Transcranial Magnetic Stimulation in Children and Adolescents: A Review

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Abstract

Repetitive Transcranial Magnetic Stimulation (rTMS) has been approved for major depressive disorder in adolescents. We review evidence of the use of repetitive rTMS for Attention-Deficit, Hyperactivity Disorder (ADHD), autism spectrum disorder (ASD), schizophrenia, Tourette's syndrome, depression, bipolar disorder, impulsivity, and borderline personality disorder (BPD) in adolescents. rTMS improves behavior and global functioning and reduces symptom severity in ADHD. Combined with atomoxetine, it improved attention, hyperactivity, and overall functioning. For ASD**,** rTMS decreased irritability, repetitive behaviors, and aggression. For schizophrenia, rTMS decreased auditory hallucinations and improved both positive and negative symptoms, agitation, and overall functioning. For Tourette's Syndrome, rTMS reduced tic and obsessive-compulsive disorder symptoms and overall illness severity. rTMS reduces depressive symptoms. Some studies showed improvement in suicidal ideation following rTMS treatment, while others showed no difference from sham. Combining rTMS with sertraline improved mood and cognitive function. Bipolar depression and bipolar mania did not improve with rTMS. A study for bipolar II reported improvement in depressive symptoms and executive function following

intermittent theta burst stimulation. rTMS reduced impulsive decision-making in healthy controls. For borderline personality disorder**, a** case study showed short-term improvements in depression, impulsivity, and emotional regulation. Two randomized controlled trials (RCTs) showed improvements in affective instability, anger, and planning, along with reductions in symptom severity, impulsivity, depression, and anxiety, respectively, following rTMS. Preliminarily, current evidence supports rTMS as a promising treatment modality.

Introduction

rTMS is being explored as a treatment option for adolescents diagnosed with depression, OCD, ASD, ADHD, and other psychiatric conditions. Research is ongoing to determine the efficacy and safety for children and adolescents. Researchers wonder whether the developing brain responds differently to magnetic stimulation than an adult brain does. Studies typically focus on determining safe parameters, including appropriate stimulation intensities and frequencies, to minimize potential adverse effects on brain development. Evidence regarding the efficacy of rTMS in children is still emerging and tends to be more limited compared to adults. While some studies show promising results, particularly for treatment-resistant conditions like depression and OCD, larger RCTs are needed to establish their effectiveness across different age groups and conditions. Ongoing research aims to better understand rTMS mechanisms in pediatric populations, optimize treatment protocols, and identify which children will most likely benefit from this therapy. Long-term studies are also needed to assess the durability of treatment effects and any potential impact on cognitive development.

The goal of this article is to summarize the findings of prior studies that explore rTMS as a potential treatment modality for children and adolescents with ADHD, ASD, schizophrenia, Tourette's syndrome, depression, impulsivity, and BPD.

Methods:
Scholar Google, Perplexity A.I., ChatGPT, and the University of Maine Libraries Search Engine were used to identify studies conducted on TMS with adolescents. All relevant studies were included.
ADHD
ADHD is a common neurodevelopment disorder among children in the United States, and the US Food and Drug Administration has approved stimulants, including methylphenidate and amphetamine, as treatment options for both adults and children with ADHD About 10-30% of patients do not respond to these treatment options, others experience adverse effects, and patients with addiction may be excluded from the use of these medications [1]. While non-stimulant medications and psychotherapy for ADHD exist, treatment for some remains inadequate. Therefore, rTMS of the brain may be an alternative treatment for adolescents with ADHD.
In 2008, Weaver et al. did a randomized sham-controlled crossover trial to assess the safety and efficacy of rTMS in patients diagnosed with ADHD per the Diagnostic and Statistical Manual of the American Psychiatric Association Version 4 (DSM-IV) criteria [2]. Following a screening phase, there were two treatment phases -- active rTMS and sham -- each lasting 2 weeks, with a 1-week no-treatment interval in between. Six of the nine participants were 18 or younger and were randomized to

active vs. sham treatment. Participants also had a 7-12-day washout for medications prescribed for ADHD before the screening phase. Participants received 5 sessions per week (10 sessions total during the active phase) of rTMS to the right dorsolateral prefrontal cortex (DLPFC) at 10 Hz, 100% of the observed motor threshold, for 2,000 pulses per session. At baseline, halfway, and at the end of the trial, the Clinical Global Impression Improvement Scale (CGI-I) and ADHD scale were assessed. There was improvement on the CGI-I and ADHD scales across both phases combined, without significant differences in efficacy between the active and sham phases. rTMS was well tolerated, with no adverse events during treatment.

In 2017, Rubio, et al. conducted a literature review around the use of rTMS in pediatric ADHD [3]. Their review further documented the safety of rTMS in over 800 healthy children and over 300 children with neurologic abnormalities.

