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Research paper

Efficacy and safety of repetitive transcranial magnetic stimulation in children and adolescents with depression: A systematic review and preliminary meta-analysis

Hui Qiu [a,1], Kaili Liang [a,1], Lu Lu [a], Yingxue Gao [a], Hailong Li [a], Xinyue Hu [a], Haoyang Xing [c,d], Xiaoqi Huang [a,b,*], Qiyong Gong [a,b]

[a] Huaxi MR Research Center (HMRRC), Department of Radiology, West China Hospital of Sichuan University, Chengdu, PR China
[b] Psychoradiology Research Unit of the Chinese Academy of Medical Sciences, West China Hospital of Sichuan University, Chengdu, PR China
[c] Huaxi MR Research Center (HMRRC), Functional and Molecular Imaging Key Laboratory of Sichuan Province, Department of Radiology, West China Hospital of Sichuan University, Chengdu, PR China
[d] School of Physical Science and Technology, Sichuan University, Chengdu, PR China

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ABSTRACT

Background: Repetitive transcranial magnetic stimulation (rTMS) benefits adults with depression while its efficacy and safety in children and adolescents with major depressive disorder (MDD) remain unclear. We conducted a preliminary meta-analysis here to objectively appraise rTMS in the youth with MDD to inform future research and clinical practice.

Methods: We searched Pubmed, Embase, Web of Science and the Cochrane Central Register of Controlled Trials from their inception to December 1, 2021. Studies with a control group or self-controlled designs and evaluating the Hamilton Depression Scale (HAM-D) or the Children's Depression Rating Scale–Revised (CDRS-R) at baseline and post-rTMS treatment were included. Two reviewers independently selected eligible studies, retrieved data in a structured fashion and assessed studies' quality. Hedges'g with 95 % confidence intervals and withdrawal rate with 95 % confidential intervals were separately used to evaluate the efficacy and safety of rTMS.

Results: Thirteen studies with six datasets (165 patients, 61.8 % female, age range from 10 to 25 years old) were included and our meta-analysis found children and adolescents with MDD benefited from rTMS treatment (Hedges'g 1.37, 95 % CI 0.85 to 1.90, $P = 0.001$). In addition, 4 % of patients (95 % CI 0.02 to 0.09) withdrew during rTMS treatment for reasons including fear, mood swings, suicide ideation and adverse events.

Limitations: This conclusion is tempered by a small number of studies included and a potentially existing placebo effect.

Conclusions: Our findings suggest rTMS could benefit children and adolescents with MDD in a relatively safe manner, and this result may help guide clinical practice.

1. Introduction

Major depressive disorder (MDD), one of the most prevalent mental health conditions worldwide, usually first occurred in youth and affected approximately 5–15 % of children and adolescents (Weersing et al., 2017; Kaiser et al., 2019; Oud et al., 2019). Patients with MDD suffered social impairment, increased suicide risk and relapsed symptoms while the treatment options available to children and adolescents now are limited by a lack of professionals, high expense, patient resistance and the invasive nature of some treatments (Duffy et al., 2019; Reangsing et al., 2020; Zhou et al., 2020). In addition, patients diagnosed with MDD in childhood and adolescence have higher risks for chronic recurrence and poor functioning and the need for an effective and safe intervention to treat depression in youth emerged (Weersing et al., 2017).

Repetitive transcranial magnetic stimulation (rTMS), as an

* Corresponding author at: Huaxi MR Research Center (HMRRC), Department of Radiology, West China Hospital, Sichuan University, Research Unit of Psychoradiology, Chinese Academy of Medical Sciences, No. 37 Guo Xue Xiang, Chengdu 610041, PR China.
E-mail address: julianahuang@163.com (X. Huang).
[1] These authors contributed equally to this work.

