magnetic stimulation has been used for nearly three decades as a focal, non-invasive technique allowing for neurostimulation and modulation of the nervous system. Detailed reviews of TMS neurophysiological principles and methodology are available elsewhere [1]. Briefly, based on the principle of electromagnetic induction, introduction of focused magnetic fields generates regional cortical electrical fields which,

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when of sufficient magnitude and density, can depolarize focal neuronal populations. Measureable outputs are produced, typically a motor evoked potential (MEP) measured by electromyography in a muscle controlled by the region of motor cortex being stimulated.

TMS can be applied in a *single pulse* method with one stimulus occurring at a time or *paired-pulse* methods where a test stimulus is preceded by a conditioning stimulus, the strength of each and the interval between them dictating specific effects reflective of cortical physiology. Single pulse methods can be used for a variety of neurophysiologic assessment purposes, including mapping motor cortical outputs, central motor conduction times, and measures of cortical excitability. Paired pulse techniques can provide information regarding intracortical facilitation and inhibition as well as cortico-cortical and transcallosal interactions. Pulses can also be paired with peripheral stimulation such as "paired associative stimulation" or other neuroplasticity protocols.

When applied repetitively, TMS can also modulate cortical excitability. Effects can be an increase or decrease in excitability depending on the parameters of stimulation; low frequency (e.g. 1 Hz) being inhibitory repetitive TMS (rTMS) while high frequency (>5 Hz) is excitatory [2]. Such effects outlast the duration of stimulation, generating a therapeutic potential. Such lasting inhibitory or facilitatory effects of rTMS are thought to occur by various mechanisms, including synaptic changes resembling experimental long term depression (LTD) and long term potentiation (LTP) as well as larger shifts in network excitability, activation of feedback loops and activity-dependent metaplasticity [2]. Interested readers should refer to excellent review articles on TMS principles, safety and ethical considerations in adults and children for further information on the basic principles of TMS [2-4].

Safety and tolerability of TMS in children

Neurobiological effects

Reviews of TMS devices suggest that harm to brain tissue from single or paired pulses is extremely unlikely [5]. Peak magnetic field strengths are 1.5-2 T, comparable to clinical MRI scanners and less than many 3 T and higher intensity clinical research scanners. TMS, however, is far more targeted upon a focal brain location compared to MRI. The magnetic field volume is small and decreases exponentially with distance so that tissues located centimetres beyond the coil are unaffected. Distributors of the MagStim TMS device (Spring Gardens, Whitland, Carmarthenshire, UK) estimate that induced current density from their MagStim 200 stimulator in nearby (>5 mm) brain tissue is 14-19 mA/cm^2/pulse phase with an estimated energy delivered to the tissue of 3.0-5.3 μJ/cm^3. By comparison, this amount of energy appears to be far lower than what is required to produce cortical tissue damage, noted at 100 μC/cm^3 of charge density from 7 hours of continuous cortical stimulation at 50 Hz in cats [6]. Of note, stimulation at 50% of maximal stimulator output induced a voltage of less than 200 mV, which is less than *half* of the voltage produced in the brain by electroconvulsive therapy [7], a treatment used for decades in adolescents with intractable depression. Even at 100% of maximal output, the rTMS-induced voltage using commercially available devices would not match that of electroconvulsive therapy [8].

Potential adverse events in TMS

After years of study and millions of cumulative stimulations in the pediatric population, it has been established that TMS is safe and well tolerated in children [5,9,10]. This safety data is further supported by the more than 10-fold greater experience in adult TMS research. Basic principles of disease specific safety and tolerability can be extrapolated from similar diseases and disease models across adults and children, such as comparing evidence from adult stroke [11-16] to children with perinatal stroke and hemiparetic cerebral palsy [17,18]. These conclusions are further supported by animal studies [19-25] and published consensus guidelines [26].

Despite an increasingly wide variety of childhood neurological conditions being studied with TMS, including epilepsy and other conditions with lowered seizure thresholds, seizures have not been reported in children with single pulse TMS [5,10]. In adults, seizures induced by single pulse TMS have occasionally been described in subjects with pre-existing brain pathology including stroke, multiple sclerosis and intractable epilepsy [5]. Isolated cases of seizures associated with repetitive TMS applied directly over known seizure foci in adults with refractory epilepsy have also been reported (see Epilepsy section below). However, numerous other studies intentionally applying TMS over established seizure foci in adults demonstrate a very favourable safety profile [27,28]. While extremely rare, existing data suggests adults with pre-existing brain lesions have a higher risk of seizure with single pulse TMS but the same small risk has not been corroborated in the pediatric population.

Systematic studies in human adult patients and healthy volunteers have not found any evidence of hearing compromise following exposure to many thousands of single pulse stimuli without hearing protection [29]. On the simplest level, decibel levels of modern TMS machines fall well within established hearing safety standards. In addition, a study of 18 children ranging from 2 months to 16 years of age reported formal testing of brainstem auditory evoked potentials, otoacoustic emissions, acoustic reflex and pure tone audiometric tests performed before and after TMS with no hearing protection. No abnormalities of hearing function were found [30]. Based on these human studies and complimentary animal data, current single and paired pulse protocols do not appear to pose a hearing risk. However, in subjects with a personal or family history or other known risk factors for hearing loss, it remains prudent to utilize earplugs to minimize any possible risk [5].

Neurocardiogenic syncope was identified as a preventable complication of TMS in adolescents participating in a pediatric stroke study [31,32]. Two teenagers experienced neurocardiogenic syncope within minutes of their first exposure to low intensity single pulse TMS. Both recovered over minutes with no long-term sequelae but one dropped out of the study. Historic risk factors identified included previous presyncope with venipuncture or

micturition, and situational variables in the TMS lab including stress and hunger. The autonomic dysmaturity common in this age range, combined with these modifiable risk factors were proposed as likely mechanisms. Suggested strategies to mitigate syncope risk include (1) historical screening for predisposition to neurocardiogenic syncope; (2) implementation of precautions including adequate hydration, recent food intake, low initial and gradually increasing stimulation intensities, blood-pressure cuff on site, and immediate supine placement upon symptoms or signs of hypotension; and (3) full disclosure of the risk for neurocardiogenic syncope in informed-consent documents and family discussions [32].

While the evidence is more limited, existing repetitive (rTMS) studies in children generally report no significant adverse events [10,33-35]. At the time of the most comprehensive review on childhood TMS safety [5], which included publications up to 2001, there were no published rTMS studies in children. Since 2001 however, there have been multiple studies using rTMS in pediatric and young adult (<25 years) populations (see Table 1). Collectively, these demonstrate good safety and tolerability with only one subject withdrawing from future participation due to scalp tenderness after 5 minutes of rTMS out of 114 subjects receiving various regimens of rTMS across a variety disease states. Many of these studies include young children in the range of six years of age who have also shown good tolerability and safety despite motor thresholds often being higher [35]. Intensive daily dosing of rTMS for weeks at a time in animals further supports the safety of currently established recommended parameters for rTMS in humans [36].