In 2018, Cao et al. conducted a 6-week study with 64 patients newly diagnosed with ADHD from January 2016 to October 2017, ages 6-13 [4]. Participants were randomly assigned to either the rTMS group, the atomoxetine group, or the rTMS + atomoxetine group [4]. rTMS was delivered in 1 25-minute session per day for 5 days per week for 6 weeks, and the atomoxetine dose was titrated to 1.2 mg/kg/day [4]. The Swanson, Nolan, and Pelham questionnaire (SNAP-IV), based on the diagnostic criteria of ADHD in DSM, was used to assess symptoms of ADHD before treatment and 6 weeks after treatment. The questionnaire consists of 26 items that focus on attention deficit, hyperactivity, impulsivity, and oppositional defiance. SNAP-IV questionnaire scores were statistically significant for attention-deficit/hyperactivity disorder, hyperactivity, impulsivity, and oppositional defiant disorder ($P < 0.05$) before and after treatment in the rTMS group, the atomoxetine group, and the rTMS + atomoxetine group. The rTMS + atomoxetine group showed greater improvements in attention-deficit/hyperactivity impulsivity, but not in oppositional defiance, as measured by pre- and post-treatment scores for each item, compared with the rTMS and atomoxetine groups alone. The study also assessed "cold" (attention deficit) and "hot" (impulsivity) executive functions in each group using the Wisconsin Intelligence Scales for Children (WISC) and the Iowa Gambling Task, respectively. The WISC test consisted of 3 subtests of the Continuous Performance Test: arithmetic (mental math), digit span (forward and backward), and coding (each figure corresponds to a symbol the participant fills in). While all three treatment groups showed improvement in both cold and hot executive functions, the rTMS + atomoxetine group had a greater effect on forward/backward number repetition and the Iowa Gambling Task, suggesting its superiority in improving ADHD symptoms compared to rTMS or pharmacological treatment alone.

In 2019, Masuda, et al. conducted a systematic review on the efficacy of rTMS in children and adolescents diagnosed with ADHD [5]. Trials conducted by Gomez et al. [6] and Weaver et al. [2] used rTMS to treat ADHD in children aged 7-12 years and adolescents aged 14-21 years. Both trials showed improved behavioral rating scores in these patient populations.

Between 2019 and 2021, Nagy et al. conducted a double-blind, randomized sham controlled clinical trial on 60 children ages 6-12 years old [7]. Thirty of the participants received 15 sessions (5 sessions per week for 3 weeks) of rTMS over the right DLPC along with atomoxetine that was titrated up to 1.2 mg/kg/day, while the other thirty participants received 15 sessions of sham rTMS and atomoxetine 1.2 mg/kg/day. All participants stopped all other medications 2 weeks before beginning the study and they were drug naïve to both stimulants and non-stimulants. To assess the severity of ADHD symptoms all participants completed the Arabic version of Conners' Parent

Rating Scale-Revised Long form (CPRS-R-L), Children's Global Assessment Scale (CGAS), and Clinical Global Impression (CGI) at the beginning of treatment (pre), after receiving 15 sessions of rTMS/sham rTMS (post), and 1 month after treatment (follow-up). Scores for the pre-, post-, and follow-up were compared to assess improvement in clinical symptoms. It was found that the rTM group had a statistically significantly lower DSM-IV inattentive total score than the sham rTMS group, both during post- and follow-up testing. There was a statistically significant improvement in the rTMS group compared to the sham rTMS group in the hyperactive-impulsive score only at the posttest. The rTMS group improved significantly more in mean CGAS scores than the sham group both during post-treatment and follow-up. With the CGI-severity score, the rTMS group showed a statistically significant greater improvement in CGI than the sham group, both post-rTMS and at follow-up. This study revealed that rTMS combined with atomoxetine is an effective treatment for children with ADHD and is more effective than atomoxetine alone in improving inattention, total ADHD symptom severity, and global functioning.

Autism Spectrum Disorder

In 2010, Baruth et al. tested 12 sessions of bilateral low-frequency rTMS on 25 subjects aged 9-26 diagnosed with ASD and 20 age-matched controls [8]. After treatment, participants showed a decrease in repetitive and restricted behavior, as measured by the Repetitive Behavior Scale (RBS), and a statistically significant reduction in irritability, as measured by the Aberrant Behavior Checklist (ABC). Notably, no significant changes were observed in social awareness or hyperactivity. Baruth et al. also studied 13 subjects aged 9-27 with high-functioning ASD who received six low-frequency rTMS treatments over 3 weeks. After treatment, participants showed decreased repetitive-ritualistic behavior, as measured by the RBS. Social awareness, irritability, and hyperactivity did not change.

In 2010, Enticott et al. reported a case of a 20-year-old woman with Asperger disorder who received nine sessions of deep rTMS targeting deep cortical structures, consisting of 15 min of 5 Hz rTMS at 100% resting motor threshold [9]. The women reported no adverse side effects and showed improvement after treatment at the one-month follow-up on the Interpersonal Reactivity Index, the Autism Spectrum Quotient, and the Ritvo Autism Asperger Diagnostic Scale. Additionally, the subject's family noticed an improvement in her social functioning. Specifically, the subject's mother described her as more considerate of others and more affectionate. She made more eye contact and showed greater interest in relationships and social situations. She was more confident, happier, and more tolerant of people.

A collection of studies from 2020 to 2025 has further supported the role of TMS in autism. In a 2024 Systematic Review of 17 Studies, rTMS improved core ASD symptoms (behavior, social, and verbal domains) [10]. A 2025 experimental study showed that rTMS could reduce hyperplasticity in AS [11]. A 2020 review found that rTMS improved symptoms, quality of life, and sleep in children across 13 studies [12]. A 2022 meta-analysis showed a 25% prevalence of mild adverse events (AEs); the safety profile was generally favorable [13]. A 2024 pre-clinical study showed that high-frequency rTMS improved ASD symptoms in animal models [14].

