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Transcranial Magnetic Stimulation for Adolescent Depression

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SYNOPSIS

Adolescent depression is a substantial global public health problem that contributes to academic failure, occupational impairment, deficits in social functioning, substance use disorders, teen pregnancy, and completed suicide. Existing treatment options often have suboptimal results and uncertain safety profiles. Transcranial magnetic stimulation may be a promising, brain-based intervention for adolescents with depression. Existing work has methodological weaknesses and larger, neurodevelopmentally informed studies are urgently needed. Treatment with transcranial magnetic stimulation may modulate cortical GABAergic and glutamatergic imbalances. Future study could inform dosing approaches for TMS based on GABAergic and glutamatergic biomarkers.

Keywords

adolescent; brain stimulation; depression; GABA; glutamate; neuromodulation; transcranial magnetic stimulation; TMS

Introduction

Adolescent Major Depressive Disorder (MDD) is a major public health problem with a lifetime prevalence estimated as high as 14–20% in epidemiological studies.[1] Worldwide,

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MDD is a leading cause of disease burden.[2,3] Adolescent depression frequently involves a profound biologic component and ensuing delayed recovery, frequent recurrences, comorbidity, substance abuse, and increased risk for suicide.[1,4] Initial management of moderate to severe MDD in adolescents involves treatment with psychotherapy and selective serotonin reuptake inhibitors (SSRIs).[5,6] Remission rates and outcomes are often poor as this treatment does not target relevant, underlying adolescent pathophysiology.[5,7] Ongoing controversy regarding the effectiveness and safety of SSRIs in young individuals underscores the importance for an improved understanding of the biological mechanisms involved in adolescent depression.[8,9] Finally, access to evidence based psychotherapy is often limited.[10]

Transcranial magnetic stimulation (TMS) has increasingly been considered as an investigational treatment for adolescents with depression who do not respond to standard treatment modalities such as cognitive behavioral therapy and SSRIs.[11,12] Treatment with TMS involves the stimulation of cortical neurons with magnetic pulses and is now widely available as a clinical treatment for adults. Current FDA cleared TMS treatments involve 5 daily treatments per week, for 4–6 weeks, with 10 Hz, 120% motor threshold stimulation applied to the left dorsolateral prefrontal cortex.[13–15] Early adolescent research was informed by this approach but there is a formidable parameter space (for example, coil location, frequency, intensity, duration of treatment, concurrent interventions, and brain state during treatment) to consider for TMS treatment.[16,17] The heterogeneity of depression in adolescents arguably presents an added layer of complexity.[1,16,18]

Types of TMS

Early therapeutic TMS research and clinical practice for depression in adults has largely utilized low frequency (1Hz) or high frequency (5–20 Hz) stimulation over the dorsolateral prefrontal cortex.[13,19] There have been a variety of variations in dosing with time to include deep TMS, accelerated protocols, synchronized TMS, priming protocols, and patterned stimulation.[20] More contemporary work has examined theta burst stimulation (TBS) dosing strategies as potentially more efficient and durable pulse sequences for the modification of cortical activity.[21] Treatment with TBS holds the promise of reducing the time burden of treatment for patients. TBS sequences deliver groups of three high frequency pulses (50 Hz) with interstimulus intervals of 200 ms (5 Hz). There are 2 primary TBS patterns that are thought to have discordant neurophysiological effects.[21,22] Continuous theta burst stimulation (cTBS) involves the delivery of TBS pulses without interruption (typically 20–40 seconds 300–600 pulses) and is thought to decrease cortical excitability.[22] Intermittent theta burst stimulation (iTBS) delivers 2 second trains of TBS (30 pulses) every 10 seconds and is thought to increase cortical excitability.[22,23] Recent work in adults with treatment resistant depression suggests that iTBS may be equivalent to standard 10 Hz rTMS in terms of effectiveness, safety, and tolerability.[24]

