



COMMENTARY

Is Repetitive Transcranial Magnetic Stimulation (rTMS) Ready for Clinical Use as a Treatment Tool for Mental Health Targets in Children and Youth?

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Abstract:

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation tool with potential for broad application in individuals with neuropsychiatric conditions. As in adults, most rTMS research in youth has focused on treatment-resistant depression. A limited number of rTMS studies have also been conducted in children and youth with primary diagnoses of Autism Spectrum Disorder (ASD), Attention-Deficit/Hyperactivity Disorder (ADHD) or Tourette's syndrome. Across the available rTMS literature, rTMS appears to be well tolerated with few adverse effects reported when applied to child and youth research samples. However, the potential efficacy of rTMS treatment for a variety of targets in children and youth remains unclear, due in part to limitations of the current literature, including studies using diverse protocols, potential for bias in existing clinical trial designs, variability in the research samples, and the use of heterogeneous outcome measures. While rTMS is unlikely to take the place of more accessible treatments (e.g., psychopharmacological, psychosocial, psychotherapeutic), rTMS may provide a valuable alternative treatment option, particularly for those individuals where conventional treatments are inaccessible, poorly tolerated, or ineffective. A more robust body of well-designed, controlled trials, is needed in order to clarify rTMS treatment efficacy across relevant neuropsychiatric conditions, optimize treatment protocols, and meet the critical need for novel mental health interventions in children and youth.

Key Words: *neurostimulation, children, youth, depression, autism spectrum disorder, attention deficit hyperactivity disorder.*

Résumé

La Stimulation magnétique transcrânienne répétitive (SMTr) est un instrument de stimulation du cerveau non invasif qui a le potentiel d'une application élargie chez les personnes souffrant de conditions neuropsychiatriques. Comme chez les adultes, la majorité de la recherche sur la SMTr chez les jeunes a porté sur la dépression réfractaire au traitement. Un nombre limité d'études sur la SMTr ont aussi été menées chez les enfants et les jeunes ayant des diagnostics primaires du trouble du spectre de l'autisme (TSA), du trouble de déficit de l'attention avec hyperactivité (TDAH) ou du syndrome de la Tourette. Dans la littérature disponible sur la SMTr, celle-ci semble bien tolérée et peu d'effets indésirables sont signalés lorsqu'elle est appliquée aux enfants et aux jeunes des échantillons de recherche. Cependant, l'efficacité potentielle

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d'un traitement par SMTr pour une variété d'objectifs chez les enfants et les jeunes demeure imprécise, partiellement en raison des limitations de la littérature actuelle, notamment des études utilisant divers protocoles, le potentiel de biais dans les méthodes d'essais cliniques existants, la variabilité des échantillons de recherche, et l'usage de mesures de résultats hétérogènes. Même si la SMTr ne prendra probablement pas la place de traitements plus accessibles (p. ex., psychopharmacologiques, psychosociaux, psychothérapeutiques), la SMTr peut procurer une option de traitement parallèle valable, chez les personnes pour qui les traitements conventionnels sont inaccessible, mal tolérés ou inefficaces. Un ensemble plus robuste d'essais contrôlés mieux conçus est nécessaire afin de clarifier l'efficacité du traitement par SMTr dans toutes les conditions neuropsychiatriques, optimiser les protocoles de traitement et répondre au besoin critique de nouvelles interventions de santé mentale chez les enfants et les jeunes.

Mots clés: *neurostimulation, enfants, jeunes, dépression, trouble du spectre de l'autisme, trouble de déficit de l'attention avec hyperactivité.*

Background

Dr. Anthony Barker and his associates first developed transcranial magnetic stimulation (TMS) in 1985 when they observed movement in the right hand upon holding a conducting coil to the scalp above the left cerebral motor strip (1). TMS has since emerged as a unique neuromodulation tool that allows for non-invasive brain stimulation with broad applications for research and therapeutic innovation for individuals with a variety of neuropsychiatric conditions. Unlike electroconvulsive therapy (ECT) (another brain stimulation technique), TMS does not require general anesthesia or the induction of seizures.