Our own center's experience with a randomized controlled clinical trial of rTMS in children with perinatal stroke provides additional safety data (http://clinicaltrials.gov/ct2/show/NCT01189058). A predefined interim safety analysis of the 1st 35 children aged 6-18 years receiving both comprehensive single and paired pulse neurophysiology (2 hour protocol administered twice over 2-3 weeks) and daily inhibitory rTMS to the non-lesioned primary motor cortex (1 Hz, 1200 stimuli x 10 days) showed favourable results. Both TMS and rTMS procedures were well tolerated with no serious adverse events and no patient drop-outs. Specifically, affected hand function in children with ipsilateral projections (a common finding imparting theoretical concerns of *decreasing* affected hand function with non-lesioned primary motor cortex inhibitory rTMS) did not decrease with rTMS compared to sham (Assisting Hand Assessment and Melbourne Assessment of Unilateral Upper Extremity Function). Unaffected hand function also did not decrease with non-lesional inhibitory rTMS as tested by grip strength and pinch strength. TMS and rTMS tolerability scores were favourable, scoring more enjoyable than "a long car ride" on average using a standardized pediatric TMS tolerability measure [37]. All side effects were mild, brief (minutes), and self-limiting with none requiring medication. Headache was common (43% during 1st TMS session) but resolved with removal of the swim cap used for mapping purposes. Headache rates decreased (20%) with the same protocol 3 weeks later. Headache was uncommon during rTMS (11%) with tolerance over time (0% at 2nd session) and comparable rates between rTMS and sham. In summary, as pediatric rTMS clinical trials have been limited to date, caution is warranted but existing data supports favourable safety and tolerability.

Limitations and challenges of TMS research in children

The use of TMS in pediatric research has some limitations and challenges as they relate to the maturation of the developing brain, both neurophysiologically as well as behaviourally. Concerns about the use of adult sized TMS stimulation coils on children with smaller head circumferences have been raised. However, despite the smaller head circumferences in children, brain volume in humans remains remarkably similar from 6 years of age onwards with only small reductions seen in infants and children below 6 years of age. It is thus assumed that age-related differences in TMS-evoked parameters in children primarily reflect developmental neurophysiological changes, such as cerebral and corticospinal myelination and intracortical synaptic and neuronal maturation [3]. Motor thresholds are higher in children, especially under the age of 6 years in comparison to adolescents and adults. The result is that muscle activation is typically required to obtain any MEP response in very young children while paradigms employing suprathreshold stimuli are more challenging in younger school-aged children [9].

In randomized clinical trials where blinding of the sham condition is imperative, this issue is equally as important in pediatric as it is in adult brain stimulation trials. As there are few randomized, clinical trials in pediatric TMS research to date, clear data on sham protocols is lacking. However, our previous [31] and ongoing clinical trials (http://clinicaltrials.gov/ct2/show/NCT01189058) of rTMS in children with stroke include 48 children randomized to 2 weeks of daily inhibitory, contralesional rTMS or sham stimulation with the coil placed perpendicular to the motor cortex. Assessment of blinding post-TMS suggests neither children nor their parents are able to ascertain which treatment they received (unpublished).

Collectively, current data supports the feasibility of nearly all established adult TMS protocols in the pediatric population. Future directions include testing of rapidly advancing adult protocols in children and exploration of new methods to assess the youngest children.

TMS assessments of developmental neurophysiology

TMS has been used to study normal developmental neurophysiology for over 20 years. Its uses in understanding the normal, age-dependent evolution of corticospinal motor tract development from birth to adulthood are the best established, providing objective and insightful measurements of motor maturation [4].

Single pulse: motor thresholds and corticospinal pathway development

The rest motor threshold following single pulse TMS of the contralateral primary motor cortex refers to the lowest stimulus intensity required to generate a motor evoked potential (MEP)

Table 1. Pediatric rTMS studies and incidence of adverse events since 2001.

Study	Disorder Subjects Ages	TMS paradigm	Results Significant adverse events
Rajapakse 2012[35]	Perinatal stroke N=35 Mean 11.25 yrs	Contralesional primary motor cortex Inhibitory 1 Hz rTMS (1200 stimuli) of the unlesioned M1 daily for 10 days	None observed.
Sokhadze 2012[38]	Autism N=20 Mean 13.5 +/- 2.5 yrs	Dorsolateral prefrontal cortex 1 Hz, 90% MT, 150 pulses daily	Post-TMS showed improved response error monitoring and post-error response correction. No adverse events reported.
Croarkin 2012[39]	Depression N=8 Mean 16.1 +/- 1.1 yrs	Left prefrontal cortex 10 Hz 120% MT 30 sessions	Prefrontal high-frequency rTMS may increase cortical excitability in adolescents with treatment-resistant depression. 1 patient had scalp discomfort after 10 trains/5 min and withdrew from study.
Enticott 2012[40]	Autism N=11 Mean 17.6 +/- 4.06 yrs	Left premotor cortex Supplementary motor area 1 Hz rTMS 100% rMT 3 sessions, q1 wkly. 900 pulses	rTMS appears to improve movement-related electrophysiologic activity in autism possibly through an influence on cortical inhibitory processes. No adverse events reported.
Wall 2011[41]	Depression 8 adolescents	Left DLPFC 10 Hz 120 % MT rTMS 30 rTMS treatments over 6 to 8 weeks.	Suicidal ideation improved in 3 subjects. CDRS-R depression scores improved significantly after rTMS. rTMS was well tolerated, no significant safety issues reported.
Kwon 2011[42]	Tourette syndrome N=10 Mean age 11.2 ± 2.0 yrs	Supplementary motor area 1 Hz 100% MT 1200 pulses daily	Tic symptoms improved significantly over the 12 weeks. No increase in anxiety, ADHD or depressive symptoms. No significant side effects.1 patient had minimal scalp pain subsiding over one day.
Hu 2011[43]	Depression N=1 Age 15 yrs	Left prefrontal cortex 10 Hz 80% MT 800 pulses	Only one rTMS treatment given due to seizure. Patient had no prior history of epilepsy but was on sertraline 100 mg daily. Had a 1 minute generalized tonic clonic seizure and given diazepam 10 mg IV treatment. Post-ictal hypomania for 8-9 hours post seizure/rTMS.
Sun 2011[44]	Refractory partial epilepsy N=17 Mean age 18.12 ± 7.4 yrs	Over epileptogenic 0.5 Hz 90% MT	Mean seizure frequencies per week and mean EEG epileptic discharges decreased significantly 4-weeks after rTMS treatment. No adverse events observed.
Kirton 2010[45]	Subcortical arterial ischemic stroke N=10 Mean age 13.9 ± 4.4 yrs	Non-stroke primary motor cortex (M1) 1 Hz 100% rMT 1200 pulses daily	Following inhibitory rTMS, increases in stroke side maximal MEP amplitudes were suggested and LIHI from stroke to non-stroke side appeared to increase. No serious adverse events reported. Two adolescents with neuro-cardiogenic syncope.[32] Tolerability scores were all favourable.
Sokhadze 2010[46]	Autism N=13 Mean age 15.6 ± 5.8 yrs	Left dorsolateral prefrontal cortex 0.5 Hz 90% MT 150 pulses daily Administered 2-3 per week for 6 treatments	Low-frequency rTMS minimized early cortical responses to irrelevant stimuli and increased responses to relevant stimuli. Improved selectivity in early cortical responses lead to better stimulus differentiation. No adverse side effects or negative complications. No changes in social awareness, irritability, or hyperactivity observed
Mylius 2009[47]	PKAN N=1 Age 6 yrs	Left motor cortex 11 Hz 95% rMT 200 pulses daily 5 treatments total	rTMS temporarily reduced generalized dystonia. None reported.
Sokhadze 2009[48]	Autism N=13 subjects N=13 controls Mean age 18.3 ± 4.8 yrs	Left DLPFC 0.5 Hz 90% MT 150 pulses daily 6 treatments total	Significant post-TMS improvement in event-related potentials (ERP), induced gamma activity, and autism behavioral measures. No adverse effects reported.
Rotenberg 2009[49]	EPC N= one child, others adults One 11 yr old	Seizure focus 1 Hz 100% MT 1800 pulses daily	Clinical and EEG seizures improved during stimulation, but returned to baseline within 30 min after each daily session. No adverse events.
Jardri 2009[50] and Jardri 2007[51]	Schizophrenia, auditory hallucinations N=1 Age 11 yrs	Right inferior parietal lobule 1 Hz 100% MT 1000 pulses daily 10 treatments total	Cessation of auditory hallucinations with q5wk rTMS. Significant improvement in adaptive functioning. No adverse effects reported.

