Brazilian Journal of Psychiatry
bjp
Revista Brasileira de Psiquiatria

Braz J Psychiatry. 2024;46:e20233428
doi:10.47626/1516-4446-2023-3428
Brazilian Psychiatric Association

CC BY

REVIEW ARTICLE

A meta-analysis of randomized sham-controlled trials of repetitive transcranial magnetic stimulation for attention deficit/hyperactivity disorder

Chia-Min **Chen**,[1]* Shun-Chin **Liang**,[2,3,4]* Cheuk-Kwan **Sun**,[5,6]* Yu-Shian **Cheng**,[7] Kuo-Chuan **Hung**[8]

[1]*Department of Natural Biotechnology, Nanhua University, Chiayi, Taiwan.* [2]*Department of Psychiatry, Jianan Psychiatric Center, Ministry of Health and Welfare, Tainan, Taiwan.* [3]*Department of Center for General Education, University of Kun Shan, Tainan, Taiwan.* [4]*Department of Optometry, University of Chung Hwa of Medical Technology, Tainan, Taiwan.* [5]*Department of Emergency Medicine, E-Da Dachang Hospital, I-Shou University, Kaohsiung City, Taiwan.* [6]*School of Medicine for International Students, College of Medicine, I-Shou University, Kaohsiung, Taiwan.* [7]*Department of Psychiatry, Tsyr-Huey Mental Hospital, Kaohsiung Jen-Ai's Home, Kaohsiung, Taiwan.* [8]*Department of Anesthesiology, Chi Mei Medical Center, Tainan, Taiwan.* * *These authors contributed equally to this study.*

Objective: To investigate the efficacy of repetitive transcranial magnetic stimulation (rTMS) for attention deficit/hyperactivity disorder (ADHD).
Methods: Randomized sham-controlled trials were identified in major databases from January 1990 to January 2023. The primary outcome was overall improvement in ADHD symptoms. Subgroup analysis focused on the efficacy of rTMS in different brain regions. Secondary outcomes were the association of rTMS with improvement in different ADHD symptoms. Outcomes were expressed as effect size based on standardized mean difference (SMD)(continuous data), and ORs with 95%CI (categorical data).
Results: A meta-analysis of six randomized sham-controlled trials involving 169 participants demonstrated no difference in overall ADHD symptoms between those treated with rTMS and sham controls (SMD = -0.24, p = 0.17). Subgroup analysis revealed that rTMS was more efficacious than sham treatment when targeting the right prefrontal cortex (SMD = -0.49, p = 0.03) but not the left prefrontal cortex (SMD = 0.01, p = 0.67). rTMS treatment was correlated with greater improvement in inattention (SMD = -0.76, p = 0.0002), but not hyperactivity (p = 0.86), impulsivity (p = 0.41), or depression symptoms (p = 0.95). The apparently higher risk of dropout in the rTMS group than the sham control group was not statistically significant (OR = 1.65, p = 0.26).
Conclusion: This review found that rTMS only had therapeutic efficacy for ADHD symptoms (particularly inattention) when targeting the right prefrontal cortex. Further large-scale randomized sham-controlled trials are required to verify our findings.
Registration number: PROSPERO CRD42023393713.

Keywords: Repetitive transcranial magnetic stimulation; attention deficit/hyperactivity disorder; meta-analysis

Introduction

Attention deficit/hyperactivity disorder (ADHD), one of the most common neurodevelopmental disorders,[1] often presents with behavioral difficulties in attentional function and impulse control during early development.[1] Although ADHD is commonly diagnosed during childhood,[1] inattention symptoms can persist into adulthood in nearly half of the children and adolescents diagnosed with ADHD.[2] While behavioral and pharmacological interventions are generally recommended for both children and adolescents with this condition,[3] treatment for adults is often more challenging,[4] not only because accurate ADHD diagnosis in adulthood can be more difficult,[4] but the treatment goals for adults may also involve more complex psychosocial aspects than merely alleviating core symptoms.[5] There is also a higher risk that adults will misuse stimulant treatments.[6] Moreover, adherence to pharmacological interventions remains a significant issue due to concerns about side effects, as well as the stigma of medication for caregivers of children/adolescents and adults diagnosed with ADHD.[7,8] However, although psychosocial interventions and environmental modification are generally recommended for anyone with ADHD,[3]

Correspondence: Kuo-Chuan Hung, Department of Anesthesiology, Chi Mei Medical Center, 901, ChungHwa Road, YungKung Dist, Tainan 71004, Taiwan.
E-mail: ed102605@gmail.com
Submitted Oct 08 2023, accepted Feb 04 2024.

How to cite this article: Chen C-M, Liang S-C, Sun C-K, Cheng Y-S, Hung K-C. A meta-analysis of randomized sham-controlled trials of repetitive transcranial magnetic stimulation for attention deficit/hyperactivity disorder. Braz J Psychiatry. 2024;46:e20233428. http://doi.org/10.47626/1516-4446-2023-3428

a significant portion of patients do respond well to these interventions.[9] Therefore, complementary alternative medicine is becoming more popular among patients with ADHD and their caregivers.[10-12]

Complementary alternative medicine for ADHD ranges from nutritional supplements[10] to more advanced brain technologies, including electroencephalography to assist neurofeedback training[13-15] and brain stimulation methods, such as transcranial direct current stimulation (tDCS) or repetitive transcranial magnetic stimulation (rTMS) to specific brain areas.[16] Given prior functional magnetic resonance imaging evidence of under-activation in several important brain regions related to executive control (i.e., the fronto-striatal and fronto-cerebellar systems) in people diagnosed with ADHD,[17] stimulation targeting these regions could be a reasonable therapeutic alternative for ADHD.[16] Two common brain stimulation approaches are used for individuals diagnosed with ADHD: tDCS and rTMS. The former passes a weak direct electric current between two electrodes (i.e., a positive anode and a negative cathode) placed on the scalp, while the latter delivers rapid magnetic pulses to the scalp with a wire coil to generate an electric current in the brain through electromagnetic induction.[16] The major differences between tDCS and rTMS are the power source (electric vs. electromagnetic) and the nature of stimulation (continuous vs. pulsatile), respectively.[16] A previous meta-analysis investigating the efficacy of tDCS found that stimulation of the dorsolateral prefrontal cortex (dlPFC), especially the left hemisphere, effectively improved inhibitory control but not working memory.[18] Another meta-analysis on brain stimulation for ADHD showed that tDCS was potentially efficacious for enhancing processing speed in children when it mainly targeted the left dlPFC,[16] although the available randomized control trials were insufficient for a meta-analysis of rTMS.[16] Since both rTMS and tDCS are considered generally safe and with minimal side effects,[19] investigating the potential therapeutic efficacy of rTMS for patients with ADHD is also worthwhile.