TMS uses a machine (built to generate a current) to deliver a short pulse of electrical current into an insulated TMS coil. Non-invasive stimulation occurs through electromagnetic induction (based on Faraday's law). The TMS coil, placed against the scalp, generates rapidly alternating magnetic fields, inducing an electrical current to flow into the cortex (2).

TMS can induce cortical excitation or inhibition by stimulating interneurons (connecting neurons in the Central Nervous System) at different frequencies (3). TMS can be delivered in a single pulse at a frequency of less than 1Hz. TMS applied repetitively (i.e., rTMS) involves the stimulation of the cortex by a train of magnetic pulses at frequencies between 1-20Hz. Generally, high-frequency rTMS is thought to increase cortical excitability and low-frequency rTMS to decrease cortical excitability (2). However, the neurobiological effect of rTMS may depend on a number of individualized factors, including a given individual's baseline neural activation pattern/state, which can be affected by sleep, fatigue/wakefulness, medications, and prior treatment history (4).

In addition to frequency, stimulation parameters include intensity, train duration, intertrain interval, and the number of stimulation trains per session. Stimulus intensity is

determined based on an individual's resting motor threshold (RMT), which is the minimal intensity needed to produce a muscle twitch in the relaxed upper or lower extremity observed visually or on electromyography (5). Conventional rTMS procedures last between ~20-45 minutes. A newer variation of rTMS called theta burst stimulation (TBS) - which mimics endogenous neural oscillatory rhythms - takes a fraction of the time needed for delivery of conventional rTMS (~one to three minutes) and appears to exert longer lasting effects on motor cortex excitability (6, 7).

Health Canada first approved a course of rTMS treatment targeting the dorsolateral prefrontal cortex (DLPFC) in 2002 for adults with treatment-resistant depression, followed by the FDA in 2008 (5). According to Canadian guidelines, rTMS is a first-line treatment for adults with MDD who have failed one antidepressant treatment (5). The FDA has since approved TBS for depression, following a Canadian trial that demonstrated the non-inferiority of TBS compared to conventional rTMS for treatment-resistant depression (8). The DLPFC was initially chosen as the target of rTMS treatment in depression due to its involvement in the emotion regulation network, as well as in cognitive and executive functioning (9). Complex cognitive functions associated with the DLPFC include maintaining and manipulating new information (as part of working memory), abstract reasoning, intention formation, and attentional control (10). Although the current FDA approved protocol involves 5 daily treatments of 10 Hz rTMS to DLPFC per week for four to six weeks (11), there is still significant variability across the research literature in choosing treatment parameters, such as: coil location, frequency, intensity, treatment schedule and the addition of maintenance treatments. However, a variety of treatment protocols targeting the DLPFC seem to have antidepressant efficacy in adults (12). For example, a recent network meta-analysis including >80 studies and >4000 adult participants recently demonstrated that rTMS treatment over DLPFC is efficacious for treatment-resistant

depression, using a variety of treatment protocols (e.g., low frequency rTMS over right, high frequency rTMS over left DLPFC, bilateral stimulation including low frequency rTMS over right and high frequency rTMS over left DLPFC, TBS) (12). rTMS in adults is well tolerated with scalp pain and headache reported as the most common side effects, which diminish over the course of treatment. Seizure risk is the most serious adverse event reported with rTMS in adults, although the overall seizure risk is low (~ 0.01 - 0.1% incidence) (5).

What's the Evidence for rTMS Treatments in Children and Youth?

As in adults, most rTMS research in youth has focused on treatment-resistant depression. A limited number of rTMS studies have been conducted in children and youth with primary diagnoses of Autism Spectrum Disorder (ASD), Attention-Deficit/Hyperactivity Disorder (ADHD) or Tourette's syndrome. Across the available rTMS literature, findings are variable regarding the utility/preliminary efficacy of rTMS as a treatment, due in part to diverse protocols, potential for bias based on clinical trial designs used to date, variability in the research samples, and the use of heterogeneous outcome measures.