continued Table 1. Pediatric rTMS studies and incidence of adverse events since 2001.

Study	Disorder Subjects Ages	TMS paradigm	Results Significant adverse events
Kirton 2008[31]	Subcortical arterial ischemic stroke N=10 Median age 13.25 yrs	Non-stroke primary motor cortex 1 Hz 100% rMT on the non-lesioned side 1200 pulses daily	Improved grip strength and hand function after rTMS. Unaffected hand function remained stable. No serious adverse events reported. 2 patients had mild headache, self resolving. One patient had mild nausea, neck stiffness on first 3 days. Two subjects with neuro-cardiogenic syncope. Participants rated rTMS experience as enjoyable (6 patients) or neutral (4 patients). Mean tolerability scores did not differ between the sham and rTMS groups.
Block 2008[52]	Depression N=9	DLPFC 10 Hz 80% MT 400 pulses daily 14 treatments total	Significantly reduced depression scores. No effect on suicidality. 5 subjects reported mild headache but no other significant adverse effects.
Rotenberg 2008[53]	Rasmussen encephalitis N=1	Seizure focus 1 Hz 100% MT 1800 stimuli daily 9 treatments total	rTMS resulted 20–30 min pause in seizures in 3/7 patients and a lasting (>1 day) pause in 2/7. Well tolerated without side effects.
Valle 2007[54]	Cerebral palsy, spastic quadriplegia N=15	Primary motor cortex Sham vs active 1 Hz or 5 Hz 90% MT 5 treatments total	1 Hz and 5 Hz rTMS showed no adverse events versus sham.
Fregni 2006[55]	Juvenile myoclonic epilepsy N=15 JME N=12 controls	Left primary motor cortex 1 Hz 90% 15 minute continuous train	In patients with low plasma valproate concentrations, rTMS had a significant inhibitory effect on corticospinal excitability as in healthy subjects. In patients with high valproate concentration, rTMS increased the corticospinal excitability significantly. No adverse events reported.
Loo 2006[56]	Depression N=2	Dorosolateral prefrontal cortex 10 Hz 110%MT 2000 stimuli qd	Both subjects improved to a clinically significant degree with rTMS treatment. No adverse events reported
Morales 2005[57]	Epilepsia partialis continua N=2	Left motor cortex Day 1: 1 Hz 2nd session: 6 Hz priming followed by 1 Hz at 100 % stimulator output 8 year-old female received extra rTMS session of 1 Hz on the following day.	rTMS not effective in treating EPC. No adverse events reported
Graff-Guerrero 2004[58]	Epilepsia partialis continua N=2	Left frontal cortex 20 Hz 50 % MT for Pt 1 56% MT for patient 2	Patient 1: seizures became intermittent until stopping in the following 24 h. Patient 2: minimal improvement with decreased of epileptic spikes only. No adverse effects reported.

of certain amplitude in a target muscle. Such motor thresholds (either at rest or with muscle activation) provide an individualized reference for setting additional stimulation parameters [1].

Using such simple, single-pulse measures, seminal studies by Eyre and others have helped define the normal evolution of cortical motor pathways from birth through early development [59,60].

Motor thresholds appears to increase over the first 3 months of life [59] then remain high with children under 10 years having higher thresholds [9] that decrease to adult levels by mid-adolesence [61]. In children, as in adults, motor thresholds are lowered by background muscle activation of the target muscle (active motor threshold) [61].

The latency of TMS evoked MEP's provides an estimate of central motor conduction time (CMCT). Active CMCT appears to reach maturity within the first 3-5 years of life while resting CMCT does not approach adult values until early adolescence [62]. In adults, the "latency jump" between rest and active CMCT is believed to reflect trans-synaptic activation of cortical motor neurons via interneurons and recruitment of faster conducting pyramidal tract neurons during higher levels of muscle activation [62,63]. Although mechanisms for this gradual decrease remain unclear, hypotheses include maturation of central myelination and motor cortex neuronal and synaptic maturation with possible aspects of central motorneuronal recruitment also at play [64].

Simple, single pulse TMS studies of primary motor cortex while measuring bilateral MEP provides robust data on corticomotor projections and their arrangement during child development. While crossed (contralateral) corticospinal tract development is known to pave the way for normal motor function, uncrossed (ipsilateral) pathways are also integral to motor development, particularly following early brain injury [65]. Seminal single pulse studies of primary motor cortex performed serially from birth through the first two years have defined the evolving balance of contra- versus ipsilateral corticospinal tracts [59]. Specifically, ipsilateral projections demonstrate similar strength and neurophysiological properties at birth but are gradually withdrawn

during the first 2 years with increasing dominance of contralateral projections. The uncrossed corticospinal pathway is faster than the crossed pathway before 6 months of age [59] and its prevalence is higher in proximal versus distal muscles in most children before the age of 10 years [66]. Clinically, preservation of these ipsilateral pathways correlates with "mirror movements" in children with unilateral early injuries and other motor developmental disorders [4] and may be associated with worse motor function. Combined with animal studies [67-69], these human TMS studies have formed the basis for developmental motor plasticity models following early brain injuries such as perinatal stroke that may define novel central therapeutic targets [70].