Although the exact mechanism of rTMS remains to be elucidated, prior studies have reported that rTMS could induce the release of brain dopamine,[20] a key neurotransmitter in attentional control[21] and the targeted neurotransmitter in stimulant therapies for ADHD.[22] Moreover, previous animal and human studies have demonstrated that rTMS could induce synaptic plasticity,[23,24] which was shown to be related to functional recovery in stroke patients.[25] Given that the dlPFC is one of most important brain regions associated with important executive control functions, including attention and inhibition,[26] it has frequently been targeted for rTMS stimulation in ADHD patients.[27-29] Nevertheless, the results of previous studies have been mixed.[2,27,28] Only one randomized control trial of rTMS that targeted the right PFC (rPFC) found significantly better therapeutic efficacy for ADHD symptoms than sham treatment.[29] However, another randomized control trial of rTMS that targeted the bilateral PFC failed to show significant improvement.[28] A more recent study on the efficacy of rTMS in different brain regions (rPFC vs. left PFC [lPFC]) also found that the rPFC, but not the lPFC, was associated with greater improvement in inattention symptoms than sham treatment.[27] In fact, previous evidence has suggested that brain dysfunction in ADHD may be more associated with the right hemisphere, although this concept remains controversial.[17,30] Although the efficacy of rTMS targeting the left or right hemispheres remains unclear,[17,30] targeting different brain regions for rTMS stimulation may have different treatment effects.[27] Nevertheless, no meta-analysis has investigated the efficacy of rTMS for ADHD symptoms and factors (i.e., stimulation target) that could influence its efficacy.

Therefore, the present meta-analysis aimed to investigate the treatment efficacy of rTMS for ADHD symptoms and identify factors that could affect the therapeutic efficacy of rTMS through subgroup analysis.

Methods

Protocol and registration

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[31] and was registered in the International prospective register of systematic reviews (PROSPERO CRD42023393713).

Search strategy and selection criteria

By using the main keywords "rTMS" and "ADHD" (Supplementary Table S1), randomized sham-controlled trials were identified in major databases, including PubMed, Embase, Cochrane CENTRAL, ScienceDirect, and ClinicalTrials.gov from January 1990 (inception) to January 2023 without no restrictions on country or language. The detailed search strategies and keywords used for each database are provided in Supplementary Table S1. We also searched for relevant studies from the reference lists of specific reviews to expand our search results. Study eligibility was based on the PICO (i.e., population, intervention, comparator, and outcomes) model as follows: 1) Population – randomized controlled trials of patients diagnosed with ADHD, regardless of psychiatric comorbidities; 2) Intervention – rTMS; 3) Comparator – sham rTMS; and 4) Outcome – standardized rating scales for assessing ADHD symptoms and any other associated psychiatric symptoms, such as depression. Studies were excluded for 1) not being sham-controlled randomized controlled trials, 2) not targeting participants diagnosed with ADHD, and 3) using interventions unrelated to rTMS.

Data extraction and quality assessment

Using a pre-defined search strategy (Supplementary Table S1), the titles and abstracts were initially screened by two independent authors (Y-S Cheng and C-K Sun), who were also responsible for identifying eligible studies and data extraction, including study characteristics (e.g., number of participants, number of rTMS sessions, and follow-up duration) and publication details. Inter-rater

reliability was examined using the kappa coefficient.[32] If any data were missing from eligible studies, the corresponding authors were contacted by email. The quality of eligible studies was rated according to version 2 of the Cochrane risk-of-bias tool for randomized trials[33] which assessed five domains of bias, including risk of bias arising from the randomization process, risk of bias due to deviations from the intended interventions, risk of bias due to missing outcome data, risk of bias in outcome measurement, and risk of bias in reporting the results. Risk of bias was classified as "low," "some concern," or "high." The Grading of Recommendations Assessment, Development and Evaluation framework was also used to rate the certainty of evidence for individual outcomes of interest.[34] Any disagreements about study eligibility or quality between the two reviewers were resolved through discussion with a third author.

Data synthesis and analysis

The primary outcome was overall improvement in ADHD symptoms, and secondary outcomes included improvement in ADHD symptom subdomains, such as inattention, hyperactivity and impulsivity, as well as changes in the severity of any other associated symptoms (e.g., depressive symptoms). Treatment acceptability was assessed by the number of participants who withdrew from study during the intervention and by group comparison. We chose the outcome assessment immediately following the final treatment session to investigate the immediate rather than the chronic effects of rTMS. While the outcomes of interest for continuous data were quantitatively expressed as effect size (ES) based on standardized mean difference (SMD) with 95%CI, those for categorical variables were presented as odds ratios (OR) with 95% CI. We used RevMan 5.4 for data analysis, the Mantel-Haenszel method for OR, and the generic inverse-variance method for continuous-variable outcomes.[35] If two rTMS treatment arms targeted different brain regions (i.e., rPFC and lPFC) in a single study, we combined the results from the treatment arms into a single SMD. Leave-one-out sensitivity analysis was used to assess the reliability of available outcomes. The I^2 statistic was used to explore heterogeneity among the included studies, although the heterogeneity results should be interpreted with caution if the number of studies included in a meta-analysis is small.[36,37] We also used the chi-square test to determine the heterogeneity of evidence. Statistical significance was defined as $p < 0.05$ for all outcomes. Finally, publication bias was examined by visual inspection of a funnel plot.

Results

Study selection and characteristics of the included studies

The study selection process, which followed PRISMA guidelines,[31] is summarized in Figure 1. In brief, of the 782 articles identified by searching major databases (e.g., ClinicalTrials.gov), 748 were excluded after title and abstract screening. Of the 34 studies eligible for full-text review, six RCTs involving 169 participants were included in the meta-analysis[27-29,38-40] after excluding 28 studies for a variety of reasons, which are summarized in Supplementary Table S2. There was no disagreement between the two reviewers regarding study selection (kappa coefficient = 1.0).