Among 17 studies selected and reviewed that took place between 2018 and 2023, four studies focused on subjects without intellectual disabilities (ID), four studies on subjects with ID, one study included subjects with a full-scale intelligence quotient (IQ) greater than 50, and the other studies did not give specific information [10]. Most study subjects were male, with only one study including a small sample of 5 female participants. The subjects' age ranged from 2 to 30 years. Seven were RCTs; the

remaining ten were open-label studies. Most studies focused on stimulating targets in the DLPFC, as this brain region plays a pivotal role in social, cognitive, and emotional functions. According to a recent consensus statement for rTMS for ASD, three cortical sites are generally agreed in particular: (1) the right inferior frontal gyrus targeting social impairments and communicative deficits, (2) the right temporoparietal junction/posterior superior temporal sulcus targeting theory of mind, social comprehension, and attention, and (3) the left dorsolateral prefrontal cortex targeting comorbid depressive disorder and executive dysfunction [15].

There is limited but suggestive evidence that rTMS may reduce aggression and violence in individuals with ASD [16]. This 2020 systematic review found that, while most studies in healthy individuals did not show significant reductions in anger or irritability with rTMS, a few pilot studies in patients with ASD reported that bilateral prefrontal cortex stimulation could satisfactorily reduce anger and irritability. The review also noted that combining brain stimulation with medications like risperidone further reduced aggressiveness in these patients.

Schizophrenia

In 2001, Walter et al. described three 18-year-old males diagnosed with schizophrenia who underwent 10 sessions of 20 Hz rTMS daily to the right frontal cortex [17]. While all subjects reported no adverse effects, two showed improvements in rating scales of both positive and negative symptoms. The third subject had improvement in hallucinations, agitation, and global functioning.

Fitzgerald et al. documented a case study where an 18-year-old female with chronic schizophrenia, diagnosed at age 9, had resistance to pharmacologic treatment, including clozapine [18]. She received 10 sessions of 1 Hertz (Hz) rTMS at 90% motor threshold applied to the left temporoparietal cortex. Measured per the Hallucinations Change Scale and the Positive and Negative Syndrome Scale, the patient had a reduction in the severity of her hallucinations following treatment. After another clozapine trial 6 months later, she received the same rTMS course, which resulted in temporary clinical improvement. Three months after that, she received a third rTMS course.

Jardri et al. described an 11-year-old boy with medication-resistant schizophrenia for two years who had a high level of impairment, aggression, and struggled with delusions and hallucinations [19]. Following treatment with 10 sessions of 1 Hz rTMS administered to the left temporoparietal cortex, he had a 50% decrease in his auditory hallucinations measured by the Auditory Hallucinations Rating Scale. He then received repeat sessions over the next 5 weeks, and his functioning improved, as measured by the Children's Global Assessment Scale. As a result of this treatment, he could go home and return to school. He experienced no adverse effects during his rTMS treatment.

Jardi et al. also conducted a case series of 10 adolescents with childhood-onset schizophrenia with drug-resistant auditory hallucinations (mean age 15.5 +/- 2.3 years old; male: female ratio 7:3) [20]. All participants received 18.5 ± 11.6 mg of Olanzapine equivalent for 8 weeks before the start of the study. Participants received 1,200 1-Hz rTMS pulses at 90% of the motor threshold, twice daily, for five consecutive days. The Auditory Hallucinations Rating Scale (AHRS) and the Global Assessment of Functioning Scale (GAF) were used to assess the severity of symptoms, and were done at baseline, immediately following treatment, and 1-month post-treatment. The differences between AHRD and GAS scores before and after rTMS treatment were compared with paired t-tests. The ADHS scores decreased significantly from baseline to immediate post-treatment assessment (p=.007) and

from baseline to the 1-month post-treatment assessment (p=.004). The GAF scores also significantly improved from the baseline to the immediate post-treatment assessment (p=.002) and from baseline to the 1-month post-treatment (p=.009).
Blanco-Lopez et al. describe a case of an 18-year-old female with schizophrenia with auditory verbal hallucinations who had previously trialed antidepressants, mood stabilizers, and antipsychotics with slight improvement in symptoms [21]. Before treatment, she scored 23 on the Patient Health Questionnaire (PHQ-9), five on the Inventory of Complicated Grief Scale (ICGS), and 25 on the Psychotic Symptoms Rating Scale (PYSRATS). While still on 350 mg/day clozapine, she received 10 daily sessions over two weeks of 1 Hz rTMS over the left temporoparietal cortex. Twelve hundred stimuli were delivered per session at 90% resting motor threshold. After the first round of rTMS treatments, the changes were minimal. The voice only stopped for 20 seconds on day 5 and 45 seconds on day 9, with the negative content of the voice remaining unchanged. Following a one-month hiatus from rTMS, the same treatment regimen was repeated. The patient stayed on clozapine during both the treatment and non-treatment periods. During the second round of rTMS on the 4th day, the voice stopped for 1 hour; on day 6, for 2.5 hours; on day 8, for 4 hours; and on day 9, the auditory hallucinations ceased completely. Without the voice, the patient had reduced distress, anxiety, and disruption of everyday life, thereby improving her quality of life significantly. After treatment, the patient had significantly reduced scores on the PHQ-9 and ICG tests, with scores of 7 and 1, respectively. At the seven-month mark, she was still not experiencing auditory hallucinations, and her clozapine was reduced to 300 mg/day.