Paired pulse: cortico-cortical connections and interhemispheric inhibition

Intracortical motor systems and their role in the maturation of motor task performance have been studied through two main paradigms in children; cortical silent periods and paired pulse methods [3].

Single pulse stimulation of the motor cortex during active contralateral muscle contraction evokes a sustained decrease in muscle activity termed the silent period. Inhibitory interneurons within the motor cortex are thought to be responsible for this contralateral silent period (CSP) [9]. The duration of the CSP at a given stimulus intensity reflects the integrity and excitability of cortical inhibitory mechanisms, thought to be mediated by gamma-aminobutyric acid-B receptors [71]. The ontogeny of the silent period may reflect maturation of cortical inhibitory interneurons in the developing brain [9]. However, the age-related changes in CSP characteristics are not well established. Studies investigating the developmental trend in CSP in children between 6-15 years of age found that CSP duration ranged widely (between 3.5 and 207 ms) using similar stimulation techniques [61,72]. Across both studies, a significant age-related increase in duration was found in one study but not the other [61,72]. Therefore, the simplicity of the CSP represents an appealing method to interrogate cortical inhibitory systems but its large variance and relatively uncharacterized nature in young children represent current barriers to understanding its utility.

Paired pulse methods have also assessed intra-cortical excitability and inhibition by delivering two stimuli in a condition-test paradigm with interstimulus intervals (ISI) varying from 1 to 70 ms [3]. The $GABA_A$ receptor mediated [73] short interval intracortical inhibition (SICI) paradigm is the most established method for the study of intracortical inhibition in adults and children. One study examined the maturation of intracortical inhibition in subjects ranging from 6-34 years of age [74]. Using a 2 ms inter-stimulus interval, the study demonstrated that SICI is nearly four times greater in adults than in children less than 10 years of age [74]. As decreased levels of SICI may be associated with increased practice-dependent plasticity [75], some have suggested that decreased SICI may reflect the neurophysiological mechanisms responsible for increased neuroplasticity in children [3]. Additional paired pulse protocols generated by varying conditioning stimulus strength and ISI, such as long interval intracortical inhibition (LICI) and intracortical facilitation (ICF), remain less defined in children and require further study.

Transcallosal, interhemispheric motor neurophysiology can also be explored through both paired-pulse and *ipsilateral* silent period (iSP) approaches in children. Application of a conditioning stimulus to one motor cortex immediately prior to a regular test stimulus over the contralateral motor cortex will diminish the amplitude of the induced MEP. Such interhemispheric inhibition (IHI) protocols are well tolerated in children and adult-like IHI affects appear to be present by school-age [45,76]. In comparable fashion, the neurophysiologic development of an ipsilateral silent period (iSP) is also proposed to reflect the maturation of cortical inhibitory neurons and myelination of the corpus callosum [3]. In this paradigm, single pulse stimulation of the motor cortex *ipsilateral* to the contracting hand results in a silent period. The iSP is absent in pre-school children but can consistently be evoked after the age of 6 years [76] with latencies decreasing and durations increasing to approach adult values by early adolescence [61]. The ontogeny of the iSP may reflect maturation of both cortical inhibitory interneurons and myelinogenesis of the corpus callosum in the developing brain [9]. Growing evidence suggests that the iSP reflects normal motor cortex development including the suppression of mirror movements. Fewer iSPs are seen in the hand which shows greater mirror movements in healthy children though the association between iSP and both mirror movements and finger tapping skills is variable [61]. Differences in the maturational profiles of the iSP and CSP suggest that the two inhibitory systems reflect different underlying neurophysiology [61]. Collectively, studies to date suggest the iSP may reflect only one aspect of interhemispheric inhibition (or even direct effects on ipsilateral projections) and further studies are warranted.

TMS in child's nervous system and neurodevelopmental disorders

Perinatal stroke and cerebral palsy

Perinatal stroke causes most hemiparetic cerebral palsy and is a leading cause of lifelong neurological disability [77,78]. Thanks to modern neuroimaging, current definitions include distinct perinatal stroke diseases with specific timing (prenatal versus neonatal), mechanisms (arterial versus venous), and locations (cortical versus subcortical) [78]. The common occurrence of such discrete, well defined injuries in an otherwise healthy brain makes perinatal stroke an ideal human model for the study of developmental motor plasticity using TMS [79]. Elegant work in animals [69] has recently combined with human TMS and imaging studies [80,81] to generate working models of developmental motor plasticity following perinatal stroke. This exciting progress has generated not only an increased understanding of disease-specific neurophysiology but has identified real central therapeutic targets and possible means by which they might be affected [70].

The value of understanding neuroplasticity is only realized upon translation into improved patient outcomes [82]. Brain stimulation given repeatedly can produce lasting changes in brain

function. Repetitive TMS (rTMS) studies have established this principle in health and disease over the past 20 years [13,14,83]. High frequency rTMS (~10 Hz) stimulates cortex which both animal [23,84-86] and adult [13] stroke studies suggest can facilitate motor function. Low frequency rTMS (~1 Hz) inhibits cerebral cortex [82,87,88]. rTMS is amenable to randomized, sham-controlled clinical trials [89]. Accumulating evidence suggests rTMS can modulate neural networks [90] to enhance motor function in chronic adult stroke [12,15,91].

The first randomized, controlled clinical trial of rTMS in children studied patients aged 6-18 years with isolated, subcortical childhood arterial ischemic stroke and hemiparesis [31]. Consistent with adult stroke trials, inhibitory rTMS was applied over the contralesional primary motor cortex at 1 Hz for 20 minutes (1200 stimulations) daily for 8 days. Results suggested that inhibitory rTMS was safe, well tolerated and feasible in children. Though preliminary and underpowered, this study appeared to demonstrate improvements in objective hand function testing in measures of upper extremity function (grip strength and Melbourne assessment) and showed improvements in treated versus sham patients, some of which persisted 1 week beyond the intervention. Function of the unaffected hand remained stable.

A larger factorial clinical trial (PLASTIC CHAMPS, http://www.clinicaltrials.gov/ct2/show/NCT01189058) of children with perinatal stroke combining contralesional inhibitory rTMS with constraint induced movement therapy (CIMT) and intensive rehabilitation is currently underway at our center. Preliminary analysis of the first 35 patients demonstrates excellent safety and tolerability including preserved normal hand function and no decrease in affected hand function even in children with prominent ipsilateral projections [35]. Taken together, the pediatric stroke population promises to be at the forefront of advancing both neurophysiological mapping and therapeutic applications of TMS in children.