Update on rTMS for Youth Depression: As in adults, rTMS to DLPFC treatment protocols have been used to target depression in youth. A recent systematic review summarized the findings of fourteen publications using rTMS in young people aged 12-25 years with depression (13). Thirteen of these studies included adolescents with treatment resistant depression (TRD) which was most commonly defined as at least one failed antidepressant trial (13). Eight of these 14 studies were independent open-label trials (uncontrolled) (total N=142 participants across studies), and six publications reported on secondary analyses using data acquired in the original open-label studies (13). Although the summarized research indicated that a course of rTMS reduced depression scores in adolescents, design challenges present in each of the available trials limit the ability to draw firm conclusions regarding treatment efficacy (13).

Not included in the above review, Croarkin and colleagues' (2020) rTMS clinical trial targeting treatment-resistant depression in youth, is the most rigorous study published to date (14). This study examining the efficacy of high frequency rTMS to the left DLPFC used a double blind, randomized, sham-controlled study design (14). Although the study did find a pre-to-post rTMS treatment reduction in depressive symptoms, symptom reduction in the active treatment group was not meaningfully different from that found following sham treatment (i.e., depression symptoms

responded across study arms) (14). These findings emphasize the strong placebo response found in depression treatment studies, which is pronounced in affected youth, and has also contributed to challenges in detecting the antidepressant efficacy of the selective serotonin reuptake inhibitors (15). Thus, while the available literature suggests that rTMS could be effective in reducing adolescent depressive symptoms (as in adults), sham-controlled RCTs have yet to demonstrate antidepressant efficacy (13). Therefore, more rigorous rTMS research is needed that incorporates strategies to mitigate the strong placebo response present in this population.

Update on rTMS in ASD: A recent review summarized 13 rTMS studies that have targeted the DLPFC or the motor system in individuals with ASD (16). Much of the available rTMS research in ASD uses inhibitory rTMS protocols (i.e., 1Hz rTMS stimulation) to enhance inhibitory function, which is hypothesized to be impaired in ASD (17).

Recent meta-analyses by Barahona-Corrêa et al. (18) (including 23 studies in participants age 15.9 ± 5.2 years) and a systematic review by Masuda et al. (17) (including 8 studies in participants ranging in age from 7-21 years), provide some indication that rTMS treatment to DLPFC may reduce repetitive behaviour, and may have promise as an intervention tool to support enhanced social interaction in ASD. However, the majority of the published literature in ASD reports on open label studies using a waitlist control group (i.e., as opposed to a sham-rTMS comparison arm with adequate blinding). Heterogeneity along a variety of dimensions also makes it difficult to compare results across studies (17, 18). Some of this heterogeneity includes variability in the cognitive ability and age of the included samples, frequency of stimulation used across studies, and differences in target sites and stimulation protocols (i.e., unilateral versus bilateral stimulation with complex and alternating stimulation schedules) (17, 18). Although the occurrence of adverse events reported thus far are mild to moderate following rTMS stimulation (17) (18), available studies have used relatively conservative protocols (i.e., low stimulus intensity and long interval between treatment sessions).

To further complicate the evaluation of treatment efficacy, we are aware of just three published rTMS studies that have used a rigorous RCT design in individuals with ASD. A recent study by Ni et al. (2021) combined a single-blind (participants and caregivers were blind to treatment assignment), sham-controlled parallel RCT of four weeks of intermittent TBS over the posterior superior temporal sulcus targeting ASD symptoms in children with ASD without co-occurring intellectual disability (n=76, age range=8-17 years). The single-blind RCT was followed by a 4-week open-label