Tourette's Syndrome

Based on the assumption that the pathophysiology of Tourette's syndrome involves the basal ganglia and a hyperactive motor cortex, rTMS has been studied as a potential treatment modality. A randomized, blinded, crossover study conducted in 2004 by Chae et al. involved 8 participants, 2 of whom were 19 years old, while the others ranged in age from 22 to 60 years, all with Tourette's syndrome [22]. Participants received either 1 Hz or 15 Hz rTMS at 110% of the motor threshold, or sham stimulation, over the left motor cortex or the left prefrontal cortex. Although there were no significant differences among treatments, there was improvement in tic and OCD symptoms, none of the subjects worsened, and rTMS was well tolerated.
Another open-label trial by Kwon et al in 2011 was conducted with 10 male children, aged 11.2 years +/- 2.0 years, with Tourette's syndrome [23]. They received 10 sessions of 1 Hz rTMS at 100% of the motor threshold, applied to the supplementary motor area [22]. Following treatment, tic symptoms, measured by the Yale Global Tourette's Syndrome Severity Scale and the CGI scale, improved over 12 weeks. All participants experienced no adverse effects from treatment nor any worsening of symptoms of ADHD, depression, or anxiety.

Depression

Major depressive disorder (MDD) in individuals aged 10-24 years old carries a significant disease burden, and about 1/3rd of these individuals who trial various antidepressants do not achieve resolution of their symptoms and develop treatment-resistant depression [24]. These individuals are often treated with polypharmacy, and treatment failure results in repeated hospitalizations, which can disrupt their development [25]. This highlights the need for alternative therapies to treat MDD in adolescents, such as rTMS.
In 2001, Walter et al. discussed the treatment of three adolescents with depression: 16 and one 17-year-old male received similar treatments of 2 weeks of 10 Hz rTMS

on the left DLPFC at 90% motor threshold, and another 17-year-old male with refractory major depressive disorder (MDD) as well as mental retardation and ADHD, received a similar rTMS treatment but with delivery at 110% motor threshold [26]. The 16-year-old male had an improvement in his depression and experienced no side effects from treatment. The 17-year-old boy had clinical improvement in his depression but experienced a tension headache as a side effect during two of the treatments. The latter 17-year-old boy had no clinical improvement but experienced no adverse effects.

In 2006, Loo et al. examined the safety and efficacy of rTMS in two 16-year-old girls in a randomized, double-blind, sham-controlled trial in which they received 10 Hz rTMS at 110% of the motor threshold for 4 weeks [27]. 'Mandy', subject 1, a 16-year-old, presented with a 2-year history of progressively worsening depressed mood, decreased interest in a range of activities, and expressed thoughts of self-harm without acting upon them. 'Karen', subject 2, a 16-year-old, presented with an 18-month history of worsening depressed mood, fatigue, lethargy, and suicidal preoccupation. They were blinded to the treatment allocation for the first four weeks of treatment. After four weeks, the subjects were allowed to continue with rTMS on an open basis. Mandy received 29 rTMS sessions over 6 weeks, whereas subject 2, Karen, tended to miss one session per week due to illness or schoolwork and experienced a 13-day interruption in treatment at the end of the 4-week blind phase. Karen then had 20 further sessions of rTMS on an open basis over 5 weeks, and her venlafaxine and methylphenidate were continued during treatment. Clinical response was assessed at baseline and at the end of each week. The following scales were administered by a psychiatrist who was blind to treatment category: the Montgomery-Asberg Depression Rating Scale (MADRS) and the CGI Severity Scale. The subject completed self-rating scales, including the Beck Depression Inventory and the Centre for Epidemiological Studies-Depression Scale for Children. To assess for change in neuropsychological functioning, the following cognitive tests were done at baseline, end of week 4 (post 20 treatments), and after rTMS treatment: Rey Auditory Verbal Learning Test, Wechsler digit span forwards and backwards and digit symbol modalities test, Trail Making Test A and B, Controlled Oral Word Association Test-letter and category. Overall, there were no significant changes in cognitive testing for either individual throughout the study. However, a clinically meaningful improvement in depression following rTMS treatment was observed for both individuals, with the improvement during the blind 4-week phase being particularly noteworthy. The improvement was sustained at 1 month follow up, consistent with results in adult rTMS treatment studies. Neither individual experienced side effects, suggesting the treatment was safe.

In 2008, Bloch, et al. published an open-label rTMS study of nine teenagers diagnosed with treatment-resistant depression who received 20 sessions of 10 Hz rTMS applied to the left DLPFC at 80% motor threshold for 20 minutes over two weeks [28]. All participants were high-functioning and were taking psychotropic medications during treatment. Per the Childhood Depression Rating Scales (CDRS) three of the participants responded to treatment.