Epilepsy

As the most common serious neurological condition of children with a fascinating array of underlying neurophysiology and the common failure of available treatments, epilepsy represents a particularly fertile area for pediatric TMS research. Early studies attempting to use TMS as an epileptogenic device for research documented a limited ability to induce seizures in rodents [92]. Some have postulated these experiments, combined with the now well established safety record of TMS in patients prone to seizures, instead reflects potential anticonvulsive and therapeutic potential of TMS in epilepsy.

TMS in the pathophysiology and treatment of epilepsy

TMS offers numerous clinically relevant neurophysiological applications to better understand and manage epilepsy in real patients. The cortical silent period has been found to be prolonged in young persons with both idiopathic generalized epilepsy [93] and motor cortex cryptogenic partial epilepsy [94]. Prolongation of the silent period has been described in epileptic patients on anticonvulsants [95] and the cSP of medicated patients with controlled seizures were longer than those in the normal group but shorter than those in unmedicated patients suggesting cSP may correlate with seizure control.

A 2008 study examined cortical motor responses in adolescents and young adults with idiopathic generalized epilepsy during intermittent photic stimulation (IPS) [96]. The photo-paroxysmal response (PPR) is an abnormal electroencephalographic response of the brain to visual stimulation and likely reflects unique neurophysiological properties of certain epilepsies. Studies of children and young adults (ages 12-22 years) have shown that IPS at 50 Hz shortens the cortical silent period (cSP) over the primary motor hand area in PPR-negative control subjects. However, the same protocol has no effect on cSP duration in either PPR-positive controls or PPR-negative patients with generalized epilepsy. The failure of IPS to shorten the cSP was independent of antiepileptic medication. Of interest, single-pulse or paired-pulse TMS only without concurrent IPS showed a higher motor threshold in PPR-positive patients with epilepsy, presumably caused by antiepileptic medication. The authors concluded that because the cSP is mediated by intracortical GABAergic mechanisms, their results support altered GABAergic inhibitory circuits in M1 in idiopathic generalized epilepsy independent of photosensitivity. Excitability changes at the cortical or thalamic level were hypothesized to mediate this abnormal cortical response pattern [96].

In adults, the effects of anticonvulsant drugs on different parameters of cortical excitability have shed light on mechanisms of action and toxicity [73,97-99]. TMS measures of cortical excitability may be able to predict responsiveness to anticonvulsants [100] or even the ketogenic diet [101]. In general, the findings of these studies have been consistent across a variety of variety of childhood epilepsies including benign rolandic epilepsy, partial epilepsies, generalized epilepsies and progressive myoclonic epilepsy. These and more advanced neurophysiological TMS applications may provide future opportunities to better understand mechanisms of seizures, epileptogenesis, and epilepsy therapies in specific childhood epilepsy syndromes. Table 2 highlights some recent advances in TMS epilepsy research.

The direct therapeutic potential of TMS in epilepsy remains undetermined. A series of five epilepsy patients who experienced in-session seizures during low frequency rTMS over their seizure focus suggests caution is required (see Table 2, Rotenberg *et al.*) [102].

A small study applying different frequencies of rTMS in 7 adults with epilepsia partialis continua suggested favourable safety and possible transient effects [49]. A randomized, sham-controlled trial of low frequency rTMS for 5 days in 21 adults with brain malformations and refractory epilepsy demonstrated decreased seizures and epileptiform discharges on EEG lasting for weeks to months [103]. A recent meta-analysis of 11 studies totalling 164 adult epilepsy patients suggested low frequency rTMS may have favourable effects on seizure frequency, particularly in patients with neocortical epilepsy or cortical dysplasia [104]. Collectively, this data supports the ongoing exploration of rTMS and other non-invasive

Table 2. TMS studies in epilepsy subjects.

Author Year	Subjects	TMS paradigms	Results/Conclusions
Badawy *et al.* 2010 [100]	99 drug naïve adult epilepsy patients 55 idiopathic generalized 44 focal	Motor threshold Cortical excitability on recovery curve analysis	Decrease in cortical excitability in seizure-free group, indicated by increased motor thresholds and intracortical inhibition not seen in the group who failed the anticonvulsant trial. Conclusion: failure to show normalization of cortical excitability upon initiation of anticonvulsant therapy may be a predictor of pharmacological resistance.
Rotenberg *et al.* 2009 [102]	5 intractable epilepsy patients Ages12-23 yrs	1 Hz rTMS for 30 minutes per session over 10-152 sessions at 100% rest motor threshold over the established "dominant" seizure focus based on clinical, imaging, and EEG parameters	In session seizures occurred in all patients studied. 1) in each instance in-session seizure was typical in of the patient's habitual seizures 2) the duration of each documented seizure was either the same or shorter than the patients' baseline seizures 3) neurological outcome on follow-up was not affected by the in-session seizures.
Rotenberg 2008 [53]	Epilepsia partialis continua in Rasmussen encephalitis 14 year old	1 Hz rTMS delivered in nine daily 30-minute sessions	Transient seizure suppression
Graff-Guerrero 2004 [58]	11 year old 7 year old	20 Hz rTMS over seizure origin, single session 600 pulses	One patient experienced a reduction in EPC with remission by 24 hours that lasted for two weeks. The other patient showed only a minimal improvement with a decrease in frequency of EEG spikes. The authors concluded that a single rTMS session could reduce focal epileptogenic activity and should be explored as an alternative approach for resistant, continuous seizures

brain stimulation modalities in the treatment of refractory epilepsy.

In children, the literature on therapeutic applications of rTMS in epilepsy is limited to cases of epilepsia partialis continua (Table 2). Emerging epilepsy applications of TMS in both children and adults include combination with neuronavigational software and advanced imaging to provide image-guided localization of epileptic foci and pre-surgical assessments of motor function (see below). There is clearly a need for expanding TMS epilepsy applications into the pediatric population.

Neuropsychiatric disease

The applications of TMS in child and adolescent developmental psychiatry are becoming more widespread as compelling evidence accumulates to support its use in understanding and managing drug-resistant depression, ADHD, tics and schizophrenia.

Depression

Major depression is a major public health problem and affects approximately 15% of adolescents [105]. It is associated with impairment in social, family, and academic functioning, and it is a major risk factor for suicide - a leading cause of death in teenagers [106,107]. Treatments are limited with the one class of approved medications and cognitive behavioural therapy having combined remission rates of only 30-45% [108]. There is overwhelming evidence that additional treatment options are urgently needed to improve outcomes for teens with depression.

One novel treatment for adolescent major depressive disorder (MDD) is rTMS whose therapeutic potential is increasingly established in adult depression [109]. The majority of adult studies have targeted the dominant dorsolateral prefrontal cortex (DLPFC) though precise mechanisms of action are not well understood. In the adult literature, over 1,300 MDD subjects have been treated safely with rTMS [109,110]. Studies in children have been limited with only 23 total published cases to date [41,52,56]. This is surprising given the urgent need mentioned above, reluctance of young depression patients to take medication, and evidence suggesting younger adults with depression respond better to rTMS [111,112]. Some illustrative studies of TMS in depression of adolescents and young adults are described in Table 3.