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important non-invasive add-on therapy for depression, has been applied to adults in the past three decades (Milev et al., 2016; Liang et al., 2021). The underlying mechanism is that the stimulation produced by a magnetic coil can reset cortical oscillatory activity and re-establish intrinsic cerebral rhythms, thereby non-invasively modulating the activity of neurons and circuits that participate in emotion and movement regulation (D'Agati et al., 2010; Leuchter et al., 2013), on the grounds that MDD and associated psychiatric conditions are disorders of distributed neural networks (Mohan et al., 2016). Many clinical trials and meta-analyses have confirmed that rTMS can significantly improve adult patients' depression symptoms, suicidal ideation, and social functioning (Perera et al., 2016; Brunoni et al., 2017; Mutz et al., 2019; Cash et al., 2021). Thus, daily, high-frequency rTMS targeting the left prefrontal cortex has been approved by the Food & Drug Administration as a standard treatment protocol for adult MDD (Center for Devices and Radiological Health, 2011).

Despite major advances in the study and clinical application of rTMS in adults with depression, the efficacy and safety of rTMS in children and adolescents with depression are still unclear. Commonly used high-frequency rTMS decrease motor threshold and elevate cortical excitability and activity through voltage-gated sodium channels, non-*N*-methyl-D-aspartate, and *N*-methyl-D-aspartate glutamatergic functioning, however, what is accompanied by increased cortical excitability is theoretically increased risk of seizures of depressed patients, especially in children and adolescents (Croarkin et al., 2012, Croarkin et al., 2016). Several pioneering studies aimed to investigate the effectiveness and safety of rTMS in children and adolescents from different angles. Cross-sectional studies suggested that rTMS was suitable for children and adolescents with depression (Bloch et al., 2008; Wall et al., 2011; Croarkin et al., 2012; MacMaster et al., 2019); longitudinal designs confirmed immediate and long-term benefits of rTMS in transitional aged youth (Mayer et al., 2012a, Mayer et al., 2012b, Wall et al., 2014, Wall et al., 2016); Zhang et al. reported better rTMS treatment outcomes in adolescents than in adults. Emily et al., however, took the opposite position based on their research (Rosenich et al., 2019; Zhang et al., 2019; Sonmez et al., 2020). While heterogeneity has been observed in outcomes, high-frequency (10 Hz) rTMS of the left prefrontal cortex at 120 % of the motor threshold in 4-second trains separated by 26-second intervals is the most commonly adopted protocol in the literature, and although the overall quality of existing studies is inadequate, most of them give discernible signs that rTMS offers an attractive option as a safe and effective treatment for children and adolescents with depression (Hett et al., 2020; Zewdie et al., 2020).

To our knowledge, only a few systematic reviews have discussed the efficacy and safety of rTMS in children and adolescents with no meta-analysis conducted. For instance, three early published reviews which included available case reports and single-arm trials summarized rTMS do benefits to pediatric depression with a variety of adverse events occurred (Magavi et al., 2017; Hett et al., 2020; Gupta et al., 2021). While a recent review indicated rTMS failed to show its superiority over placebo for young patients with MDD and only some minor and self-limited side effects happened among patients (Majumder et al., 2021). Divergence appeared among these studies and meta-analyses that can settle divergences between conflicting studies are needed. Here, we updated the systematic review by enlarging the search scale and conducting a preliminary meta-analysis that combines all available studies, examines the same trait in the same age group, and finally try to reach a more reliable conclusion. In this study, we comprehensively collected studies involving rTMS-treated depressed patients below 25 years old. We hypothesized that rTMS could attenuate depression in children and adolescents in a relatively safe manner. We determined the efficacy based on the difference between pre-treatment and post-treatment Hamilton Depression Scale (HAM-D) or Children's Depression Rating Scale-Revised (CDRS-R) scores. We determined safety based on the withdrawal rate and the occurrence of adverse events.

2. Materials and methods

We followed the newly released Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines for systematic review (Page et al., 2021). The study was registered in the Prospective Register of Systematic Reviews (PROSPERO) under the number CRD 42021229489.

2.1. Search strategy and selection criteria

Eligible studies were identified from a database search of Pubmed, Embase, Web of Science and the Cochrane Central Register of Controlled Trials from their inception to December 1, 2021. Keywords selected for the article search included 'rTMS' or 'repetitive transcranial magnetic stimulation' AND 'depression' AND 'children' or 'adolescent'. Manual searches were also conducted within the reference lists of identified articles to obtain additional reports and previously published reviews were also used to cross-check for studies that might be potentially missed out. Two authors (H. Qiu and K. Liang) did the literature search independently.