Studies of TMS in Depressed Adolescents

Table 1 summarizes existing therapeutic studies of TMS for adolescents with depression. At present there are 10 publications describing the treatment of 112 unique participants.[12,25–33]

Existing literature is almost entirely comprised of case reports and open-label studies. The 2006 study by Loo and colleagues[26] describes a randomized controlled trial. However, the results from 2 participants assigned to active TMS treatment are all that is described in the publication.[26] The study by Lee and colleagues[30] describes the treatment of 25 children with Tourette syndrome. These participants did not have a diagnosis of MDD at baseline. However, depressive symptoms were tracked and demonstrated group level improvement over the course of TMS treatment.[30] This study is also unique and important to consider as it examined 1 Hz TMS which has not been adequately studied in child and adolescent populations with psychiatric disorders.[11] Otherwise, the majority of studies examined 10 Hz TMS sessions with protocols adapted from landmark adult studies of TMS.[12,14,15,26–28,31,34] Farzan and colleagues[32] have pioneered work with iTBS in adolescents and young adults. Given the increased efficiency of iTBS in terms of both delivery and potential impact on synaptic plasticity, this line of research is critical for future optimization of TMS protocols involving adolescents.[32,35]

Safety

Systematic data on the safety of TMS in children and adolescent are lacking.[11,36] While, generally considered safe, TMS interventions could have divergent tolerability and safety profiles across various stages of neurodevelopment. Common concerns include the rare risk of seizure induction, adverse neurocognitive effects, new or exacerbated psychiatric symptoms (such as increased suicidality, hypomania, or mania), aberrant alterations in neuroplasticity, and pain related to the procedure.[36] Recent, erudite commentaries have highlighted these concerns and the depth of existing knowledge gaps.[37,38]

Krishnan and colleagues[36] recently reviewed existing literature focused on both TMS and transcranial current stimulation. The review included data from 35 publications focused on the use of TMS in children and adolescents 3–18 years of age. There were very few reported adverse events or tolerability problems among the 322 participants undergoing TMS procedures. Four of these participants (1.2%) had a major negative side effect. Two participants (0.62%) had a seizure and two other participants had syncopal episodes (0.62%). Minor side effects such as headache (11.5%) and scalp pain (2.5%) were described as short-lived and typically resolved without intervention or with the use of over the counter nonsteroidal anti-inflammatory drugs. Other reported adverse events included musculoskeletal problems, twitching, and fatigue. These effects were described as mild and transitory. These data are encouraging and suggest that TMS is relatively safe and tolerable in children and adolescents with appropriate precautions. However, existing work also underscores that in a majority of instances, systematic adverse effect and tolerability data from TMS exposure in children and adolescents are not collected. Systematic, long-term, follow-up studies are also lacking.[36]

The clinical effects and safety of TMS have been examined in numerous other publications.[20] Published guidelines have been successful in ensuring subject safety.[39–41] In most cases TMS cannot be applied to individuals with metal in their head (except the mouth). The greatest safety concern is the potential of inducing a seizure. The risk of this is small even with rTMS. The incidence of this has been estimated as no greater than 0.1 to 0.6 % (or 1–6

in 1,000), which is comparable to the incidence of spontaneous seizures in patients taking antidepressant medications.[42] In cases in which seizures have been induced in participants, these individuals have recovered with no recurrences.[36,39,43] There are 3 prior reported seizures in adolescents receiving TMS.[44–46] In 2 instances the participants were concurrently taking epileptogenic medications (sertraline and olanzapine).[44,45] One of these participants had also consumed large amounts of alcohol prior to the TMS session (a reported 0.20% blood alcohol level 30 minutes after the seizure).[44] In another instance a depressed patient with no risk factors had a seizure with the application of deep TMS.[46] Presently, it is not clear if the risk for seizure induction during TMS with adolescents is different from that of adults.[43]