Multiple cautionary issues were identified in a 2008 [52] study described in Table 3. While it is impossible to say whether rTMS had any direct causal relationship to the symptoms of increased anxiety, mood lability, hypomania and attempted suicide it is imperative that children studied with mood disorders treated with rTMS be monitored closely during and after treatment for worsening of their psychiatric symptoms.

Attention deficit hyperactivity disorder (ADHD)

TMS neurophysiology may provide particularly novel insights into common developmental neuropsychiatric disorders like ADHD, which feature complex dysfunction at the cellular level without the distinct anatomical, lesional features seen in other childhood neurological disorders.

In a study aimed at understanding the neurobiology of ADHD, Gilbert *et al.* [114] correlated motor cortex TMS measures with behavioural and motor development measures. This case-control study of 49 children aged 8-12 years with ADHD found that dominant primary motor cortex short interval intracortical inhibition (SICI; a $GABA_A$ mediated measure of inhibition in the motor cortex) was reduced by 40% and lesser SICI was strongly correlated with higher ADHD severity. The authors concluded that reduced

Table 3. TMS studies in depression subjects.

Author Year	Subjects	TMS paradigms	Results/Conclusions
Bloch 2008 [52]	9 subjects 16-18 yrs	Treatment-resistant depression who received 20 sessions of 10 Hz rTMS over the left DLPFC at 80% RMT for 20 minutes over 2 weeks.	One patient stopped treatment early due to anxiety and mood lability, 1 had hypomania and 1 attempted suicide 3 weeks after rTMS.
Mayer 2012 [113]	8 young adults Mean 20.4 yrs	10 Hz 80% rest motor threshold for 20 minutes per day over 14 days.	Improvements in depressive symptoms and cognitive functioning immediately which persisted at long-term (3 years) follow-up. Limitations: small sample size, lack of controls and a heterogeneous sample (some received ECT and medications in addition to rTMS).
Wall 2011 [41]	8 adolescents	Open label - subjects maintained on a stable dose of selective serotonin reuptake inhibitor (SSRI). Treated with 30 sessions of 10 Hz TMS at 120% motor threshold applied to the DLPFC.	One adolescent dropped out due to poor tolerance. Depression improved significantly from baseline over the 30 treatments and persisted at 6 month follow-up. There was no neurocognitive decline in function compared to baseline.

TMS-evoked SICI correlates with both ADHD severity and motor skill development [114]. A proposed mechanism suggests that the surround inhibition produced by GABAergic interneurons and modulated by dopamine may be important for refining cortical signals involved in the accurate selection and control of motor responses in ADHD [115].

Disturbed transcallosal motor inhibition in children with ADHD has also been evaluated. Buchmann *et al.* [116] used TMS to explore motor cortex and corpus callosum physiology in 13 children with ADHD compared to controls. The authors concluded the shortened duration of iSP in ADHD children could represent an imbalance of inhibitory and excitatory drive on the neuronal network between cortex layer III—the projection site of transcallosal motor-cortical fibers - and layer V, the origin of the pyramidal tract [116]. They suggested that longer iSP-latencies might reflect differences in myelination of fast conducting transcallosal fibers in ADHD. They also suggested iSP may be a useful supplementary diagnostic tool to discriminate between ADHD and normal children, a finding echoed in a later case-control study by Garvey *et al.* who examined iSP in 12 boys with ADHD aged 7-13 years [117]. These authors proposed the presence of complex abnormalities of interhemispheric interactions (iSP latency) may be associated with delayed maturation of neuromotor skills in ADHD. A more recent study has drawn a possible clinical connection to these neurobiological differences, demonstrating that such differences in intracortical motor circuits were partially reversed following methylphenidate treatment [118]. Such neurophysiological biomarkers of treatment effects are invaluable, particularly in diseases such as ADHD that lack imaging or other definitive markers and must instead rely on subjective, complex clinical outcome measures.

A recent clinical trial has attempted to translate these new understandings of ADHD neurobiology [119]. A randomized, sham-controlled, crossover study of 9 subjects (ages 15-20 years) applied rTMS to the right prefrontal cortex at 10 Hz (100% motor threshold) for 2000 pulses per session in a 10-session course over 2 weeks. Results showed TMS to be safe, with no serious adverse events and no discontinuations. Though there was a significant improvement in both measures across the entire population, time-dependent changes between active and sham TMS did not differ [119]. This study was limited by small sample size, difficulty in blinding rTMS versus sham in a cross-over design, and a short time interval between phases. Additional preliminary evidence suggests rTMS of the DLPFC may be beneficial in treating adults with ADHD [120]. Additional therapeutic trials of non-invasive brain stimulation studies in both pediatric and adult ADHD populations appear warranted.

Tourette syndrome (TS)

Tourette syndrome is another example of a common childhood neurodevelopmental disorder with complex, poorly understood neurobiology. Table 4 illustrates some of the pioneering childhood and young adult studies of TMS in Tourette syndrome.

Other potential neuropsychiatric applications

Based on a limited number of predominantly adult studies, TMS may have additional applications across other psychiatric conditions in children. A modest but growing literature suggests possible therapeutic applications of rTMS in common adult psychiatric conditions including anxiety disorders [123], obsessive compulsive disorder [124], and schizophrenia [125]. The use of TMS in the treatment of the positive (delusions, disordered thoughts and hallucinations) and negative (blunted affect, poverty of speech, lack of motivation, inability to experience pleasure, etc.) symptoms of childhood schizophrenia has been limited to date. A small, open label series of three 18 year old males with schizophrenia applied 10 sessions of 20 Hz rTMS over the right frontal cortex at 110% MT for a total of 1600 stimuli over 2 weeks. Two of the patients showed improvements in their positive and negative symptoms and the third patient had improvement in hallucinations, agitation and global functioning. No adverse effects were reported [126]. Other reported cases of adolescents with medically refractory schizophrenia responding to similar rTMS paradigms [51,127] suggest favourable tolerability and safety and the possibility

Table 4. TMS studies in Tourette syndrome.