In 2011, Wall et al. published an open-label trial involving eight adolescents with treatment-resistant depression who received SSRIs concurrently with 30 sessions of 10 Hz rTMS at 120% motor threshold over the DLPFC [29]. In these participants, the mean CDRS score improved significantly from baseline at the end of 30 sessions and at 6-month follow-up. No control group was included in this study, but it showed that

TMS was well tolerated, even with aggressive treatment regimens such as the protocol used in this trial.

In 2021, Zhang et al. studied 146 patients in the acute phase of depression [30]. Add-on rTMS treatment significantly improved suicidal ideation, especially in adolescents treated with the high frequency left DLPFC rTMS protocol

In 2021, Croarkin et al. conducted a randomized sham-controlled trial of 10 Hz of L DLPFC TMS in adolescents with treatment-resistant depression ages 12-21 [31]. Eligible participants were between 12 and 21 years old, met the DSM-5 criteria for diagnosis of unipolar MDD in a current major depressive episode without psychotic features, and had a Hamilton Depression Scale 24 (HAM-D-24) score of 2 or more for item 1 and a total score of 20 or more at screening. Of the 177 patients considered, 65 did not meet the inclusion criteria, and 112 were randomly assigned for acute rTMS treatment in phase I (54 in the active treatment group; 58 in the same group). Phase I of the trial involved 30 rTMS sessions over 6 weeks as monotherapy. After week 1 of screening, patients were randomly assigned in a 1:1 ratio of treatment and sham-treatment. Patients, treaters, and raters were blind to treatment assignments. Phase II involved a nonrandomized, open-label 30-treatment, 6-week rTMS, followed by a nonrandomized, open-label 6-month follow-up. Results showed that high frequency rTMS was tolerated and safe in adolescents with no adverse neurocognitive effects or structural brain changes. Both sham and active treatment groups experienced an improvement in depressive symptoms without statistically significant differences between groups. Croarkin and his colleagues hypothesized this was likely due to a high placebo response.

Hett et al. sought studies that used rTMS among people aged 12 to 25 years who had been diagnosed with depression. Fourteen studies were identified, including eight open-trial studies (N = 142 participants) and six follow-up studies using the same open-trial datasets. All studies reported reduced depression scores in adolescents using rTMS. A single study on theta burst stimulation also found a beneficial effect. No studies included a sham control. Side effects of rTMS included scalp pain, headache, and dizziness. Study methodologies precluded a meta-analysis [32].

They concluded that rTMS could reduce adolescent depressive symptoms, but sham-controlled randomized trials are needed. They concluded that rTMS may be a promising treatment option for adolescents with depression.

Sigrist et al. conducted a systematic literature review and synthesized data using random-effects models [33]. Ten studies (including 2 randomized trials) were included. Quantitative synthesis of aggregated data revealed statistically significant mean improvements (pooled SMCC = 2.04, 95% CI [1.46; 2.61], SE = 0.29, $p < .001$), as well as a significant overall treatment response rate (Transformed Proportion = 41.30%, 95% CI [31.03; 51.57], SE = 0.05; $p < 0.001$), considering data from baseline to post-treatment. Exploratory analyses suggested that rTMS might be more effective in younger individuals and individuals with more severe depression. Efficacy might be enhanced with more TMS sessions, longer treatment durations, and unilateral stimulation.

Qiu et al. conducted a meta-analysis to appraise rTMS in youth with MDD [34]. They included 13 studies with 6 datasets (165 patients; 61.8% female; age range: 10 to 25 years old). Their meta-analysis found that children and adolescents with MDD benefited from rTMS treatment (Hedges' g = 1.37, 95 % CI 0.85 to 1.90, P = 0.001). Four percent of patients (95 % CI 0.02 to 0.09) withdrew during rTMS treatment for reasons of fear, mood swings, suicidal ideation, and other adverse events. They

concluded that rTMS could benefit children and adolescents with MDD relatively safely.

Chen et al. explored the early effects of rTMS in combination with sertraline in adolescents with first-episode major depressive disorder [35]. They randomly assigned 100 teenage patients with first-episode depression to two study groups. Both groups were treated with sertraline. The study group received ten sessions of add-on rTMS. Depressive symptoms and cognitive function were assessed using the Hamilton Depression Rating Scale-17 (HAMD-17), the Children's Depression Rating Scale-Revised (CDRS-R), and the Integrated Visual and Auditory Continuous Performance Test (IVA-CPT). The number of early improvers after 2 weeks of treatment in the study group was statistically significantly higher compared to the control group (95.83% vs 73.47%, $\chi 2 = 9.277$, $P = 0.002$). There was a significant difference in responder rates (62.50% vs. 28.57%; $\chi 2 = 11.262$, $P = 0.001$) and in remission rates (31.25% vs. 6.12%; $\chi 2 = 10.130$, $P = 0.001$) between the two groups at 4 weeks. The scores on the HAMD-17 and CDRS-R in the study group were significantly lower than the control group (F group = 12.91 vs 10.21, $P < 0.05$). The Attention Quotient (listening, visual, and full-scale) of the IVA-CPT in the study group was higher than that in the control group after treatment, and the differences were statistically significant ($P < 0.05$). The study group showed higher Spotter scores than the control group after treatment ($P < 0.05$). Add-on rTMS accelerated the efficacy of the antidepressants, improving the depressive symptoms and cognitive function in first episode adolescent depression.