extension phase where TBS treatment was given across groups, with a follow up assessment at week 12. Although findings from the first 4-week single-blinded phase of the study showed no advantage of active over sham rTMS, improvement in ASD symptoms from baseline to follow-up at week 12 was found across study participants (i.e., across participants regardless of whether they were initially randomized to active or sham treatment) (19). Similarly, Ameis et al. (20) did not find a significant difference between active and sham treatment following a 20-session treatment course of high frequency 20Hz (90% RMT) rTMS to bilateral DLPFC, targeting executive function deficits that used a randomized, double-blind sham-controlled study design in a pilot sample (n=40 participants aged 16-35 years with ASD without intellectual disability). However, a subgroup of the clinical trial participants with lower baseline everyday functioning experienced greater improvement in executive function performance compared to the sham group following a course of rTMS. In the only other prospective, double blinded, randomized, sham-controlled study of a course of rTMS in individuals with a diagnosis of autistic disorder (without co-occurring intellectual disability), Enticott et al. (21) tested whether ten treatments of 5Hz deep rTMS at RMT to the bilateral dorsomedial prefrontal cortex improved self-reported social relating [based on self-report on the Ritvo Autism Asperger's Diagnostic Scale (RAADS)] and social cognitive performance in n=28 adults with age range 18-59 years. While a significant reduction in self-reported social relating impairment was found in the active vs sham group following stimulation, no active-sham difference on objective social cognitive performance measures was found (21). Of note, adverse events reported across RCTs including autistic children, youth and adults were mild to moderate (e.g., pain at stimulation site, headache) (19-21). Thus, while there is the potential for further rTMS treatment development in ASD for a variety of outcomes, the available rigorous research is limited to small samples without clear indication of preliminary efficacy. Therefore, no conclusions can be drawn nor is any protocol ready for translation to the clinical context.

Update on rTMS in ADHD: Three studies in a recent systematic review have applied rTMS in children and youth with ADHD, targeting either motor or DLPFC sites (16); including two randomized sham-controlled studies (22, 23) and one open-label tolerability and safety study (24), each including ≤ 25 participants, age range=7-20 years, and using heterogeneous treatment protocols. Treatment protocols involved single pulse 1Hz TMS then 1Hz rTMS (900 pulses) over the left motor cortex delivered in counter-balanced order, 30 minutes apart (22), a 2-week (10-session) treatment course with 10 Hz rTMS at 2,000 pulses per

session (23), and five consecutive daily sessions of 1 Hz rTMS to left DLPFC with a total of 1500 stimuli per session (24). While Weaver et al. (23) showed reduced ADHD symptoms following active rTMS, differences between sham and active rTMS arms were not significant. Helfrich et al. (22) suggested a decrease in intracortical inhibition but did not study change in clinical/behavioural symptoms after rTMS, and Gómez et al. (24) noted that qualitative reports from parents and teachers revealed improvements in inattentiveness and hyperactivity/impulsivity. However, without a control group, the reliability of this finding is unclear. It is promising that these studies only reported mild adverse events such as transient headaches, or scalp discomfort with stimulation.

Update on rTMS in Tourette's syndrome and tic disorders: Three studies have used rTMS to reduce tics targeting the supplementary motor area (SMA) due to its connections with cortical and subcortical motor areas (16, 25-27). Only the study by Wu et al. (27) involved a randomized, double blinded, sham controlled design. In this study, participants with Tourette syndrome/chronic tic disorders between 10 and 22 years of age (n=12) were randomized to functional MRI navigated sham or active 30Hz continuous theta burst stimulation (cTBS) on two consecutive days. No differences in tic reduction were identified between active and sham groups, though cTBS was well tolerated (27).

Tolerability of rTMS in Children and Youth

As with adults, rTMS appears to be well tolerated with few adverse effects reported when applied to child and youth research samples (2). As an example of the qualitative experience of undergoing rTMS, a sample of youth (n=24, age range 12-22 years) with treatment-resistant depression ranked rTMS as worse than playing games, watching TV, going to a birthday party, and a long car ride, *but better* than getting a shot at the doctor, going to a dentist, and throwing up, and 85% of the surveyed sample reported that they would undergo rTMS again (9). A review of 51 studies involving more than 513 young people between the ages of 2.5 to 17.8 years concluded that rTMS is safe and poses minimal risk to children and youth with neurologic and neuropsychiatric conditions (2). Seizures are the most serious potential side effect; however, seizure risk is extremely low (roughly 0.1%) in children when rTMS is delivered according to recommended safety guidelines (5). For context, the rate of these events is comparable to the incidence of spontaneous seizures in patients taking antidepressant medications (28). More common side effects are mild and transient: headaches (11.5%), scalp discomfort at

the stimulation site (2.5%), twitching (1.2%), mood changes (1.2%), fatigue (0.9%), and tinnitus (0.6%) (2). Mitigation strategies (e.g., offering earplugs to protect against sound effects of rTMS) may reduce discomfort with rTMS in children and youth (29). Although initial research indicates that rTMS is safe and tolerable in children and youth, further studies with larger samples, longer treatment duration, and follow-up periods are required to understand and further characterize the short and longer term effects of neurostimulation in this vulnerable group (2).

