Curr Treat Options Neurol (2019) 21:58
DOI 10.1007/s11940-019-0600-3

Pediatric Neurology (A Yeshokumar, Section Editor)

Transcranial Magnetic Stimulation for the Treatment of Pediatric Neurological Disorders

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This article is part of the Topical Collection on *Pediatric Neurology*

Keywords Transcranial magnetic stimulation · Repetitive TMS · Pediatric neurology · Headache · Depression · Stroke

Abstract

Purpose of review Repetitive transcranial magnetic stimulation (rTMS) is a form of noninvasive brain stimulation that is used for the treatment of migraine and major depression in adults and is now being evaluated for use in other disorders. The purpose of this review is to summarize the physiology underlying TMS, the safety and tolerability in pediatric patients, and the evidence for TMS efficacy in the treatment of pediatric neurologic disorders.

Recent findings Studies investigating rTMS for adolescent depression, hemiparesis due to pediatric stroke, autism, and tics/Tourette syndrome have demonstrated some therapeutic benefit. rTMS has been insufficiently studied for migraine in children despite benefits demonstrated for adult migraine. Evidence for rTMS in childhood epilepsy and ADHD remains mixed.

Summary Repetitive transcranial magnetic stimulation is emerging as a safe, tolerable, and potentially effective therapeutic strategy in a number of pediatric neurological disorders, though high-quality, randomized controlled trials are needed. Ongoing studies should focus on optimization of treatment protocols, development of biomarkers to identify children who will benefit from the technique, and identification of the most appropriate indicators of response.

Published online: 13 November 2019

Introduction

Transcranial magnetic stimulation (TMS) is a form of noninvasive brain stimulation that was initially designed to painlessly activate and assess the integrity and function of the motor cortex and corticospinal tracts [1]; however, as more protocols have been designed and studied, the uses for TMS have vastly expanded. Though TMS has been used for decades in neuroscience research, its role as a therapeutic modality for an array of neurologic and psychiatric disorders has more recently been explored.

The US Food and Drug Administration (FDA) has approved TMS devices for pre-neurosurgical functional motor and language mapping and treatment of major depression and migraine in adults [2–4]. Despite promising data in adults, translation to the pediatric population has been limited, in part due to the incomplete understanding of the effects of noninvasive brain stimulation on the developing brain. Modifications to adult stimulation protocols may be warranted to limit adverse events and improve tolerability in children. Furthermore, timing and intensity of delivered pulses to achieve optimal results may differ in children due to age-related differences in skull thickness, tract length, connectivity, and myelination. Despite these concerns, multiple studies have shown TMS to be a safe and potentially effective tool in pediatric populations, and in particular, children with neurological disorders. Here, we will review the physiology underlying TMS, safety and tolerability in pediatric patients, including those with epilepsy and central nervous system (CNS) dysfunction, and the evidence for TMS efficacy in treatment of pediatric neurologic disorders.

Physiology of TMS

Transcranial magnetic stimulation is a noninvasive technique in which magnetic coils held over the scalp create rapidly changing magnetic fields around the brain. These magnetic fields induce intracranial currents, whereby the neurons in the path of this current depolarize and fire synchronously [5, 6]. This is in contrast to applications such as magnetic resonance imaging (MRI) which utilize slowly changing or static magnetic fields [6]. Various stimulation protocols have been designed for TMS including single pulse, paired pulse, repetitive, and theta burst techniques. These diverse protocols have different uses—some probe the connectivity between neurons while others create neuromodulatory effects on the brain tissue of interest that are transient but can outlast the simulation period. Single pulse TMS (spTMS) was the first technique to be developed and is most commonly utilized to assess corticospinal tract excitability by stimulating the motor cortex and measuring the electromyographic response. The latency and amplitude of the motor evoked potential (MEP), which is felt to the subject as a muscle twitch, can be measured at a peripheral muscle such as the biceps or first dorsal interosseous muscle. Paired pulse TMS (ppTMS) is a protocol by which two pulses are transmitted within milliseconds of one another, allowing for interrogation of the effect the first (typically subthreshold) "conditioning" pulse has on the second suprathreshold "test" pulse. Different intervals may produce varying effects including short interval intracortical inhibition, long interval intracortical inhibition, and intracortical facilitation [6, 7]. The interaction between the conditioning and test pulses is thought to be mediated by gamma-aminobutyric acid (GABA)–ergic and glutamatergic activity.