The characteristics of the included studies are summarized in Table 1. Five of the six eligible studies only included adults ⩾18 years), while the other also included adolescents.[38] The participants were aged 14-65 (mean 32.67) years and the proportion of women ranged from 33-82.76%. The treatment protocols varied: two studies reported a treatment duration of ~14 minutes with one session a day, 5 days a week for 3 weeks[27,29]; one study reported a treatment duration of ~20 minutes with one session a day, 5 days a week for 4 weeks[28]; one study reported a treatment duration of ~26 minutes with one session a day, 5 days a week for 4 weeks[40]; one study reported one treatment session a day, 5 days a week for 4 weeks, but provided no clear information about individual session duration[38]; and one study only mentioned a single ~22-minute treatment session with no other information.[39] The median number of rTMS treatment sessions was 15 (range: 1-20) and the median treatment duration was 3 weeks (range: 1-4). Three of the six studies only showed outcome data immediately after treatment,[38-40] while the remaining three provided follow-up data after cessation of rTMS therapy, ranging from 1-8 weeks after the last treatment.[27-29] Regarding comorbid psychiatric conditions, the studies primarily focused on participants experiencing ADHD symptoms but no other psychiatric conditions, except for two that allowed mild depression or anxiety.[27,38] None of the studies combined rTMS with other therapies, and most did not allow psychostimulant use during the study period, although two provided no such information.[15,39] The studies were conducted in Israel (n=4) and the United States (n=2) (Table 1). Because one study had three treatment arms (rTMS targeting the rPFC; rTMS targeting the lPFC; and sham control),[27] data from the two rTMS groups targeting different brain locations were combined for comparison with sham treatment in our analysis.

Risk of bias assessment

In terms of study quality according to version 2 of the Cochrane risk-of-bias tool for randomized trials, the risk of bias due to deviating from the intended intervention and the risk of bias due to outcome measurement were considered low in all studies because they were double-blind RCTs. However, three studies with unclear reporting about the randomization process were rated as having "some concern." Nevertheless, the consistency of the overall outcome after excluding the impact of each of these three studies[15,28,39] through leave-one-out sensitivity analysis indicated that the randomization process had a negligible influence on the quality of the final outcome. The risk of bias for each eligible study is shown in Figure 2. Overall, the risk of bias was low given the studies' strict selection criteria and double-blind randomized sham-controlled design.

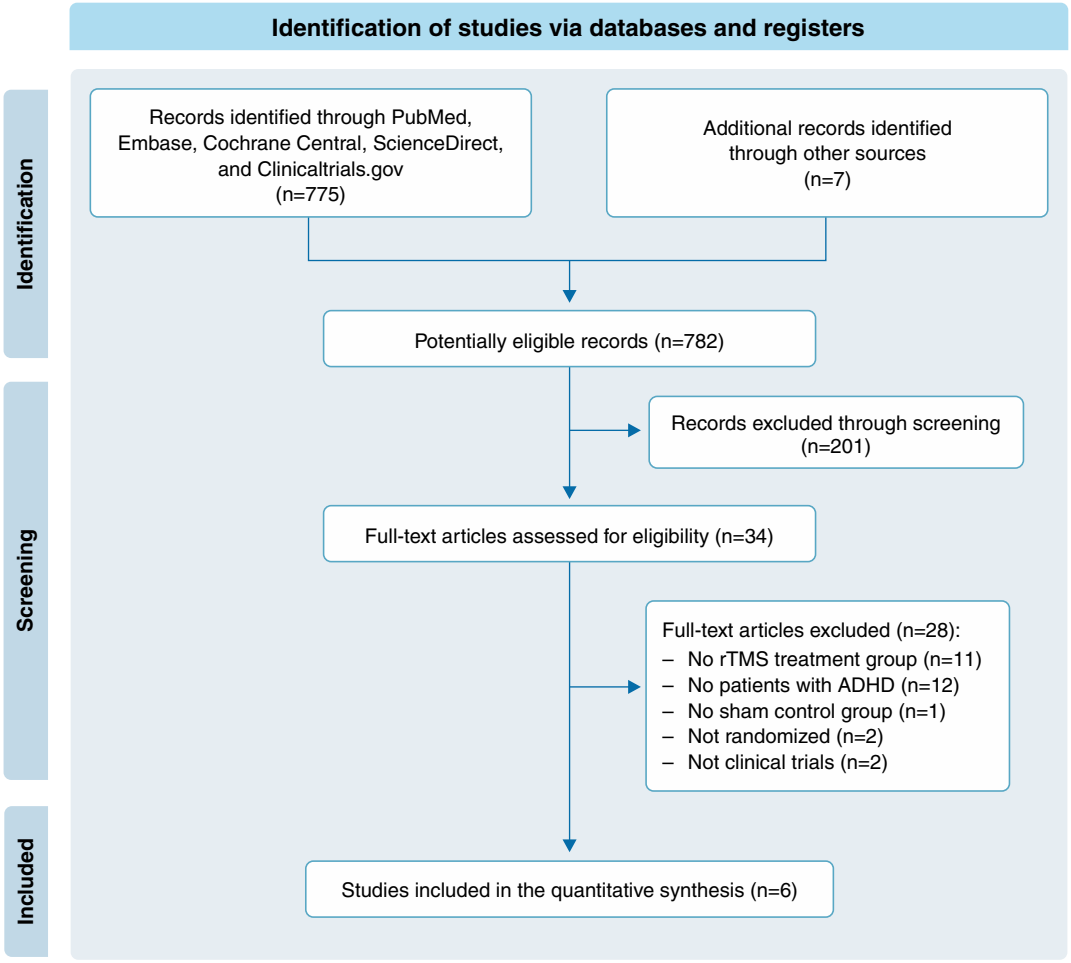


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses study selection flowchart. ADHD = attention deficit/hyperactivity disorder; rTMS = repetitive transcranial magnetic stimulation.

Results of the syntheses

The meta-analysis failed to demonstrate greater overall improvement in ADHD symptoms in the rTMS group than the control group (SMD = -0.24, 95%CI -0.58 to 0.1, p = 0.17, five studies with 149 participants) (Figure 3). The robustness of the findings remained unchanged in sensitivity analysis without significant heterogeneity (I^2 = 4%, χ^2 = 4.18 and p = 0.38). Visual inspection of the funnel plot revealed no obvious asymmetry, indicating non-significant publication bias (Supplementary Figure S1).