Cao et al. searched for randomized, controlled trials of rTMS combined with antidepressants in which treatment efficacy was assessed by changes in depression rating scale scores [4]. They assessed safety by the incidence of adverse effects. They identified 18 acceptable studies across 10 datasets (1,396 patients; 64.7% female; age range: 8–24). The pooled mean-endpoint scores of the depression scale for rTMS combined with the antidepressant group were significantly lower than those of sham combined with the antidepressant group both in two weeks (MD = -4.68, 95 % CI: [−6.66, −2.69]; I2 = 91 %; $P < 0.05$) and four weeks (MD = −5.53, 95 % CI: [−9.90, −1.16]; I2 = 98 %; $P < 0.05$). There were no differences in safety (OR = 0.64, 95 % CI: [0.20, 2.04]; I2 = 64 %; $P = 0.45$) and acceptability between the two groups (3/70 vs 3/70). They concluded that rTMS enhanced the efficacy of antidepressants for adolescents without any significant increase in adverse events.

Thai et al. conducted a pilot study of 15 adolescents with treatment-resistant depression (Age, years: M = 16.4, SD = 1.42) who completed a six-week daily rTMS protocol targeting the DLPFC (BrainsWay H1 coil, 30 sessions, 10 Hz, 3.6 s train duration, 20s inter-train interval, 55 trains; 1980 total pulses per session, 80 % to 120 % of motor threshold) [36]. Participants completed clinical, safety, and neurocognitive assessments before and after treatment. The primary outcome was depression symptom severity measured by the CDRS-R. Fourteen of 15 participants completed the rTMS treatments. One participant experienced a convulsive syncope: the other participants only experienced mild side effects (e.g., headaches). There were no serious adverse events, and cognitive performance showed minimal change. Depression symptom severity significantly improved pre- to post-treatment and decreased to a clinically significant degree after 10 treatment sessions. Six participants met the criteria for treatment response.

In 2022, Gordon et al. conducted a pilot randomized controlled trial of adolescents comparing rTMS applied to the left and right sides of the head, using CDRS-R depression scores at 1-month follow-up compared with baseline [37]. Fourteen adolescents who had been previously treated for MDD but had continued to suffer for an average of 2 years were randomly allocated to right (low frequency) or left (high frequency) rTMS applied to the scalp over the dorsolateral prefrontal cortex over 20 treatments for four weeks. CDRS-R scores improved significantly across the 20 rTMS treatments, with peak response at 1-month follow-up. Two (14%) adolescents had ≥50% improvement in score, and a further four (29%) demonstrated partial response (25-50% reduction) at 1-month follow-up. Treatment gains were sustained at 6-month follow-up. There was no significant difference in efficacy between left- and right-sided treatment. They concluded that adolescents with MDD benefited from rTMS.

Majumder et al. searched the Medline and Cochrane databases and included 18 articles in a systematic review [38]. They found level 1 evidence that rTMS is safe but failed to show its superiority to placebo as a stand-alone treatment for resistant depression among children and adolescents. They found level 2 evidence favoring add-on rTMS to medication to treat major depression among children and adolescents. Subjects tolerated rTMS treatment well with some minor and mostly self-limited side effects. Risks of treatment-emergent hypomanic symptoms and seizures were very low. Suicidal ideation or cognitive decline did not occur during rTMS treatment.

Jiao et al. evaluated the efficacy of repeated transcranial magnetic stimulation (rTMS) combined with fluoxetine in enhancing the early antidepressant response in 135 adolescents experiencing their first depressive episode [39]. Participants were randomly assigned to receive sham rTMS plus fluoxetine, or both rTMS and fluoxetine. Therapeutic effects were assessed by comparing changes in HAMD-17 scores, cognitive function scores on the Wisconsin Card Sorting Test (WCST), and CGI-I scores, and by recording adverse reactions. The total effectiveness rate in the rTMS groups (Low, 95.56%; High, 97.78%) was significantly higher than in the Sham rTMS group (80%) ($F = 11.15$, $P<0.0001$). Both high-frequency and low-frequency rTMS groups exhibited more significant reductions in HAMD-17 (Low, 21.05; High, 21.45) and CGI-I scores (Low, 3.44; High, 3.60) compared to the Sham rTMS group (HAMD- 17, 16.05; CGI-I, 2.57) (two weeks: $F = 7.889$, $P = 0.0006$; four weeks: $F = 15.900$, $p<0.0001$). The two rTMS groups exhibited fewer erroneous responses and persistent errors in the WCST and completed more WCST categorizations than the Sham rTMS group. There was no significant difference in adverse reaction rates between the groups ($F=4.421$, $P=0.0794$). They concluded that the combination of fluoxetine with rTMS demonstrates enhanced therapeutic effectiveness in treating adolescent depression, effectively controlling disease progression, reducing depressive symptoms, and improving cognitive function, making it a valuable clinical approach.