While spTMS and ppTMS protocols can assess integrity and strength of connections between neurons, the technique that has been proposed to be a

potential therapeutic intervention for neurological conditions is repetitive TMS (rTMS). rTMS studies have shown that the underlying cortical excitability can be altered by repetitive trains of stimulation. High-intensity, rapid-rate TMS pulses (> 1 Hz) are thought to induce long-term potentiation effects or upregulate brain regions or networks of interest. In contrast, low-intensity, slow TMS pulses (≤ 1 Hz) induce long-term depression effects and downregulate the area of interest [1, 6]. While these effects are temporary, they have been shown to outlast the stimulation period by minutes to hours or longer, making rTMS an enticing therapeutic treatment candidate. Finally, theta-burst simulation (TBS) is a newer form of rTMS where 3 pulses are delivered at 50 Hz every 200 ms either continuously (cTBS) or in intermittent 2-s trains every 10 s (iTBS). In comparison with conventional rTMS, the different stimulation protocols are thought to create longer lasting excitation (with iTBS) or inhibition (with cTBS) [8]; however, it has been less well studied than rTMS.

Safety and tolerability

There are increasing data that TMS is safe in children with neurologic disorders, including those with epilepsy [7]. Single- and paired-pulse TMS techniques are overall felt to be very safe, and they have been utilized as early as the newborn period in both healthy children and in children with CNS lesions such as perinatal stroke [9, 10]. Repetitive TMS has been studied in children as young as 3 years of age [11].

In a recent review of all studies between 1985 and 2016 involving TMS, Allen and colleagues identified 23 studies using rTMS and 3 studies using TBS [7]. In rTMS studies, of 230 children with CNS disorders and 76 children with pre-existing epilepsy, there were 81 adverse events identified, of which 94% were classified as Common Terminology Criteria for Adverse Events (CTCAE) grade 1, indicating that the event was mild and no intervention was needed. Mild adverse events included headache in the majority of cases ($n = 45$), dizziness ($n = 8$), jaw twitching ($n = 4$), nausea/vomiting ($n = 4$), anxiety ($n = 3$), neck stiffness ($n = 3$), sensory changes ($n = 3$), scalp pain ($n = 2$), neck pain ($n = 2$), restlessness ($n = 1$), and sleepiness ($n = 1$). Moderate adverse events included generalized tonic clonic seizures in 3 children and 1 case of rapid mood swings. Notably, two of the three children who had new onset seizures were being treated for depression and were on sertraline with or without olanzapine, drugs which may lower seizure threshold. There was only one event classified as severe which involved an 8–9-h episode of hypomania, also in a child on a selective serotonin reuptake inhibitor (SSRI), and the hypomania was felt to most likely be a side effect of the SSRI instead of rTMS. The risk of any adverse event was 0.0378 per session in children with CNS disorders and 0 per session in children with epilepsy.

Pediatric TBS studies involved 90 healthy children and 40 children with CNS disorders. There were 9 adverse events in healthy children (risk of 0.0978 per session) and 9 adverse events in children with CNS disorders (risk of 0.1011 per session). Adverse events, which were mostly mild and self-limited, included headache ($n = 8$), sensory changes ($n = 4$), finger twitching ($n = 1$), neck stiffness ($n = 1$), weakness ($n = 1$), other pain ($n = 1$), and other ($n = 1$). Only one child experienced a moderate adverse event, described as arm/other pain.

These data suggest that adverse events associated with rTMS are uncommon and typically mild and self-limited. Headache, dizziness, sensory changes, scalp pain, neck pain, and jaw twitching must be discussed as possible side effects of the stimulation, and the risk of new onset seizure and mood changes, though very rare, should also be disclosed prior to participation in rTMS treatment given the potential severity of these events.

There are also data that suggest that the majority of children find TMS to be painless. In a study using questionnaires to evaluate the subjective experience of single-pulse TMS in 38 children ages 6–13 years, 34 said they would repeat the experience [12]. Overall, it was ranked as being less pleasant than watching TV but more pleasant than a long car ride. Taken together these studies show that TMS, including rTMS, is generally safe and tolerable in children.