Subgroup analysis on the efficacy of rTMS targeted at different brain regions demonstrated that rTMS was significantly more efficacious than sham treatment when the rPFC was targeted (SMD = -0.49, 95%CI -0.93 to -0.06, p = 0.03, three studies with 87 participants) but not when the lPFC was targeted (SMD = 0.01, 95%CI -0.39 to 0. 60, p = 0.67, two studies with 65 participants) (Figure 4), which suggests that targeting the rPFC may be a more effective approach. Nevertheless, subgroup comparison between treatments targeting the rPFC and lPFC failed to achieve statistical significance (p = 0.07).

In the secondary outcome results, rTMS was associated with greater improvement in inattention symptoms (SMD = -0.76, 95%CI -1.16 to -0.53, p = 0.0002, three studies with 104 participants) but not hyperactivity (SMD = 0.04, 95%CI -0.41 to 0.049, p = 0.86, two studies with 91 participants), impulsivity (SMD = -0.43, 95%CI -1.46 to 0.6, p = 0.41, two studies with 91 participants), or depression symptoms (SMD = -0.02, 95%CI -0.58 to 0.55, p = 0.95, three studies with 104 participants) (Supplementary Figures S2 to S5). There was a higher, but non-significant, risk of dropout in the rTMS group than the control group (OR = 1.65, 95%CI 0.69 to 3.97, p = 0.26, five studies with 176 participants) (Supplementary Figure S6). Sensitivity analysis through the leave-one-out approach indicated stable results for inattention and depression symptoms, but it was not performed for hyperactivity and impulsivity since only two studies were available for each outcome. Impulsivity was the only secondary outcome with significant heterogeneity in the results. Visual inspection of a funnel plot revealed no obvious asymmetry (Supplementary Figures S7 to S11).

Table 1 Characteristics of the studies in the meta-analysis

Study	Diagnosis (criteria)	Design	Comparison (duration per session)	n	Treatment duration (weeks)	Sessions per week/ total	Outcome	Comorbidities	Medications	FU† (weeks)	Mean age (years)	Women (%)	Country
Bleich-Cohen[27]	ADHD (DSM-5)	RCT	rTMS: rPFC (~14 minutes) rTMS: lPFC (~14 minutes) Sham	24 22 16	3	5/15	1. CAARS (SR) Total 2. CAARS (SR) Inattention 3. CAARS (SR) Hyperactivity 4. CAARS (SR) Impulsivity 5. BDI	All psychiatric disorders were excluded except mild depressive or anxiety symptoms that had been well controlled over the previous 3 years.	Only SSRI and SNRI allowed; neuroleptics and psychostimulants not allowed.	8	35.1 (18-60)	34.70	Israel
Alyagon[29]	ADHD (DSM-5)	RCT	rTMS: rPFC (~14 minutes) sham	15 14	3	5/15	1. CAARS (SR) Total 2. CAARS (SR) Inattention 3. BAARS Hyperactivity 4. BAARS Impulsivity 5. BDI	Any additional axis I or II diagnosis was excluded, including anxiety, depression (major or bipolar), obsessive-compulsive disorder, personality disorder, or substance abuse; anti-psychotic, anti-depressive or mood stabilizer users excluded.	Psychostimulants not allowed.	4	27.1 (21-64)	82.76	Israel
Paz[28]	ADHD (DSM-5)	RCT	rTMS: bil.PFC (~20 minutes) sham	12 14	4	5/20	CAARS (SR) Total	Additional psychiatric or neurological disorders were excluded.	Neuropsychiatric medications not allowed.	1	31.6 (⩾ 18)	46.15	Israel
Weaver[38]	ADHD (DSM-IV-TR)	RCT/ crossover	rTMS: rPFC(N/A) sham	9 9	2	5/10	CGI-I	Comorbid anxiety disorders allowed, except for obsessive-compulsive disorder and PTSD. Comorbid bipolar disorder, conduct disorder, tic disorders, any psychotic disorder, mental retardation, PDD, and history of substance abuse/dependence were excluded.	Psychotropic medications and psychostimulants not allowed.	0	18.11 (14-21)	33.00	United States
Bloch[39]	ADHD (DSM-IV)	RCT/ crossover	rTMS: rPFC (~22 minutes) sham	11 11	1	1/1	1. PANAS - Inattention 2. PANAS - Mood	Any additional psychiatric disorders were excluded.	N/A	0	43.1 (26-63)	46.15	Israel
University of Pennsylvania[40]	ADHD (SCID-5)	RCT	rTMS: lPFC (~26 minutes) sham	18 14	4	5/20	CAARS (SR) Total	History/current diagnosis/ treatment for alcohol or drug abuse, psychosis or symptoms consistent with a mood disorder, low or borderline intellectual functioning, and neurological disorders were excluded.	N/A	0	34.4 (18-65)	33.00	USA

ADHD = attention deficit/hyperactivity disorder; BAARS = Barkley Adult ADHD Rating Scale; BDI = Beck Depression Inventory; bil.PFC = bilateral prefrontal cortex; CAARS = Conners' Adult ADHD Rating Scale; CAARS (SR) = Conners' Adult ADHD Rating Scale-self-report; CGI-I = Clinical Global Impression - Improvement; lPFC = left prefrontal cortex; N/A = not available; PANAS = Positive and Negative Affect Schedule; PDD = pervasive developmental disorder; PTSD = posttraumatic stress disorder; RCT = randomized controlled trial; rPFC = right prefrontal cortex; rTMS = repetitive transcranial magnetic stimulation; SCID-5 = Structured Clinical Interview for DSM-5; SNRI = serotonin and norepinephrine reuptake inhibitors; SSRI = serotonin reuptake inhibitor.

† Follow up assessment after the last rTMS session.

The overall certainty of evidence for each outcome of interest is shown in Supplementary Table S3. Although most studies had a low risk of bias and no serious indirectness or inconsistency in most outcomes of interest, the certainty of evidence was only graded as moderate for the primary outcome and subgroup findings due to the limited number of randomized controlled trials and their small sample sizes. Similarly, although the certainty of evidence was deemed moderate for most secondary outcomes, including inattention, hyperactivity, and dropout rate, it was downgraded to low for impulsivity and depressive symptoms due to additional consistency problems.