In 2023, Sun et al. Conducted a meta-analysis of RCTs to explore the therapeutic effects, tolerability, and safety of rTMS as an adjunct treatment in adolescents with first episode of major depressive disorder (FE-MDD) [40]. A total of six RCTs involving 562 adolescents with FE-MDD were included. Adjunctive rTMS was superior in improving depressive symptoms over the control group [standardized mean difference (SMD) = −1.50, 95% confidence interval (CI): −2.16, −0.84; $I2 = 89\%$, $p < 0.00001$] in adolescents with FE-MDD. Adolescents

with FE-MDD treated with rTMS had significantly greater response [risk ratio (RR) = 1.35, 95% CI: 1.04, 1.76; I2 = 56%, p = 0.03] and remission (RR = 1.35, 95% CI: 1.03, 1.77; I2 = 0%, p = 0.03) over the control group. All-cause discontinuations were similar between the two groups (RR = 0.79, 95% CI: 0.32, 1.93; I2 = 0%, p = 0.60). No significant differences were found regarding adverse events, including headache, loss of appetite, dizziness, and nausea (p = 0.14-0.82). Four out of six RCTs (66.7%) showed that adjunctive rTMS was more efficacious than the control group in improving neurocognitive function (all p < 0.05). They concluded that adjunctive rTMS was a beneficial strategy for improving depressive symptoms and neurocognitive function in adolescents with FE-MDD.

Garzon et al. addressed the durability of rTMS-related improvement in adolescents [41]. Their six-month randomized, controlled trial followed adolescents (12-21 years) with treatment-resistant depression (TRD) who had responded to rTMS or sham rTMS and provided rTMS retreatment for 66 adolescents with a partial relapse, 41 of whom completed the 6 months. Participants with a partial relapse (≥1 point increase in Clinical Global Impression-Severity) received retreatment with daily 10 Hz rTMS sessions until depressive symptom severity returned to the baseline score or after 30 TMS treatments. Twenty-eight participants (42%) were retreated with rTMS. rTMS retreatment courses had a mean of 22 sessions. At the 6-month follow-up, the complete sample exhibited reduced depressive symptoms (mean HAMD24 of 5.24) compared with baseline (mean HAMD24 of 8.21). These findings demonstrate the feasibility and clinical effects of a rTMS retreatment protocol for adolescents with TRD, following a standard course of acute rTMS.

In 2022, the Mayo Clinic began a randomized controlled trial that aims to identify if rTMS, specifically bilateral accelerated theta burst stimulation, reduces suicidal ideation in adolescents ages 12-18 with MDD of at least moderate severity [42]. The active treatment group will receive three daily sessions for 10 days, while the comparison group will receive three daily sham sessions for the same duration. The study continues until December of 2027, but this is the first randomized controlled trial of its kind and can potentially bolster the evidence for using TMS in adolescent psychiatry.

Bipolar Disorder

In 2001 Walter et al. reported a case of an 18-year-old female with bipolar depression who received 14 sessions of 1-Hz rTMS delivered to the right DLPFC at 110% MT [17]. Following treatment, she had no clinical improvement. She experienced no adverse effects from treatment.

In 2015, Pathak et al. conducted a randomized sham-controlled trial of 26 patients aged 12-17 years old diagnosed with bipolar mania that received daily sessions of either active or sham rTMS over the R DLPFC for 10 days [43]. The Young Mania Rating Scale (YMRS) was used to measure mania, and the CGI was used to assess illness severity at baseline and after the 5th and 10th rTMS sessions. There was no significant difference in YMRS or CGI scores after rTMS treatment. There were no serious side effects, including seizures, during rTMS or sham treatment.

In 2022, Luo et al. conducted a single-blinded, randomized, placebo-controlled trial with 50 adolescents with bipolar II disorder to receive either a sham treatment (n=20) or active treatment (n=22) for three weeks [44]. In the active group, they received intermittent theta-burst stimulation to the DLPFC, inferior temporal gyrus, and posterior parietal cortex, along with medication. Following treatment, the active group

had improved depression symptoms and executive function. This shows that, in conjunction with medication, transcranial magnetic stimulation can be an effective therapeutic intervention to mitigate the symptoms of bipolar II disorder.

Impulsivity

Although preliminary, numerous studies investigate the effects of rTMS on suicidal thinking and impulsivity [45]. Regarding suicidality, a 2014 study by George et al., involving 377 inpatients, administered 10 Hz rTMS to the left DLPFC three times per day for 3 days [46]. They found improvements in suicidal ideation measured by the Beck Scale of Suicidal Ideation (SSI) without differences from the sham arm of the study. In another uncontrolled study of 19 patients, the researchers found a rapid reduction in both depression symptoms and SSI scores in 5-10 days with daily high-dose sessions of 10 Hz rTMS. In healthy controls, impulsivity, as measured by the delayed discounting task, is decreased by rTMS of the right DLPFC, left DLPFC, or dorsomedial prefrontal cortex.

Borderline Personality Disorder

In a 2013 case report, Arbabi et al. described a 22-year-old girl diagnosed with BPD who received 10 sessions of high-frequency rTMS over her left DLPFC [47]. She was assessed before and after TMS sessions and at both one and three months after the last session using the Barratt Impulsiveness Scale, the Borderline Personality Severity Index (BPDSI), Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), Beck Suicidal Ideation Scale, Positive and Negative Affect Schedule (PANAS), and the Borderline Personality Disorder section of self-report version of the Structured Clinical Interview for DSM-IV Personality Disorders (SCID-II). One month after treatment, there was a notable decrease in depression level (BDI score), negative affect (PANAS score), impulsivity (Barratt impulsivity scale score), and general BPD score (SCID-II). Per the patient, rTMS resulted in decreased sleep duration, increased emotional control and stability, greater self-awareness of her behavior, increased motivation for change, increased sociability, increased self-esteem, increased happiness, increased attention to others' behavior toward her, and increased ability to plan. At the three-month mark after the last rTMS treatment, the assessments showed a regression in function and behaviors.