Depression: most well-established indication for therapeutic TMS

The most widely studied use of rTMS has been for treatment of major depressive disorder; multiple sham-controlled studies demonstrate clinical benefit in adults [13]. For this reason, the US FDA approved the use of TMS for treatment of medically refractory major depressive disorder in adults in 2008 [14]. The rationale for the use of rTMS in this setting derives from prior imaging studies demonstrating that the left dorsolateral prefrontal cortex (DLPFC) is less active in patients with depression compared with healthy controls [15], and application of rTMS at a frequency of 10 Hz can upregulate activity in this area. Yang and colleagues proposed that the mechanism of rTMS-induced improvement in depression is related to elevations in glutamate levels in the DLPFC [16]. Patients suffering from depression typically receive 10-Hz rTMS over the left DLPFC daily for 3–6 weeks.

For adolescents, multiple small clinical trials have shown efficacy of rTMS protocols for the treatment of medically refractory major depressive disorder with results that last months to years post-treatment [17, 18••, 19]. MacMaster and colleagues conducted a study with 32 adolescents and young adults (ages 13–21 years) with moderate to severe treatment-refractory major depressive disorder, defined as having failed at least 2 medication trials [18••]. Subjects in the study received rTMS over the left DLPFC for 15 consecutive weekdays. To assess outcome, the authors utilized the Hamilton Depression Rating Scale (Ham-D), which longitudinally assesses 17 different symptoms of depression; patients with higher scores are considered to have more severe depression. The study showed Ham-D scores significantly decreased after rTMS treatment, with 56% of subjects achieving ≥ 50% reduction in Ham-D score and 75% of subjects achieving ≥ 30% reduction, which is felt to be a clinically meaningful response based on the ACNP (American College of Neuropsychopharmacology) guidelines [18••]. Moreover, participants tolerated the protocol well with the most common side effect being mild headaches [18••].

A recent study suggests that responsiveness to rTMS for major depressive disorder might actually be better in adolescents compared with adults [20]. This is particularly exciting given that one of the most commonly used classes of

antidepressants, SSRIs, carries a black box warning for risk of suicidal ideation and behaviors in adolescents. One major concern for rTMS has been adverse effects on neurocognitive function on the developing brain in children and adolescents. In a small study of 9 patients who received rTMS in adolescence for depression, subjects received the Cambridge Neuropsychological Test Automated Battery (CANTAB), a computerized assessment consisting of tests of motor speed, working memory, attention, and planning throughout the rTMS treatment and 3 years later; investigators did not find any worsening of neuropsychological functioning associated with rTMS treatment [21]. Although studies have been small and limited, rTMS over the dorsolateral prefrontal cortex does not appear to adversely affect neurocognitive function in adolescents at the time of treatment or years after treatment [21–23].

Taken together, these small studies have shown that rTMS could be an effective and relatively safe treatment option for adolescents with major depressive disorder; however, larger clinical trials are needed to confirm long-term safety and efficacy.

TMS therapy for neurological disorders

Migraine

Single-pulse TMS is an approved abortive treatment option for migraine in Europe and the USA for adults [24, 25], but rTMS has also been studied as a preventative therapy to reduce the frequency of migraines over time [25, 26]. For chronic migraine, protocols differ widely but the one that has shown the most promising results is 3 sessions of high-frequency rTMS on alternate days [25, 26]. Two targets have been proposed for preventative treatment of migraine—the left DLPFC and the left motor cortex; however, effectiveness has been more consistently demonstrated with stimulation of the left motor cortex. Yet, in systematic reviews of noninvasive brain stimulation to treat chronic migraine, rTMS has not reliably shown benefits [27, 28]. This could be due a small number of studies ($n < 5$) in the meta-analyses, different stimulation sites, various protocols, inconsistent outcome measures, or the complex nature of chronic pain. Even though older teenagers are included in some of these studies, most subjects in the study population are adults. Unfortunately, there have not been any dedicated studies of TMS for treatment of chronic migraine in the pediatric population.

Notably, a case report was published in 2018 in which a 16-year-old female using rTMS to treat migraine with aura had a self-resolving provoked generalized tonic clonic seizure [29]. The study protocol used a rTMS frequency of 10 Hz and an intensity of 110% of the resting motor threshold (RMT) over the left motor cortex [29]. This patient had no seizure risk factors and had a normal neurological examination and 24-h EEG after this event, so it was hypothesized the seizure was an adverse event from TMS due to cortical hyperexcitability. As a result, the authors of this study suggested that when targeting the motor cortex in adolescents with migraine with aura, the "stimulation intensity should be less than 80% RMT at 20Hz, 90% RMT at 10Hz, 100% RMT at 5Hz, and the total number of daily pulses should be less than 1000" [29]. As cortical excitability differs by developmental stage, dedicated studies aimed at determining safe and effective stimulation intensities and frequencies in the pediatric population are needed.