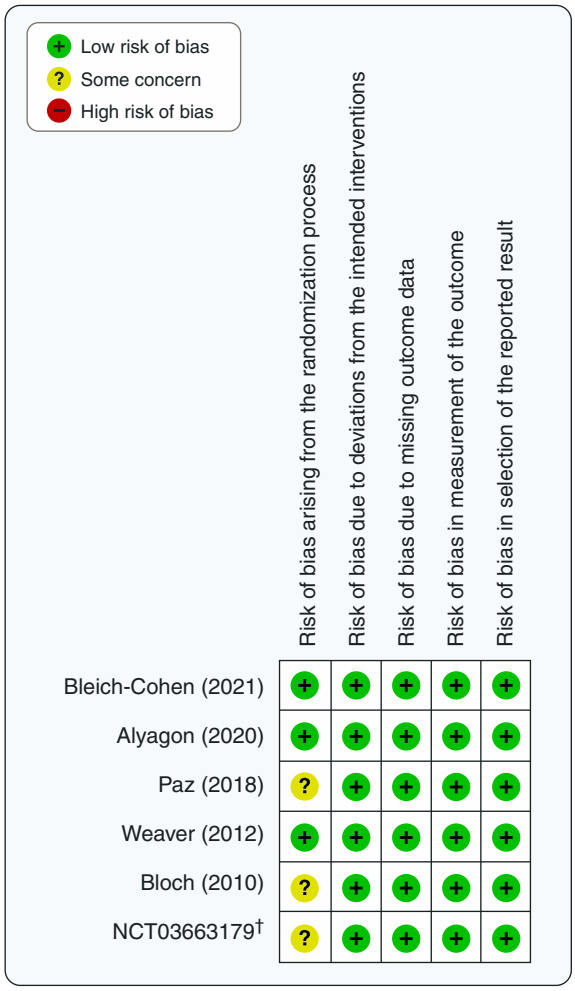


Figure 2 Risk of bias for eligible studies. † Unpublished clinical trial from clinicaltrials.gov.

Discussion

Although rTMS has mainly been used as an alternative therapy for depression,[41] positive responses have been reported for a variety of psychiatric and neurodevelopmental disorders.[42] A recent meta-analysis focusing on adults with autism spectrum disorder reported some improvements in cognitive outcomes in those treated with rTMS,[43] but no previous meta-analysis has focused on patients with ADHD. To the best of our knowledge, ours is the first meta-analysis to investigate the treatment efficacy of rTMS for ADHD. Although the inclusion of only six studies might affect the reliability of our findings, rTMS did not lead to significantly greater improvement in overall ADHD symptoms than sham treatment. However, in our subgroup analysis, rTMS targeting the rPFC led to greater improvement in overall ADHD symptoms than sham treatment, but rTMS targeting the lPFC led to (non-significantly) poorer outcomes than sham treatment. Our secondary analysis showed that rTMS was effective for inattention symptoms but not hyperactivity, impulsivity, or depression symptoms in this population. Regarding treatment acceptability, dropout rates did not differ significantly between the rTMS and control groups, which suggests that rTMS was generally well-tolerated. Although the certainty of evidence was hampered by the limited number of eligible trials (six RCTs, 169 participants), our result that rTMS targeting the rPFC was more efficacious than that targeting the lPFC may serve as an important reference for further research on the therapeutic efficacy of rTMS for ADHD symptoms. In summary, our study, which supported rTMS targeting the rPFC but not the lPFC for ADHD, demonstrated that rTMS was mainly effective against inattention symptoms. Nevertheless, these preliminary findings should be confirmed in further large-scale clinical studies.

Although rTMS was not more efficacious than sham treatment for overall ADHD symptom improvement, the results for targeted brain regions were different among the included studies. It was interesting that targeting the rPFC generally had better therapeutic effects than sham treatment.[29,38] Conversely, the study focusing on the

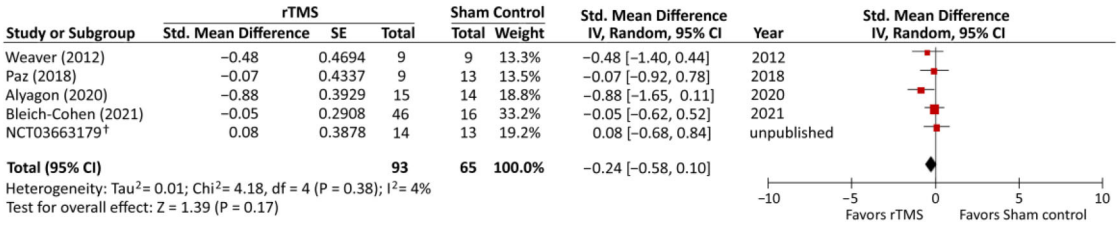


Figure 3 Forest plot of the effect size for overall attention deficit/hyperactivity disorder symptom improvement between repetitive transcranial magnetic stimulation (rTMS) and sham control groups. SE = standard error; Std = standardized. † Unpublished clinical trial from clinicaltrials.gov.

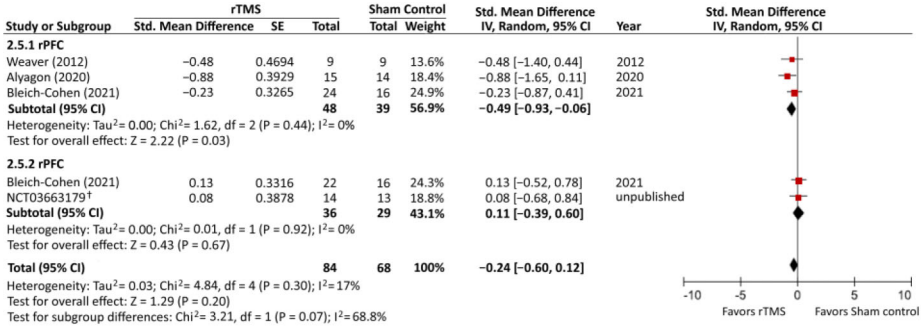


Figure 4 Subgroup analysis – forest plot of the effect sizes in different subgroups of studies targeting different brain regions. rTMS = repetitive transcranial magnetic stimulation; SE = standard error; Std = standardized. † Unpublished clinical trial from clinicaltrials.gov.