We included studies with a control group or self-controlled designs exploring the efficacy and safety of rTMS in children and adolescents (both sexes, $\leq$25 years old) with a diagnosis of MDD according to the Diagnostic and Statistical Manual of Mental Disorders. Participants who received rTMS as an additional therapy (add-on therapy) were those who failed to respond to antidepressant drugs, and they were allowed to continue medications when receiving rTMS treatment. The studies needed to include the HAM-D or the CDRS-R to evaluate the severity of symptoms at baseline and post-rTMS treatment. Additionally, we included only articles written in English. Articles focusing on other Axis I disorder or other therapeutic approaches were excluded, and articles using different rTMS pulse sequences from those used in conventional rTMS, such as theta-burst stimulation (TBS), and low-field synchronized TMS (sTMS), were also excluded to eliminate the influence of pulse sequences.

2.2. Data extraction

We retrieved data in a structured fashion. First, study characteristics such as the title, author's name, publication year, sample size, subject age distribution, subject gender distribution and study protocols were extracted. Then, we extracted the mean and standard deviation values of HAM-D/CDRS-R scores at baseline and post-rTMS treatment. Also, rTMS targets, rTMS frequency, total session, percentage of resting motor threshold (% RMT), and total number of pulses were extracted. Finally, we extracted types of adverse events that occurred during the rTMS treatment and the number of patients who dropped out due to any adverse events to evaluate the withdrawal rate. Data on the same clinical trial from different articles were merged, and only the dataset with the largest sample size was included. The missing data that could not be retrieved from the original publications were acquired from corresponding authors.

2.3. Study quality assessment and data analysis

The papers selected were assessed by two independent reviewers (H. Qiu and K. Liang) using the New-castle Ottawa scale, a star scoring depended system. The maximum score of this system is nine for a case-control study and studies that received scores above 6 were considered high quality.

We used the Stata (version 16.0) and R (Version 4.1.2) to perform the statistical analyses. The Hedges'g, which could adjust for small sample bias, was used to present the effect sizes of pre-post HAM-D/CDRS-R score changes within-subjects (Gibbons et al., 1993). We calculated and pooled the Hedges'g with 95 % confidence intervals (Cis) to assess the efficacy of rTMS using the random-effects model. The withdrawal rate

with 95 % confidential intervals (using a fixed-effect model with Freeman-Tukey Double arcsine transformation) was used to evaluate the safety (Balduzzi et al., 2019). We evaluated heterogeneity by using the Cochrane Q statistics and I^2 statistics and heterogeneity was classified according to I^2 statistics' ranges: low (0–40 %), moderate (30–60 %), substantial (50–90 %), and considerable (75–100 %) (Beaudry et al., 2021, Higgins et al., 2021). Furthermore, we performed sensitivity analysis (excluding articles one by one) and meta-regression analysis to explore the sources of heterogeneity, and we assessed publication bias using funnel plots and Egger's test.

3. Results

3.1. Characteristics of the included studies

Of 724 references, 711 were excluded for a variety of reasons; ultimately, thirteen studies published from 2008 to 2020 were included in our systematic review (for the selection process, see Fig. 1; for the characteristics of the studies, see Table 1) (Bloch et al., 2008, Wall et al., 2011, Croarkin et al., 2012, Mayer et al., 2012a, Wall et al., 2013, Croarkin et al., 2016, Wall et al., 2016, Croarkin et al., 2018, MacMaster et al., 2019, Rosenich et al., 2019, Zhang et al., 2019, Croarkin et al., 2021, Sonmez et al., 2020). Overall, 240 MDD patients were included, their ages ranged from 10 to 25, and more than half (62.9 %) of the patients were female. All 13 studies except 1 targeted the left prefrontal cortex (a study conducted by Rosenich et al., applied rTMS stimulation bilaterally and they have proved in previous research that efficacy was similar among patients between bilateral and unilateral rTMS protocols). The frequency used was consistent at 10 Hz. Eight out of 13 studies used 30 sessions of stimulation at 120 % RMT, two studies used 14 sessions of stimulation at 80 % and 110 % RMT separately, two studies reported 120 % RMT with different numbers of sessions separate at 10, 15, and the remaining study gave rTMS stimulation at 80 % RMT for 20 sessions. The total number of pulses given to each patient ranged from 24,000 to 90,000, and the treatment duration ranged from 2 weeks to 8 weeks. Patients in all studies except one (Croarkin et al., 2021) were allowed to take antidepressant medications and/or mood-stabilizing medications.