Recent Studies

In 2015, NeuroStar Advanced Therapy® launched the largest, randomized controlled trial of TMS for adolescents (12–21 years of age) with MDD to date.[47] This trial is scheduled to conclude in late 2018 and will examine the safety and efficacy of NeuroStar TMS® in approximately 100 adolescent participants. The protocol is a randomized, sham-controlled, triple-masked design for the acute treatment of MDD, with a subsequent open-label phase and posttreatment follow-up study. Eligible patients are adolescents aged 12–21 with MDD that has failed to respond to at least 1 but not more than 4 prior antidepressant trials. Phase I offers 6 weeks of either active 10 Hz TMS or sham treatment applied to the left dorsolateral prefrontal cortex. Phase II provides 6 weeks of open-label 10 Hz TMS to patients who did not receive protocol-defined clinical benefit in Phase I. Patients with protocol-defined clinical benefit in Phase I or II are eligible for Phase III, a 6-month follow-up study that provides retreatment with TMS for the re-emergence of depressive symptoms. The protocol and study will provide the largest data set to date for the examination of tolerability, safety, and clinical effects of 10 Hz TMS for MDD in adolescents.[47]

Future Directions

Neurostimulation technologies such as TMS have great potential as enduring, brain-based interventions for depression in adolescents.[11,35] Treatment with rTMS likely addresses pathologic imbalances in cortical GABAergic inhibitory and excitatory glutamatergic frontolimbic neurocircuitry.[35,48] However, at present there are many unknowns regarding optimal stimulation parameters and potential biomarkers for depressed adolescents receiving TMS.[11,16] Later this year, a National Institute of Mental Health funded, dose-finding, biomarker validation, and effectiveness study of 1 Hz vs. 10 Hz TMS for adolescents with depression will begin enrollment with the aim of addressing these questions (NIMH R01MH113700).[49]

Imbalances in GABAergic and glutamatergic tone play a key role in depression,[50,51] pathophysiologic stress responses,[52,53] and emotional numbing or anhedonia found in behavioral manifestations of the negative valence system.[54] These GABAergic and glutamatergic imbalances have differential causes, effects, and behavioral manifestations in adolescents as compared to adults.[50,54–57] For example, recent preclinical work has demonstrated that repeated stress in adolescent rats inhibits GABAergic projections to the

amygdala thereby impairing regulatory neurocircuitry.[58] In adult rats, chronic stress facilitates glutamatergic excitatory neurotransmission with ensuing effects on the lateral nucleus of the amygdala, hippocampus, and frontal cortex.[58–62] Developmental differences in frontolimibic GABAergic and glutamatergic tone may underlie variances in adolescent depressive symptom presentations and treatment responsivity.[54,62] A deeper understanding of frontolimbic GABAergic and glutamatergic tone in adolescent depression would assist with precision medicine approaches and intervention development.[16] Transcranial magnetic stimulation (TMS) and magnetic resonance spectroscopy (MRS) provide complementary measures or cortical GABAergic and glutamategeric tone.[63–66] Single and paired-pulse TMS paradigms are used to study the physiology of the brain. Neurophysiological measures collected with transcranial magnetic stimulation (TMS) such as intracortical facilitation (ICF), short-interval intracortical inhibition (SICI), long-interval intracortical inhibition (LICI), and the cortical silent period (CSP) are noninvasive measures of cortical GABAergic and glutamatergic tone.[65–67] Prior work suggests that ICF is a valid marker of glutamatergic tone and it may have utility as a biomarker for depression in adolescents.[56,68] Ultra-high field, 7 tesla (7 T) MRS adequately quantifies GABA, glutamate, and glutamine concentrations in the cortex for complementary data examining GABAergic and glutamatergic tone.[69] Concurrent measures with TMS neurophysiological paradigms and 7 T MRS would provide a refined understanding of GABAergic and glutamatergic tone in disorders of the negative valence systems and mechanistic studies of brain stimulation treatments such as TMS.[69,70]