lPFC had a poorer outcome than sham treatment[40] (ES = 0.08; a positive ES indicates results favoring sham control). Moreover, in Bleich-Cohen et al.,[27] only rTMS targeting the rPFC was associated with improvement in inattention symptoms; there was no significant difference between rTMS targeting the lPFC and sham treatment for any outcome. Although the exact mechanism for rTMS' effect on cognition remains unclear, a previous imaging study reported that rTMS induced brain dopamine release,[20] which is one of the key neurotransmitters involved in cognition and attention regulation.[21] Given that the PFC is the most important brain region for executive control of attention,[44] it is a reasonable target for brain stimulation.[27] However, previous evidence has suggested that brain dysfunction in ADHD may be more associated with the right hemisphere than the left.[17,45] Thus, rTMS targeting different brain regions may have a varied therapeutic response.[27] Our subgroup analysis found greater overall improvement in ADHD symptoms than sham treatment when rTMS targeted the rPFC but not the lPFC. Although subgroup comparison only reached near significance ($p = 0.07$), probably due to the limited number of included trials, the large difference and opposite direction of ES (e.g., SMD = -0.49 vs. 0.11; a negative ES indicates results in favor of rTMS) suggests that the targeted brain region may influence the therapeutic outcome of rTMS.

Regarding secondary outcomes, the therapeutic efficacy of rTMS was only significantly better than sham for inattention symptoms, not for hyperactivity or impulsivity symptoms. This is further supported by the results of several studies, which found that rTMS has a beneficial impact on attention in patients diagnosed with different psychiatric disorders, such as autism spectrum disorder and Alzheimer's disease.[46-48] Of note, only three of the six studies in our meta-analysis provided analyzable data for inattention symptoms. Of these, two targeted the rPFC,[29,39] while the outcome of the other was obtained by combining rPFC- and lPFC-targeted treatment arms.[28] Therefore, our results on the therapeutic efficacy of rTMS for inattention symptoms may be more representative of the rPFC than the lPFC. Overall, the subgroup analysis and secondary outcome results indicated the efficacy of rPFC-targeted rTMS (moderate ES, moderate quality of evidence) for ADHD treatment, mainly for inattention symptoms (moderate-to-large ES, moderate quality of evidence).

Nevertheless, the therapeutic goals for ADHD include not only maintaining attention, but sustained concentration, which involves both motor response suppression and interference inhibition.[17] A previous meta-analysis on functional magnetic resonance imaging among patients with ADHD found that the right dlPFC is more related to attention, while the right inferior frontal junction and the left caudate head are more associated with motor response inhibition and interference inhibition, respectively.[17] Thus, although we failed to find a significant correlation between rTMS targeting the lPFC and improved inattention symptoms, the evidence was not strong enough to rule out any benefits from targeting the lPFC in other cognitive dysfunctions. For instance, another meta-analysis investigating the effects of brain stimulation on ADHD symptoms found that (mainly) anodal (i.e., 10 of 12 studies) tDCS targeting the left dlPFC that was (mainly) administered in a single session (i.e., 11 of 12 studies) was more efficacious than sham treatment for the inhibition task but not the attention task.[16] Therefore, it is possible that not only are different brain regions responsible for various cognitive functions (i.e., the right dlPFC for attentional function and the right inferior frontal junction for inhibitory control), but brain lateralization may also play a part.[17,45] Prior evidence seems to indicate that attentional control is more related to the right dlPFC, the area immediately beneath the rTMS stimulation site in the rPFC. Together with our finding that only rTMS targeting the rPFC could improve inattention symptoms (but not hyperactivity or impulsivity symptoms), our results further suggest the importance of the rTMS site for optimal therapeutic effects.

Our analysis did not show significantly greater improvement in depressive symptoms in the rTMS group than the control group despite the fact that alleviating depressive symptoms is the most important indication for rTMS in the general population.[49] However, because only three studies provided data on depressive symptoms,[27,29,39] our evidence is inconclusive. More importantly, since depressive symptom improvement was not the primary outcome in all of the included studies that reported a

minimal baseline depression score for most participants (i.e., below the cut-off scores for mild depressive symptoms),[27,29,39] the lack of correlation between rTMS and depressive symptom improvement should not be applied to individuals with comorbid clinically diagnosed depression. In terms of treatment acceptability, there was no significant difference in the OR of dropout between the rTMS and control groups, despite an apparently higher risk in the rTMS group, indicating comparable acceptability. The only reported adverse effects of rTMS treatment were mild discomfort, including transient headaches and scalp discomfort. Overall, rTMS treatment seemed well-tolerated in most participants.

Regarding the impact of age on treatment efficacy, the study that primarily enrolled adolescents (i.e., mean age 18.11 [range 14-21] years)[38] had a larger ES (0.48) than all six studies combined (0.24). Considering the mean overall participant age of 32.67 years in our review, one study that recruited relatively young participants (mean age 27.1 years)[29] also had a relatively larger ES (0.88) than the others.[27,28,39,42] Thus, age may have affected the efficacy of rTMS for ADHD. Indeed, brain development varies with age in the normal population, and slower development has been observed in individuals diagnosed with ADHD.[50] Considering the advantage of stimulating the brain while it still has a high level of neuroplasticity,[51] it is possible that rTMS therapy may have better outcomes in in younger populations than older populations. Since a reliable meta-regression analysis was impossible in this review due to the limited number of eligible trials (i.e., $<$ 10) further clinical investigations are needed to verify our findings.

The current meta-analysis had several important strengths. Considering the notable placebo effect associated with rTMS in a previous meta-analysis,[49] we only included RCTs with sham controls to minimize this risk. Moreover, our inclusion of studies with similar rTMS protocols, such as high frequency ($>$ 10 Hz), reduced heterogeneity and enabled more reliable comparison between lPFC and rPFC treatment. One of the most important findings was the large discrepancy in therapeutic efficacy of rTMS targeting the rPFC and the lPFC. However, our meta-analysis has some limitations. First, our findings, which are based on only six RCTs with a total of 169 participants, may not be robust enough to provide solid evidence. Second, because four of the six included trials were conducted in Israel and the remaining two in the United States, our results may not apply to populations from other regions. Third, all of included studies enrolled adults, with five focusing exclusively on adults. Although the other study also recruited adolescents, the mean participant age was 18.11 years.[38] Therefore, our results may be more representative of the adult population. Fourth, since we used only self-rated assessment tools for outcome measurements, our results may not reflect improved neurocognitive ability. Fifth, because only two studies provided information on follow-up efficacy $>$ 4 weeks after treatment,[27,29] we only analyzed treatment outcomes immediately after the final treatment session. Thus, the long-term effects of rTMS on ADHD symptoms remain unclear. Finally, the limited number of eligible trials precluded a reliable meta-regression analysis to identify other factors (i.e., age and sex) that could influence the therapeutic efficacy of rTMS for ADHD symptoms. Further large-scale clinical trials are needed to determine the best rTMS protocols for ADHD.