3.2. Risk-of-bias assessment

We assessed risk of bias using the Newcastle-Ottawa scale (NOS) across three domains: Selection, Comparability and Exposure/Outcome (Hett et al., 2020). For Croarkin et al., conducted a randomized sham-controlled trial, The NOS scale for the case-control study was used for this study and the other 12 studies were assessed according to the NOS scale for cohort study. According to our criteria (Supplementary Tables 1 and 2), there was 1 high-quality study, and the rest 12 studies are all average-quality studies.

3.3. Efficacy

After the comparison between the thirteen studies in terms of Clinical Trials registration number and sample characteristics, we included six articles in our meta-analysis due to sample overlapping (including a total of 165 patients, of whom 102 (61.8 %) were female) (Bloch et al., 2008, Croarkin et al., 2018, MacMaster et al., 2019, Rosenich et al., 2019, Zhang et al., 2019, Croarkin et al., 2021).

The meta-analysis showed children and adolescents with depression received benefits after high-frequency rTMS over the prefrontal cortex (Hedges'g 1.37, 95 % CI 0.85 to 1.90, $P < 0.001$; Fig. 2) with high heterogeneity ($I^2 = 99.4$ %), and the result did not change substantially in the sensitivity analysis by excluding studies one by one (Supplementary Fig. 1a–f). Next, in meta-regression analyses, we found no significant associations between study characteristics (gender ratio (defined as the number of females divided by the number of males), mean age, sample size, RMT, sessions, study quality) and efficacy of rTMS treatment in these analyses (Supplementary Table 3).

We found evidence of publication bias from both the visual inspection of the asymmetric funnel plot and the result of Egger's test ($z = 3.12$, $P < 0.05$), which indicated small-study effects (Fig. 3). Three small studies were identified, and the funnel plot was symmetric after three imputed studies were added using the trim-and-fill method (pooled estimate = −1.493, 95 % CI -1.655 to −1.331, Q = 17.468, $P > 0.05$,