Stroke

Repetitive TMS has been studied as a treatment modality after stroke in adults, with studies largely investigating the use of rTMS in the chronic stage (> 6 months after stroke) and significantly fewer studies evaluating rTMS use in the acute or subacute phases [30]. The premise of using rTMS to increase excitability of the ipsilesional motor cortex or decrease excitability of the contralesional motor cortex is based on the idea of interhemispheric inhibition (IHI), in which the healthy hemisphere exerts unopposed inhibition on the damaged hemisphere. This imbalance between the two hemispheres has been postulated to hinder recovery. Based on this model, rehabilitative approaches aimed at rebalancing IHI have been developed and studied [31–34], though recent data suggests that poor motor recovery is not directly caused by interhemispheric imbalance and calls these rehabilitative strategies into question [35]. Nonetheless, multiple studies have demonstrated benefit of adjunctive rTMS therapy for stroke-induced motor impairment in adults [20, 36].

Childhood stroke patients would potentially derive an even greater benefit of rTMS treatment due to longer expected post-stroke lifespans, significant burden of motor disability, and a belief that higher levels of neural plasticity exist compared with their adult counterparts. The first randomized trial of rTMS for childhood hemiparesis, published in 2008, studied inhibitory rTMS in ten subjects ages 8 to 20 years with mild to severe hemiparesis related to chronic subcortical childhood ischemic stroke [37]. Low-frequency rTMS applied over the contralesional hemisphere for 8 sessions over 2 weeks resulted in improved grip strength when compared with sham controls. A subsequent 2014 study randomized children ages 8 to 17 years to receive 6-Hz primed, low-frequency rTMS or sham, combined with constraint-induced movement therapy (CIMT) [38]. Subjects in the rTMS/CIMT group had significantly greater improvement in the Assisting Hand Assessment (AHA) score, a play-based measure of bimanual function in children with unilateral upper limb dysfunction [39], compared with the sham/CIMT group. In the largest pediatric rTMS trial to date, the PLASTIC CHAMPS trial, 45 children and adolescents ages 6–19 years with hemiparetic cerebral palsy as a result of a perinatal stroke were randomized to intensive motor therapy (80 h of therapy over 2 weeks) alone or in combination with low-frequency (inhibitory) rTMS of the contralesional primary motor cortex, CIMT, or both [40••]. Addition of rTMS or CIMT to intensive therapy doubled the chances of clinically significant improvement as measured by the AHA, with an additive effect when both treatment modalities were used together. Sustained functional gains were demonstrated after 6 months; however, they did gradually decrease over time. These trials, though relatively small, demonstrate the promise of intensive multimodal therapy (intensive rehabilitation with rTMS) to achieve sustainable, clinically significant motor gains in children with stroke-induced hemiparesis. Optimal stimulation parameters, timing, concurrent therapies, and patient selection criteria will need to be determined before rTMS can be incorporated into clinical practice.

Epilepsy

The ability of rTMS to downregulate cortical excitability makes it an attractive therapeutic approach for epilepsy, though clear, high-quality evidence that it provides benefit in seizure reduction is lacking. A 2011 meta-analysis of 11

articles consisting of 164 participants, including pediatric patients suggested that low-frequency rTMS reduces seizure frequency, and that the effect was particularly robust in patients with neocortical epilepsy or cortical dysplasia [41]. Subsequently, Sun and colleagues studied 60 patients (mean age 20 years) with refractory focal epilepsy, and they found that seizure frequency decreased by 80% from baseline following 2 weeks of high-intensity rTMS treatment [11]. However, a recent Cochrane review evaluated 7 randomized controlled trials of rTMS for drug-resistant epilepsy in adults and children. The authors concluded that, although rTMS was safe in this population and was effective at reducing epileptiform discharges, there was not compelling evidence that rTMS was effective for seizure reduction.

Though epilepsy is significantly more common in children, rTMS studies have been largely limited to adults. Published clinical observations suggest that rTMS may confer some benefit for pediatric epilepsia partialis continua [42, 43], but in the absence of randomized, controlled data, the efficacy of rTMS in pediatric epilepsy remains elusive. For now, the clinical role of TMS in epilepsy remains largely confined to presurgical motor and language functional mapping [44, 45].