Cailhol et al. conducted a randomized controlled trial of high-frequency rTMS on 10 patients diagnosed with BPD per DSM-IV between the ages of 20 and 45 years old [48]. There were two groups: the active and sham groups. The active group, composed of 5 participants, received 2 sets of 5 days of daily rTMS to the right DLPFC, with a 2-day break between sets. The sham group, composed of 4 participants, followed the same protocol, but did not receive treatment because the coil was tilted 90 degrees. Of the 9 participants who completed the study, all tolerated rTMS well. Moreover, two from the active group and one from the sham group experienced a 30% reduction in BPDSI, specifically with statistically significant improvements in both affective instability and anger subcomponents in the active group 3 months after treatment [31]. Furthermore, the active group also showed a statistically significant improvement in planning, as measured by the Tower of London test, 3 months after treatment.

Reyes-Lopez et al conducted a randomized controlled trial on individuals between the ages of 18 and 45 with BPD over 12 months [49]. Participants were randomly assigned to either the 5 Hz to the Left DLPFC or 1 Hz to the Right DLPFC rTMS protocols. Before and after each rTMS session, assessments were administered to assess the change in BPD symptom severity, impulsiveness, anxiety, and depression. Assessments included: Clinical Global Impression Scale for BPD (CGI-

BPD), Spanish Version of the Borderlines Evaluation of Severity Over Time (BEST), Barratt Impulsiveness Scale (BIS), Hamilton Anxiety Rating Scale (HAM-A), and Beck Depression Inventory (BDI). For the CGI-BPD, summing the scores for the first nine domains yielded a total score, and a Wilcoxon test showed a significant reduction in total score from baseline after rTMS ($p=0.001$ for both groups), with 29.4% and 28.7% changes in the 1 Hz and 5 Hz groups, respectively. Both groups showed significant reductions in all domains ($p < 0.005$), especially in abandonment, impulsiveness, emotional stability, and anger. There was no significant difference in total score at baseline ($p>0.05$) or after rTMS ($p >0.05$) between the two rTMS groups or a significant between-group difference in individual CGI-BPD domain scores. Total BEST scores in both the 1 Hz ($p=0.001$) and 5 Hz ($p=0.003$) reduced by 20.4% and 36.9% respectively, from baseline for the 1 Hz and 5 Hz rTMS groups. For the BEST total score, no significant between-group differences at baseline ($p>0.05$) or after rTMS ($p>0.05$) [32]. Specifically, thoughts, feelings, and negative behaviors on the BEST scale showed significant reductions in both rTMS groups. BIS testing shows a significant reduction in total scores in the 1 Hz group ($p=0.001$) and 5 Hz group ($p=0.017$), with changes of 18.96% and 11.83% in each group, respectively. Specifically, significant reductions were found in both groups for motor impulsiveness and, for the 1 Hz group, for cognitive impulsiveness. In both the 1 Hz and 5 Hz rTMS groups, BDI scores decreased significantly, by 49% ($p=0.002$) and 60% ($p=0.001$), respectively. Additionally, HAM-A scores decreased in both groups ($p=0.005$ with a 60.3% change at 1 Hz, $p=0.003$ with a 58.7% change at 5 Hz).

The Economics of TMS

Considering the economics of TMS, machine prices vary by type and whether they are FDA-approved; FDA-approved machines are generally more expensive. Currently, FDA-approved TMS machines for adults range in price from $50,000 for CloudTMS, $ 70,000- $ 90,000 for MagVenture, and $140,000 for deep TMS machines (prices from manufacturers' booths at the World Congress of Psychiatry, 2025). Currently, the only FDA-approved TMS machine for adolescents is NeuroStar, and it has specific requirements for use, including leasing the chair rather than buying it outright. Most major insurance companies cover TMS treatment if there are indications. Specifically, Medicare will cover 80% of the cost of TMS treatment if the patient has treatment-resistant depression and has tried and failed two different classes of antidepressants as well as tried evidence-based psychotherapy. Medicaid will also cover TMS treatment for approved indications, with reimbursement rates varying based on multiple factors, including the provider, and averaging around $160 per treatment (personal communication, V. Amarendren, 2025). Currently, all TMS in the State of Maine are in private practice settings, including those that accept Medicaid and Medicare reimbursement.

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42.
Title: “Transcranial Magnetic Stimulation for Adolescent Depression”
Sponsor: Mayo Clinic
Status: Ongoing, recruiting/active as of 2025
This trial is designed to evaluate the safety and efficacy of daily, active Neurostar® TMS (versus sham) in adolescents (under 18) with Major Depressive Disorder who

have failed to improve with standard treatments. Daily treatments are given over several weeks, with open-label follow-up offered after the blinded phase.
For up-to-date recruitment status and outcomes, see: . (2025). Accessed: 12 November, 2025: https://clinicaltrials.gov/ct2/show/NCT02586688.
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