Figure 1 summarized the protocol of the pending study. Participants in Phase I will be stratified based on ICF testing (high or low) at baseline. An ICF of >1.5 at baseline is considered “high” and an ICF ≤ 1.5 is considered “low”. After stratification, adolescents are randomized to either LDLPFC 1 Hz rTMS with 2400 continuous pulses per session at 120% motor threshold or LDLPFC 10 Hz rTMS with 4 seconds on 36 seconds off for 2400 pulses each session at 120% of resting motor threshold. Hence sessions in each treatment arm with two different types of rTMS (1 Hz and 10 Hz) will have identical intensities (120% motor threshold) durations (40 minutes), number of pulses (2400), and treatment location (LDLFPC). Participant non-responders in Phase I will be offered to the opportunity to enroll in a Phase II. Participants will be undergo therapeutic rTMS sessions with a Neurostar XPLOR system® magnetic stimulator. The research team will localize rTMS treatment sites with the Beam F3 method.[71] Prior research demonstrates that this is a valid and reliable method for scalp location of the dorsolateral prefrontal cortex with comparable results to more expensive, time intensive, MRI-guided approaches.[72] Our prior research demonstrates that the Beam F3 method is a feasible and reliable method for rTMS treatment localization in adolescents.[12] Efficacy measures (Children’s Depression Rating Scale Revised [CDRS-R])[73] and TMS biomarkers will be collected at baseline and weekly. The TMS biomarker panel includes ICF, Motor threshold (MT) Short-interval intracortical inhibition (SICI), long-interval intracortical inhibition (LICI), and cortical silent period (CSP). Adolescent participants receiving TMS will have the opportunity to undergo pre and post 7 T MRS scans to collect cortical GABA, glutamate, and glutamine levels.[49]

Participants in Phase II will be assigned to 2 weeks of cTBS if their intracortical facilitation measure (baseline assessment for TBS extension trial) is >1.5. Participants will be assigned

to 2 weeks of iTBS if their ICF (baseline assessment for TBS extension trial) is < 1.5. Extension trial TBS will be applied to the LDLPFC with the Beam F3 method. Participants receiving cTBS will receive 10 daily (5 sessions per week for two weeks) 120 second trains of uninterrupted TBS for 1800 pulses at 80% motor threshold. Participants receiving iTBS will receive 10 daily (5 sessions per week for two weeks) 2 second trains every 10 seconds for a total of 570 seconds for 1800 pulses at 80% motor threshold. Efficacy measures (CDRS-R) and TMS biomarkers will be collected at baseline, 1 week, and 2 weeks. The TMS biomarker panel includes ICF, Motor threshold (MT) Short-interval intracortical inhibition (SICI), long-interval intracortical inhibition (LICI), and cortical silent period (CSP).[49]

Summary

Safe, effective, brain-based treatments for depression in adolescents could alleviate substantial morbidity and mortality.[16] Early investigational TMS for adolescent depression is promising.[11,36] These data suggest that the clinical effects, safety, and tolerability of TMS in adolescents may be similar to what has been described in adults.[11,36] However, enthusiasm must be tempered by considerations for neurodevelopment and the unknowns associated with TMS exposure in adolescents.[16,37,38] Larger studies will soon provide more systematic data to examine the clinical tolerability, safety, and clinical effects of TMS in adolescents with depression.[47] Planned dose-finding and biomarker development studies hold the prospect of expanding the knowledge base of TMS use in depressed adolescents, the pathophysiology of depression in youth, and how TMS modulates cortical GABAergic and glutamatergic neurochemistry.[49]

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KEY POINTS

- Adolescent depression is a substantial global public health problem which contributes to academic failure, occupational impairment, deficits in social function, substance use disorders, teen pregnancy and completed suicide.
- Existing treatment approaches such as psychotherapy, pharmacotherapy, or combination treatment often have suboptimal results and uncertain safety profiles.
- Brain stimulation modalities such as transcranial magnetic stimulation have the potential for enduring, brain-based interventions for adolescents with depression.
- Existing work with transcranial magnetic stimulation in adolescents is nascent and larger, developmentally informed studies are needed.
- Treatment with transcranial magnetic stimulation may address imbalances in cortical GABAergic and glutamatergic neural circuitry.