Author Year	Subjects	TMS paradigms	Results/Conclusions
Kwon 2011 [42]	Ten male children Mean 11.2±2.0 yrs	12 week, open label cohort study Inhibitory rTMS supplementary motor area (SMA) for 10 daily sessions (1 Hz, 100% rest motor threshold, 1200 stimuli/day	All subjects completed the study with no side effects or worsening of ADHD, depressive, or anxiety symptoms. Tic symptoms improved significantly over the 12 weeks. Authors concluded low-frequency rTMS over the SMA appears to be effective for treatment of TS in children.
Moll 1999 [121]	21 children Ages 10-16 yrs	Cortical silent period Intracortical inhibition	Cortical silent period duration shortened. Intracortical inhibition not affected. Possible age dependent clinical evolution as adults show reduced intracortical inhibition
Gilbert 2004 [122]	36 children & adults	Short interval intracortical inhibition (SICI)	Severity of ADHD symptoms and motor tics were independently and inversely associated with short interval intracortical inhibition (SICI), particularly in subjects not receiving neuroleptic therapy. Measures of cortical disinhibition were more strongly correlated with ADHD symptom severity compared to tic severity.

of therapeutic effect. Numerous issues in neuropsychiatry potentially amenable to TMS applications await further exploration in young adults and children.

Headache

Headache is the leading cause of both recurrent and chronic pain in children [128]. Understanding of disease pathophysiology is poor and evidence based treatments are lacking, opening the door for TMS applications in children with headache. TMS carries the potential to interrogate cortical pathophysiological mechanisms in migraine patients. Phosphenes elicited through TMS of the occipital cortex are artificial visual perceptions representative of regional cortical excitability. Phosphene thresholds (PT) provide a simple, single pulse TMS method by which differences in occipital lobe physiology have been extensively examined in adult migraine [129]. Preliminary studies have begun to explore PT in children with migraine [130]. A small study of children aged 8-18 years received TMS to study regional excitability of the occipital lobe (PT) as well as motor cortex (resting motor threshold, cortical silent period). Ten children with migraine without aura were compared to age-matched healthy controls [130]. As seen in adults, migraineurs had lower PT, suggestive of increased occipital cortical excitability. The increase in occipital excitability was attenuated 1–2 days before a migraine attack, demonstrated by a relative increase in PT. In contrast, motor excitability was not altered in patients and did not change during the migraine cycle. The authors concluded that migraine without aura in pediatric population is associated with a systematic shift in occipital excitability preceding migraine attacks. They proposed that the fluctuations in cortical excitability may reflect either a protective mechanism or an abnormal change in cortical excitability that predisposes an individual to a migraine attack. Future studies may better define both the underlying neurobiology of migraine in pediatric population as well as mechanisms of effective treatments. It remains to be determined if preliminary evidence of therapeutic applications of brain stimulation in adult migraine [131] can be translated to children with headache.

Traumatic brain injury / concussion

By the age of ten, over 1 in 10 children will sustain a mild traumatic brain injury/ concussion and 1 in 7 school children will suffer post-concussion syndrome (PCS) [132]. PCS is a constellation of clinical symptoms including physical (i.e. headaches), cognitive (i.e. learning/memory dysfunction), and behavioral (i.e. mood) disturbances and is associated with significant disability for children and their families, with lack of understanding regarding its neurobiological underpinnings and a paucity of evidence based treatments [132]. There are no pediatric studies examining PCS neurobiology using TMS but adult studies [133] provide a glimpse into the diagnostic and therapeutic potentials of non-invasive brain stimulation. A prolonged cortical silent period and enhanced long interval intracortical inhibition was found in a group of 12 asymptomatic athletes with a history of multiple concussions compared to healthy controls [134]. The authors concluded that multiple concussions lead to specific, long-term neurophysiological dysfunctions of intracortical GABAergic inhibitory mechanisms in primary motor cortex with sparing of sensory systems [134]. A study of 9 collegiate athletes examined acutely (<24 hrs) after a concussion [135] found suggested changes in MEPs persisting up to 10 days after injury.

Recent adult reviews suggest a potential for non-invasive brain stimulation to understand and enhance neuroplasticity following traumatic brain injury (TBI) [132,133,136]. A study examining 17 patients with severe TBI and diffuse axonal brain injury showed higher overall motor thresholds, smaller MEP area under the curve values, and narrower recruitment curves [137]. The authors suggested impairment of both excitatory and inhibitory motor cortex systems may occur but do not proceed in parallel, instead demonstrating distinct patterns across different degrees of TBI.

The ability of TMS to improve deficits such as hand motor function and mood disorders that occur frequently in TBI suggest it might also be considered as a therapeutic modality. With such diverse dysfunction, targets might include emerging rTMS targets such as visuospatial and language dysfunction, working memory and executive function, spasticity, pain and gait abnormalities [133]. These approaches await exploration in the pediatric population.

Neurogenetic and metabolic diseases

TMS has seen limited application toward the understanding of the neurobiology of neurogenetic disorders and inborn errors of metabolism. To assess the role of the L1 cell adhesion molecule (L1CAM) in corticospinal tract migration and its association with X-linked recessive spastic diplegia, a 2001 study [138] examined eight mother-son pairs; 8 carrier females and 10 affected young males. The TMS protocol delivered twenty stimuli parasagitally at 120% rest motor threshold and estimates of bilateral total motor conduction delay were obtained. In contralateral biceps and quadriceps, the responses had high thresholds and delayed onset compared with normal subjects. Ipsilateral responses in biceps were smaller, with higher thresholds and delayed onsets relative to contralateral responses. Subthreshold corticospinal conditioning of the stretch reflex of biceps and quadriceps was abnormal in both hemizygous males and carrier females suggesting there may have also been a reduced projection to inhibitory interneurons. The study concluded that L1CAM played a role in corticospinal tract development in hemizygous males and 'carrier' females, but did not support a critical role for corticospinal axonal guidance [138].

TMS identified neurophysiologic abnormalities in patients with Rett syndrome (RS) are unique and distinct from other neurogenetic developmental disorders. Children during the rapid destructive stage of RS (~1-3 years of age) have been found to have an abnormally *short* central motor conduction time (CMCT). Despite the non-localizing nature of this finding, it has not been reported in any other neurogenetic developmental disorder and suggests the presence of abnormal synaptic organization within the motor cortex or abnormalities of cortical or spinal motoneurons [24]. Later work by Nezu and colleagues [139] performed TMS in 3 RS patients aged 4, 6 and 13 years. The younger two were in the pseudo-stationary stage (Stage III RS) with the older child already having lost ambulation (Stage IV RS). In comparison to age matched normal children, CMCT in the stage III cases was shorter (6.9-7.1 ms, $P < 0.05$). In the stage IV case, CMCT was markedly short (6.6 ms) but there was also a significant increase in required TMS threshold intensity (100%). The authors concluded that the CMCT shortening implied cortical hyperexcitability unique to RS. The impaired corticospinal tracts in the stage IV case were also thought to correspond well to the clinically evident progressive spastic paresis [139]. Whether TMS can be used as a reliable biomarker of progressive neurological deterioration in Rett syndrome remains to be seen.