This review found that rTMS only had therapeutic efficacy for ADHD symptoms (particularly inattention) when targeting the rPFC, not the lPFC. However, due to the limited number of included trials and that factors such as age and brain stimulation region may have influenced the therapeutic efficacy of rTMS, further large-scale RCTs with younger participants that separately target the rPFC and lPFC are needed.

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Disclosure

The authors report no conflicts of interest.

Author contributions

C-MC: Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing.
S-CL: Conceptualization, Data curation, Software, Supervision, Writing – original draft.
C-KS: Investigation, Methodology, Writing – original draft, Writing – review & editing.
Y-SC: Data curation, Formal analysis, Writing – original draft, Writing – review & editing.
K-CH: Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing.
All authors have read and approved of the final version to be published.

Handling Editor: Lucas Borrione

References

1 Zhou R, Xia Q, Shen H, Yang X, Zhang Y, Xu J. Diagnosis of children's attention deficit hyperactivity disorder (ADHD) and its association with cytomegalovirus infection with ADHD: a historical review. Int J Clin Exp Med. 2015;8:13969-75.
2 Posner J, Polanczyk GV, Sonuga-Barke E. Attention-deficit hyperactivity disorder. The Lancet. 2020;395:450-62.
3 Wolraich ML, Hagan JF, Jr., Allan C, Chan E, Davison D, Earls M, et al. Clinical Practice Guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. Pediatrics. 2019;144.
4 Culpepper L, Mattingly G. Challenges in identifying and managing attention-deficit/hyperactivity disorder in adults in the primary care setting: a review of the literature. Prim Care Companion J Clin Psychiatry. 2010;12:PCC.10r00951.
5 Mühlbacher AC, Nübling M. Analysis of patients' preferences: direct assessment and discrete-choice experiment in therapy of adults with attention-deficit hyperactivity disorder. Patient. 2010;3:285-94.
6 Fields SA, Johnson WM, Hassig MB. Adult ADHD: Addressing a unique set of challenges. J Fam Pract. 2017;66:68-74.