Tourette syndrome/tics

The underlying pathophysiology behind Tourette syndrome is still being explored; however, research has suggested that there is an imbalance between the excitatory glutamatergic activity and the inhibitory GABAergic system in these patients [46]. Some studies suggest that the motor cortex is hyperexcitable in patients with Tourette syndrome [46, 47]; yet, when investigators targeted the left primary motor cortex or left premotor cortex directedly with 1-Hz rTMS (i.e., downregulating the activity), it did not impact tic frequency or severity [46, 48, 49]. Instead, what has been suggested to be an effective target has been the supplementary motor area (SMA) [50], which integrates information from the limbic system to cognitive and motor circuits. Subjects who received 1-Hz rTMS over the bilateral SMAs daily for 10–20 sessions had improvement in tic severity for up to 6 months [47, 50]. Moreover, resting motor threshold in the primary motor cortex was increased after this treatment protocol [47]; this was thought to be a downstream effect of the neuromodulation and suggested that repetitive stimulation over the SMA affected primary motor cortex physiology.

Some studies suggest that the presence and severity of comorbid conditions can influence the therapeutic effects of rTMS in patients with tics [46, 51]. Tourette syndrome is commonly associated with other neuropsychiatric disorders such as attention deficit hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD), conditions in which an imbalance of excitatory and inhibitory control within brain regions similar to those affected in Tourette syndrome has been demonstrated [52]. As a result, some have suggested that rTMS over the SMA may be more effective in patients with Tourette syndrome comorbid with ADHD or OCD compared with those with isolated Tourette syndrome [46]. More studies are needed to investigate the complex interaction that exists between Tourette syndrome and these common co-morbid conditions and how rTMS affects this interplay.

Attention deficit hyperactivity disorder

The use of rTMS in the treatment of ADHD is founded on the premise that the disorder is related to decreased motor inhibition and that rTMS can alter cortical excitability, thereby improving ADHD symptoms. To date, there has been only one randomized, sham-controlled study of rTMS in children with ADHD that measured behavioral outcomes. In this study, children who received 10 sessions of high-frequency (10 Hz) rTMS targeting the right DLPFC over 2 weeks had the same symptomatic improvement as the sham-treated control subjects [53]. Recent studies of adult ADHD have largely had similarly disappointing results [54].

Autism

Non-invasive brain stimulation techniques have gained substantial interest for treatment of autism spectrum disorders, particularly in light of the lack of pharmacologic therapies available. This line of inquiry is founded on the concept that aberrant GABAergic signaling leads to dysfunction of intracortical inhibition in autism spectrum disorders that can be altered using rTMS targeting the DLPFC and motor pathways [55]. A recent systematic review of the literature evaluated 23 reports, of which 12 were controlled clinical trials, which studied the effect of rTMS on autism spectrum disorder or associated cognitive symptoms [56]. The meta-analysis suggested a moderate benefit in the domains of stereotyped behaviors, social behavior, and executive function. However, only a minority of studies reported a sustained benefit. Furthermore, the authors note that the studies were limited by inadequate control conditions and absence of blinding to treatment allocation, and therefore, the evidence was considered to be preliminary and insufficient. Nonetheless, further investigation appears warranted.

Conclusions and future directions

Repetitive transcranial magnetic stimulation is emerging as a safe, tolerable, and potentially effective therapeutic strategy in a number of pediatric neurological disorders. Studies investigating rTMS for childhood depression, hemiparesis due to childhood stroke, autism, and tics/Tourette syndrome have demonstrated therapeutic benefit, though ongoing studies are needed to optimize treatment protocols, develop biomarkers to identify children who will benefit from the technique, and identify the most appropriate indicators of response. The use of rTMS in children with migraine should be explored given benefits demonstrated in their adult counterparts, though stimulation protocols that are safe and effective in the pediatric population must be developed. Evidence for rTMS in epilepsy and ADHD remains mixed, which could be related to suboptimal stimulation intensity, timing, or targets, poor patient selection, or ineffectiveness of this technique in these conditions. In addition to these applications, a potential role for therapeutic rTMS has been postulated in a variety of other neurologic disorders affecting children, with promising preliminary results in post-concussive syndrome [57], functional neurologic disorders [58–60], narcolepsy [61], and dystonia [62].

The application of therapeutic rTMS is still in its infancy. In order to move this promising technique forward clinically and best serve pediatric neurology

patients, we encourage the inclusion of pediatric patients in rTMS studies and urge publication of the protocols used in both positive and negative trials.

Compliance with Ethical Standards

Conflict of Interest
The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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