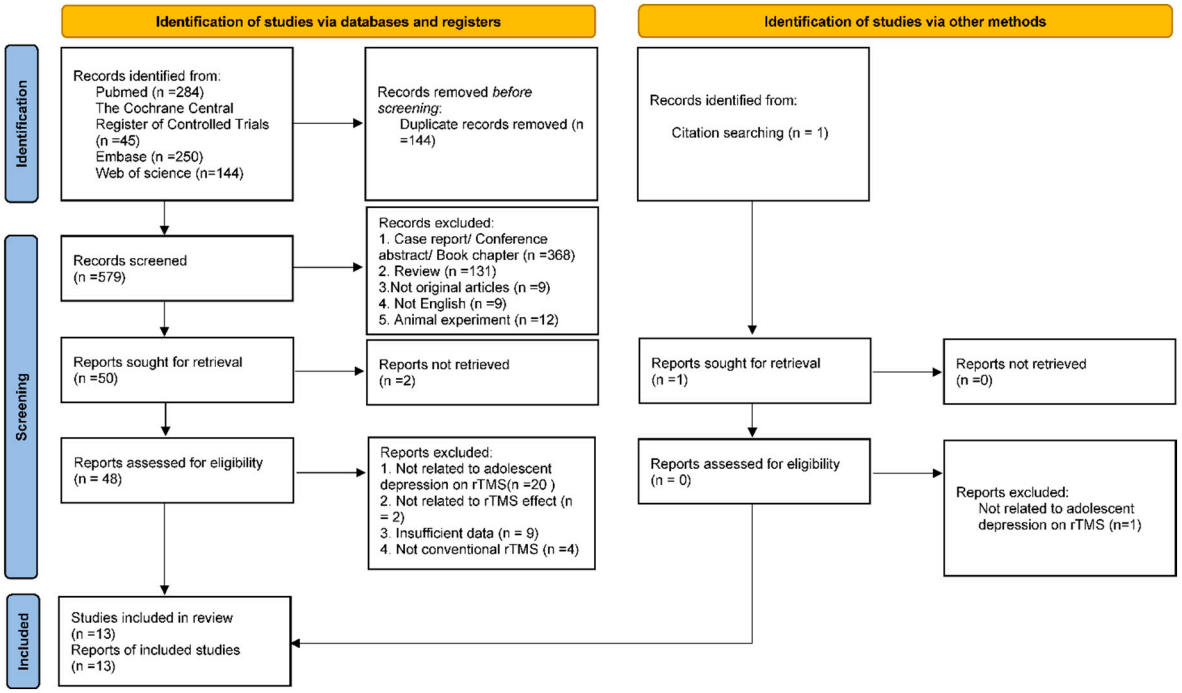

Fig. 1. Preferred reporting items for systematic reviews and meta-analysis flow diagram.
The literature search resulted in 724 potentially relevant studies, of which 13 eligible studies were pooled for systematic review.

Table 1
Demographic characteristics and rTMS parameters for all 13 studies included in the systematic review.

Study	Demographic			rTMS parameters							Protocols
	n	Age (years)	Female/ male (n)	Cortical target	Frequency (Hz)	Sessions	% RMT	Total pulse	Treatment duration (weeks)	Follow-up period (weeks)	
Sonmez_2020[a]	17	13–19 (15.94 ± 1.35)	12/5	L-DLPFC	10	30	120	–	6–8	24	NCT00587639 NCT01502033 NCT01804270
Croarkin_2020	48	12–20 (17.6 ± 2.28)	30/18	L-DLPFC	10	30	120	90,000	6	–	NCT02586688
Zhang_2019	42	10–17 (14.6 ± 2.0)	29/13	L-DLPFC	10	10	120	24,000	2	4	–
Rosenich_2019	15	17–25 (20.69 ± 2.55)	8/7	L/R-DLPFC	10	14	110	–	6	–	–
MacMaster_2019	32	13–21 (17.57 ± 1.98)	15/17	L-DLPFC	10	15	120	45,000	3	–	NCT01731678
Croarkin_2018[b]	19	13-19 (16.00 ± 1.29)	13/6	L-DLPFC	10	30	120	90,000	6–8	–	NCT00587639 NCT01502033 NCT01804270
Wall_2016[a]	10	13.9–17.4 (15.9 ± 1.1)	4/6	L-DLPFC	10	30	120	90,000	6–8	24	– (dataset was similar with Croarkin_2016)
Croarkin_2016[a]	10	13.9–17.4 (15.9 ± 1.1)	4/6	L-DLPFC	10	30	120	90,000	6–8	24	NCT01502033
Wall_2013[a]	14	13.9–17.8 (16.3 ± 1.1)	9/5	L-DLPFC	10	30	120	90,000	6–8	–	NCT00587639
Mayer_2012	8	19–22 (20.4)	6/2	L-DLPFC	10	14	80	–	2	–	–
Croarkin_2012[a]	8	14–17 (16.1 ± 1.1)	7/1	L-PFC	10	30	120	90,000	6–8	–	– (dataset was similar with Wall_2011)
Wall_2011[a]	8	14.6–17.8 (16.5 ± 1.18)	7/1	L-DLPFC	10	30	120	90,000	6–8	24	NCT00587639
Bloch_2008	9	16-18 (17.2 ± 0.83)	7/2	L-DLPFC	10	20	80	–	2	144[c]	–

Abbreviations: n = number; yrs. = years; Hz = hertz; RMT = resting motor threshold; L = left; DLPFC = dorsolateral prefrontal cortex.
[a] Duplicate publications of the same study population.
[b] The largest dataset among studies.
[c] Data acquired from another article (Mayer et al., 2012a, 2012b).