7 O'Callaghan P. Adherence to stimulants in adult ADHD. Atten Defic Hyperact Disord. 2014;6:111-20.
8 Pappadopulos E, Jensen PS, Chait AR, Arnold LE, Swanson JM, Greenhill LL, et al. Medication adherence in the MTA: Saliva methylphenidate samples versus parent report and mediating effect of concomitant behavioral treatment. J Am Acad Child Adolesc Psychiatry. 2009;48:501-10.
9 Owens EB, Hinshaw SP, McBurnett K, Pfiffner L. Predictors of response to behavioral treatments among children with ADHD-inattentive type. J Clin Child Adolesc Psychol. 2018;47:S219-32.
10 Searight HR, Robertson K, Smith T, Perkins S, Searight BK. Complementary and alternative therapies for pediatric attention deficit hyperactivity disorder: a descriptive review. ISRN Psychiatry. 2012; 2012:804127.
11 Cortese S, Ferrin M, Brandeis D, Buitelaar J, Daley D, Dittmann RW, et al. Cognitive training for attention-deficit/hyperactivity disorder: meta-analysis of clinical and neuropsychological outcomes from randomized controlled trials. J Am Acad Child Adolesc Psychiatry. 2015;54:164-74.
12 Westwood SJ, Parlatini V, Rubia K, Cortese S, Sonuga-Barke EJS, Banaschewski T, et al. Computerized cognitive training in attention-deficit/hyperactivity disorder (ADHD): a meta-analysis of randomized controlled trials with blinded and objective outcomes. Mol Psychiatry. 2023;28:1402-14.
13 Chiu HJ, Sun C-K, Fan H-Y, Tzang RF, Wang M-Y, Cheng Y-C, et al. Surface electroencephalographic neurofeedback improves sustained attention in ADHD: a meta-analysis of randomized controlled trials. Child Adolesc Psychiatry Ment Health. 2022;16:104.
14 Lin F-L, Sun C-K, Cheng Y-S, Wang MY, Chung W, Tzang RF, et al. Additive effects of EEG neurofeedback on medications for ADHD: a systematic review and meta-analysis. Sci Rep. 2022;12:20401.
15 Fan H-Y, Sun C-K, Cheng Y-S, Chung W, Tzang RF, Chiu HJ, et al. A pilot meta-analysis on self-reported efficacy of neurofeedback for adolescents and adults with ADHD. Sci Rep. 2022;12:9958.
16 Westwood SJ, Radua J, Rubia K. Noninvasive brain stimulation in children and adults with attention-deficit/hyperactivity disorder: a systematic review and meta-analysis. J Psychiatry Neurosci. 2021; 46:E14-33.
17 Hart H, Radua J, Nakao T, Mataix-Cols D, Rubia K. Meta-analysis of functional magnetic resonance imaging studies of inhibition and attention in attention-deficit/hyperactivity disorder: Exploring task-specific, stimulant medication, and age effects. JAMA Psychiatry. 2013;70:185-98.
18 Salehinejad MA, Wischnewski M, Nejati V, Vicario CM, Nitsche MA. Transcranial direct current stimulation in attention-deficit hyperactivity disorder: A meta-analysis of neuropsychological deficits. PLoS One. 2019;14:e0215095.
19 Dayan E, Censor N, Buch ER, Sandrini M, Cohen LG. Noninvasive brain stimulation: from physiology to network dynamics and back Nat Neurosci. 2013;16:838-44.
20 Strafella AP, Paus T, Barrett J, Dagher A. Repetitive transcranial magnetic stimulation of the human prefrontal cortex induces dopamine release in the caudate nucleus. J Neurosci. 2001;21:RC157.
21 Nieoullon A. Dopamine and the regulation of cognition and attention. Prog Neurobiol. 2002;67:53-83.
22 Dela Peña I, Gevorkiana R, Shi WX. Psychostimulants affect dopamine transmission through both dopamine transporter-dependent and independent mechanisms. Eur J Pharmacol. 2015;764:562-70.
23 Dalhuisen I, Ackermans E, Martens L, Mulders P, Bartholomeus J, de Bruijn A, et al. Longitudinal effects of rTMS on neuroplasticity in chronic treatment-resistant depression. Eur Arch Psychiatry Clin Neurosci. 2021;271:39-47.
24 Siebner HR, Rothwell J. Transcranial magnetic stimulation: New insights into representational cortical plasticity. Exp Brain Res. 2003;148:1-16.
25 Lefaucheur JP. Stroke recovery can be enhanced by using repetitive transcranial magnetic stimulation (rTMS). Neurophysiol Clin. 2006; 36:105-15.
26 Jones DT, Graff-Radford J. Executive dysfunction and the prefrontal cortex. Continuum (Minneap Minn). 2021;27:1586-601.
27 Bleich-Cohen M, Gurevitch G, Carmi N, Medvedovsky M, Bregman N, Nevler N, et al. A functional magnetic resonance imaging investigation of prefrontal cortex deep transcranial magnetic stimulation efficacy in adults with attention deficit/hyperactive disorder: A double blind, randomized clinical trial. Neuroimage Clin. 2021;30:102670.
28 Paz Y, Friedwald K, Levkovitz Y, Zangen A, Alyagon U, Nitzan U, et al. Randomised sham-controlled study of high-frequency bilateral deep transcranial magnetic stimulation (dTMS) to treat adult attention hyperactive disorder (ADHD): Negative results. World J Biol Psychiatry. 2018;19:561-6.
29 Alyagon U, Shahar H, Hadar A, Barnea-Ygael N, Lazarovits A, Shalev H, et al. Alleviation of ADHD symptoms by non-invasive right prefrontal stimulation is correlated with EEG activity. Neuroimage Clin. 2020;26:102206.
30 Dickstein SG, Bannon K, Castellanos FX, Milham MP. The neural correlates of attention deficit hyperactivity disorder: An ALE meta-analysis. J Child Psychol Psychiatry. 2006;47:1051-62.
31 Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4:1.
32 McHugh ML. Interrater reliability: The kappa statistic. Biochem Med (Zagreb). 2012;22:276-82.
33 Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898.
34 Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336:924.
35 Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. Cochrane handbook for systematic reviews of interventionsOxford: John Wiley & Sons; 2019.
36 Von Hippel PT. The heterogeneity statistic I(2) can be biased in small meta-analyses. BMC Med Res Methodol. 2015;15:35.
37 Migliavaca CB, Stein C, Colpani V, Barker TH, Ziegelmann PK, Munn Z, et al. Meta-analysis of prevalence: I(2) statistic and how to deal with heterogeneity. Res Synth Methods. 2022;13:363-7.
38 Weaver L, Rostain AL, Mace W, Akhtar U, Moss E, O'Reardon JP. Transcranial magnetic stimulation (TMS) in the treatment of attention-deficit/hyperactivity disorder in adolescents and young adults: A pilot study. J ECT. 2012;28:98-103.
39 Bloch Y, Harel EV, Aviram S, Govezensky J, Ratzoni G, Levkovitz Y. Positive effects of repetitive transcranial magnetic stimulation on attention in ADHD subjects: A randomized controlled pilot study. World J Biol Psychiatry. 2010;11:755-8.
40 University of Pennsylvania. ClinicalTrials.gov [Internet]. Transcranial magnetic stimulation for attention deficit/hyperactivity disorder (ADHD) NCT03663179. 2018 Sep 06. https://clinicaltrials.gov/study/NCT03663179
41 McClintock SM, Reti IM, Carpenter LL, McDonald WM, Dubin M, Taylor SF, et al. Consensus recommendations for the clinical application of repetitive transcranial magnetic stimulation (rTMS) in the treatment of depression. J Clin Psychiatry. 2018;79:16cs10905.
42 Blumberger DM, Barr MS, Daskalakis ZJ. Repetitive transcranial magnetic stimulation for psychiatric disorders other than depression. In: Hamani C, Holtzheimer P, Lozano AM, Mayberg H, editors. Neuromodulation in psychiatry. Chichester: John Wiley & Sons; 2016. p. 181-201.
43 Smith JR, DiSalvo M, Green A, Ceranoglu TA, Anteraper SA, Croarkin P, et al. Treatment response of transcranial magnetic stimulation in intellectually capable youth and young adults with autism spectrum disorder: A systematic review and meta-analysis. Neuropsychol Rev. 2023;33:834-55.
44 Rossi AF, Pessoa L, Desimone R, Ungerleider LG. The prefrontal cortex and the executive control of attention. Exp Brain Res. 2009;192:489-97.
45 Wasserstein J, Stefanatos GA. The right hemisphere and psychopathology. J Am Acad Psychoanal. 2000;28:371-95.
46 Sokhadze EM, Lamina EV, Casanova EL, Kelly DP, Opris I, Tasman A, et al. Exploratory study of rTMS neuromodulation effects on electrocortical functional measures of performance in an oddball test and behavioral symptoms in autism. Front Syst Neurosci. 2018; 12:20.
47 Casanova MF, Baruth JM, El-Baz A, Tasman A, Sears L, Sokhadze E. Repetitive transcranial magnetic stimulation (rTMS) modulates event-related potential (ERP) indices of attention in autism. Transl Neurosci. 2012;3:170-80.

48 Hauer L, Sellner J, Brigo F, Trinka E, Sebastianelli L, Saltuari L, et al. Effects of repetitive transcranial magnetic stimulation over prefrontal cortex on attention in psychiatric disorders: A systematic review. J Clin Med. 2019;8:416.
49 Razza LB, Moffa AH, Moreno ML, Carvalho AF, Padberg F, Fregni F, et al. A systematic review and meta-analysis on placebo response to repetitive transcranial magnetic stimulation for depression trials. Prog Neuropsychopharmacol Biol Psychiatry. 2018;81:105-13.
50 Kakuszi B, Szuromi B, Bitter I, Czobor P. Attention deficit hyperactivity disorder: Last in, first out - delayed brain maturation with an accelerated decline? Eur Neuropsychopharmacol. 2020; 34:65-75.
51 Chorna O, Cioni G, Guzzetta A. Chapter 24 - Principles of early intervention. In: Gallagher A, Bulteau C, Cohen D, Michaud JL, editors. Amsterdam: Handbook of Clinical Neurology. Elsevier; 2020. p. 333-41.