What would be needed for rTMS to be clinic ready?

Although we do not have a clear indication of efficacy for any mental health target in child and youth populations, we are aware of >50 published studies in >500 children between the ages of 2.5 and 17.8 years of age exploring potential therapeutic uses (2). Nonetheless, researchers need to confirm the efficacy of rTMS treatment in well-powered samples, and ensure that the adverse event profile remains mild to moderate (as current studies indicate). Not only are studies of larger samples required, but these studies should be rigorously designed with the appropriate control groups, and with the aim of identifying optimal treatment parameters. Furthermore, the field would benefit from a clear understanding of the long-term effects of rTMS, including the specific mechanisms of treatment efficacy and the potential influence of rTMS treatment on brain development. Once efficacy is established in particular clinical populations with specific clinical targets, further work will also be needed to refine and optimize precision targeting at the individual level.

More practically, rTMS is not currently scalable and is primarily offered at tertiary care centres servicing individuals with complex mental health presentations. As rTMS becomes increasingly available (e.g., in the community), clinicians will need standardized treatment approaches and parameters for treatment of specific neuropsychiatric conditions along with clear criteria for when rTMS is indicated along a standardized clinical treatment pathway (13, 30). It is important to note that the limitations of the rTMS literature are not unique and similar challenges are present across treatment efficacy research (i.e., for pharmacologic and psychosocial interventions) in children and youth, including methodological design limitations in RCTs, significant variability in outcomes reported, and lack of long-term data for most current indications (31, 32).

What is on the horizon?

Emerging neurostimulation techniques include transcranial direct stimulation (tDCS), transcutaneous vagus nerve stimulation (tVNS), magnetic seizure therapy (MST), and deep brain stimulation (DBS). However, like TMS, there is a paucity of data applying these interventions to child and youth populations. Like rTMS, tDCS is generally safe and well tolerated in children (33). However, tVNS, MST, and DBS are invasive and carry significant risks, of particular consideration in applying these treatments for vulnerable child/youth populations (34).

What are the potential advantages of developing rTMS as an intervention in children and youth?

Currently, 40% of adolescents with major depressive disorder (MDD) fail to respond to treatment with an antidepressant medication or evidence-based psychotherapy (14), resulting in treatment-resistant depression. In successfully treated youth, the relapse rates for depression are as high as 50-75% (15). Additional limitations include the need for monitoring adherence to antidepressant medications which are often discontinued due to difficulties tolerating side effects (15). In autism, there are no effective biomedical interventions that target core symptoms. Although rTMS requires a commitment of time and resources up front, it is an attractive option as it targets specific brain circuitry, treatment can be personalized and its use may limit or eliminate the need for long term medication treatment or monitoring for adherence. rTMS may also be helpful in minimizing multiple psychotropic medication treatments used in treating refractory depression and the resulting exposure to adverse effects (35).

While rTMS is unlikely to take the place of more accessible treatments, rTMS may in future provide a valuable alternative mental health treatment option, particularly for those individuals where conventional treatments are inaccessible, poorly tolerated, or ineffective. The fact that at least half of mental health conditions have their onset in the adolescent period (36, 37) and evidence that ineffective treatment leads to long term morbidity underscores the critical need to develop promising new mental health treatments for children and youth (38). Thus, while rTMS is not clinic-ready for any mental health target in children and youth, for the above reasons, further research and development of rTMS intervention options are critically needed.

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Conflicts of Interest

The authors have no conflicts of interest to declare.

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