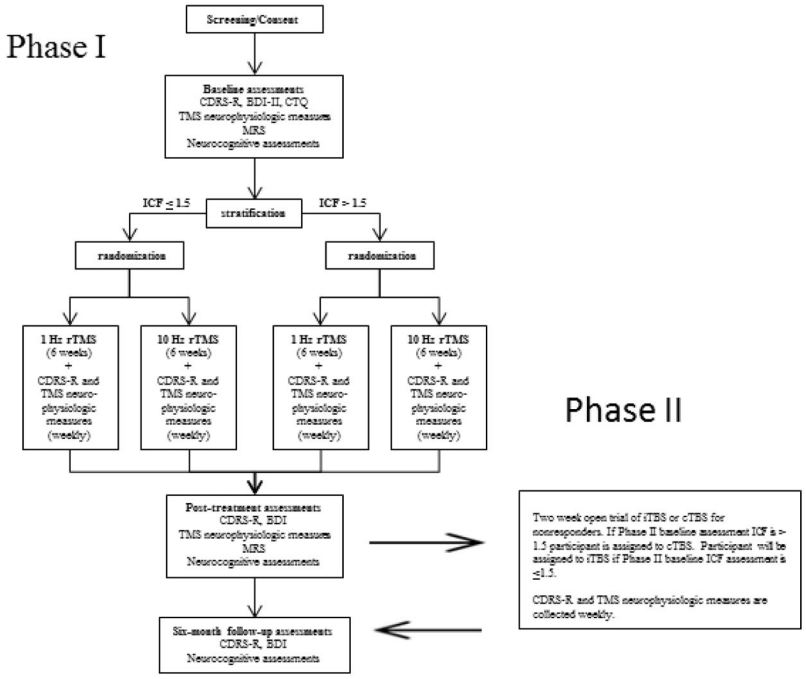

Figure 1.
Study schema

Table 1

Summary of Therapeutic TMS Studies for Adolescent Depression

References	N	Mean Age (yrs)	Frequency	Intensity	Location	Clinical Outcome
Walter et al. 2001	4	16	1–10 Hz (variable)	90–110%	LDLPFC	2 responders (one non-responder had bipolar depression)
Loo et al. 2006	2	16	10 Hz	110%	LDLPFC	2 responders
Bloch et al. 2008	9	17	10 Hz	80%	LDLPFC	3 responders 1 partial responder
Wall et al. 2011	8	16	10 Hz	120%	LDLPFC	6 responders
Mayer et al. 2012 (3 year follow-up from Bloch et al. 2008 study)	8	17	10 Hz	80%	LDLPFC	Improvement in depressive symptoms was durable at follow-up
Le et al. 2013	25	11	1 Hz	110%	SMA	Group level improvement in depressive symptoms
Yang et al. 2014	6	18	10 Hz	120%	LDLPFC	4 responders
Wall et al. 2016	10	15	10 Hz	120%	LDLPFC	6 responders
Farzan et al. 2017	16	21	iTBS and cTBS	80%	LDLPFC (iTBS) RDLPFC (cTBS)	4 responders 9 partial responders
MacMaster et al. 2018	32	17	10 Hz	120%	LDLPFC	18 responders

cTBS: continuous theta burst, Hz: hertz, iTBS: intermittent theta burst, LDLPFC: Left Dorsolateral Prefrontal Cortex, RDLPFC: Right Dorsolateral Prefrontal Cortex, SMA: Supplementary Motor Area

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