Sleep disorders

TMS provides an opportunity to study the mechanisms of sleep disorders and the effects of the medications used to treat them. The use of modafinil to treat narcolepsy provides a good example. A double-blind and placebo-controlled study [140] of 24 drug-naïve narcoleptic patients with cataplexy and 20 control subjects began with administration of modafinil or placebo over a period of 4 weeks. TMS was performed twice during the awake state before and at the end of treatment. Measures of cortical excitability included RMT, CMCT, SICI and ICF. These measures were each correlated to the Multiple Sleep Latency Test (MSLT) and the subjective Epworth Sleepiness Scale. Motor threshold and SICI were significantly increased in patients with narcolepsy. Modafinil reversed this cortical hypoexcitability but only the SICI differences reached statistical significance. Since SICI is thought to be directly related to GABA(A) intracortical inhibitory activity, the authors concluded that the dose of modafinil that induces a satisfactory wakefulness-promoting response in narcoleptic patients may do so by affecting GABAergic transmission [140].

Emerging applications of non-invasive brain stimulation in children

Novel TMS methods

Theta-burst stimulation (TBS) has been recently developed as an alternative method for modulating cortical function. Similar to rTMS, a series of short high-frequency bursts of magnetic pulses are applied over the scalp. The potential advantages of TBS over rTMS, particularly for children, include shorter overall stimulation duration and lower stimulation intensity [141]. Despite this, its use has been limited in research thus far. A recent safety and tolerability study of TBS examined intermittent and continuous TBS over the primary motor cortex in children with Tourette syndrome and typically developing children [141]. Intermittent TBS consisted of three 50 Hz magnetic pulses repeating every 200 milliseconds for 2 seconds, with each cycle repeating every 10 seconds for 20 times. Continuous TBS consisted of three 50 Hz magnetic pulses repeating every 200 milliseconds for 200 times. There were no serious adverse events reported. Five of the 40 children reported mild, self-limited adverse events varying from finger twitching, neck stiffness and mild headache. Children were rated as mostly happy and calm during the procedure. This study is the largest to date in children receiving TBS and suggests that, like single pulse and rTMS, TBS is a safe and well tolerated procedure [141]. This unique form of rTMS has potential advantages in the pediatric population, making it an appealing TMS method to investigate further.

Pre-neurosurgical evaluation

A retrospective review of children examined the major modalities used currently in the mapping of sensorimotor function in patients prior to epilepsy surgery. They found that electrical cortical stimulation, somatosensory evoked potentials (SSEP), fMRI, and high gamma electrocorticography generally produced concordant localization of motor and sensory function in children [142]. However, many of these methods are invasive and alternative, non-invasive methods are continuously sought to provide complementary data to improve the precision of mapping cortical areas prior to surgery, especially those areas with eloquent function. Additional challenges associated with preoperative functional mapping in children under the age of 5 years include the difficulty of awake fMRI requiring patient cooperation and the invasive nature of the current gold standard of intraoperative direct cortical stimulation.

TMS may provide a complimentary tool in such circumstances. A 3 year old boy with a rolandic ganglioglioma underwent preoperative functional motor cortex mapping with the aid of navigated TMS [143]. MR

studies including fiber tracking via diffusion tensor imaging correlated to the findings of navigated TMS, showing posterior dislocation of the corticospinal tract near the cystic lesion. The surgical approach was planned according to the preoperative findings. Intraoperative direct cortical stimulation verified the location of the navigated TMS hotspots, and complete resection of the precentral tumor was achieved [143]. TMS may also prove useful in the preoperative mapping of cerebrovascular anomalies that may impair the quality of data collected using fMRI through hemodynamic artifacts [144]. While navigated TMS has been used in adults for preoperative mapping of central cortical regions with data showing good correlation to fMRI in detecting central motor cortex [145], this case suggests it may also be feasible in young children.

Transcranial direct current stimulation in children

Transcranial direct current stimulation (TDCS) is a non-invasive brain stimulation tool that can modulate brain activity via weak electrical currents applied to the scalp through placement of an anode and a cathode. This modality is being transitioned from the adult research world into pediatrics including the study of epilepsy [146,147], dystonia [148], and headache [149].

A recent study in children suggests that cathodal TDCS, which typically is thought to suppress regional cortical excitability, showed some mild decreases in focal seizure activity and electrical EEG activity for 48 hours in a population of 36 children aged 6-15 years who received a single treatment with 1 mA cathodal TDCS for 20 min with the cathode positioned over the seizure focus and anode on the contralateral shoulder [146]. However, in a small series of 5 children who received cathodal TDCS for refractory continuous spike wave in sleep epilepsy, the TDCS did not reduce the frequency of continuous epileptiform activity in any of the patients [147]. Thus, the use of TDCS requires further examination in the developing epilepsy population.

In childhood dystonia, inhibitory cathodal TDCS was hypothesized to reduce increased motor cortex excitability and was applied to 10 children with dystonia. Four patients showed improvements in either involuntary overflow activity and/or muscle control [148].

Finally, a recent subpopulation of 44 adolescents who received TDCS with chronic post-traumatic headaches after mild head injury showed improvements in their symptoms equivalent to current available pharmacologic therapies, the effects of which lasted 5-9 months with good tolerance of the TDCS procedure [149]. It was noted that the effectiveness depended on the localization of stimulating electrodes used for different types of headaches studied, providing avenues for ongoing research in the area of headache treatment.

In general, it appears that TDCS is well tolerated in the children studied in the emerging literature, however more research is required to truly establish its safety and efficacy in the pediatric population.

Controversial applications of TMS

While TMS has shown therapeutic efficacy in a variety of pathological disorders, neuroethical concerns arise in its potential application towards "neuroenhancement" in the healthy population. A review highlighting the bioethics of TMS and neuromodulation discusses the though, provoking aspects of "managing unexpected effects" of TMS including unpredictable and unintentional behavioural responses and the potential for neuroenhancement in areas of memory, attention and cognitive performance, athletic performance, and even artistic ability [150-152]. Parallels are noted between TMS and fMRI/neuroimaging research, with the potential for TMS to discover of "incidentalomas" of no health significance and even clinically significant functional brain abnormalities. Questions are raised about the potential significance to subjects and society of activities as minor as inadvertently shouting an obscenity during stimulation and more seriously, the potential for hallucinations, flashbacks or vivid dreams and even the extreme possibility of confession to a criminal offense during or after a TMS session [151]. A recent review article in collaboration with an air force research laboratory in the United States suggests that the potential for using "non-invasive brain stimulation to transcend the current limitations of human cognition" is indeed being examined as a possible tool allowing for "augmentation and enhancement of human operator performance" [153]. These serious issues raise some important points for discussion regarding the future of TMS as a safe and ethical tool to manage illness and improve quality of life in humans.

Conclusions

Non-invasive brain stimulation in the developing brain is rapidly becoming an intensive area of research and translational medicine in an effort to find new treatment paradigms for a variety of neurological diseases. While children have certain features in their maturational and brain characteristics that can make non-invasive brain stimulation a challenge, the potential for understanding disease neurobiology and harnessing brain plasticity in recovering from disease is unmatched and demands further careful study.

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