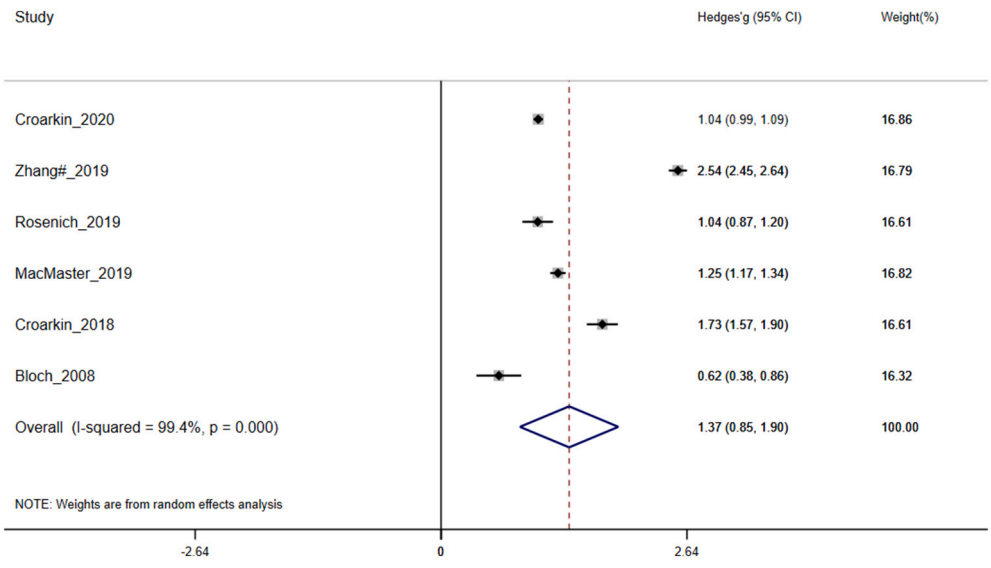

Fig. 2. Forest plot of efficacy in children and adolescents with depression receiving repetitive transcranial magnetic stimulation treatment. Six studies provided data on efficacy of repetitive transcranial magnetic stimulation treatment. Error bars show 95 % confidence intervals.

supplementary Fig. 2) (Duval and Tweedie, 2000; Higgins and Sterne, 2011).

As for long-term follow-up results, we reach an encouraging conclusion from existing publications. Wall et al., conducted an open trial in 2011 with 8 patients, they gave these patients thirty daily rTMS treatments 5 days per week over 6–8 weeks and they found rTMS can effectively improve patients' symptoms at the end of treatment and 6 months later (Wall et al., 2011). Another study also found improvement got by adolescents upon completion of rTMS treatment still maintained 6 months later (Wall et al., 2016). Mayer et al., made a three-year follow-up to assess recipients' depressive symptoms after rTMS and their small pilot study provide promising evidence of long-term stability of effectiveness and safety for the first time (Mayer et al., 2012a).

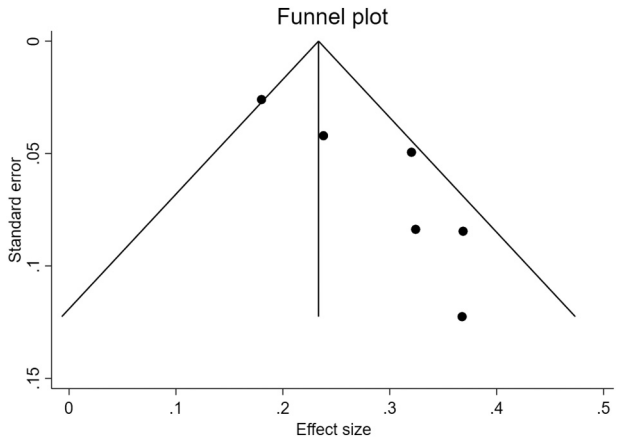

Fig. 3. Funnel plot overseeing publication bias of six studies included in the meta-analysis.
Funnel plot of the meta-analysis. The x-axis on the plot represents the effect size, and the y-axis is standard error. The black circles represent included studies.

3.4. Safety

In terms of the withdrawal rate, our result showed 4 % (95 % CI 2 % to 9 %) patients dropped out during treatments (Fig. 4), including four patients quit their therapy due to adverse events like headache, eye pain and other common side effects; one patient quit his therapy for academic expectation and one for worsening suicide ideation. The last patient stopped his treatment because of fears and mood swings. There was no evidence of significant heterogeneity between trials ($I^2 = 0$ %, $P = 1.00$) and no subgroup analyses were conducted due to a small number of studies.

The adverse event rate could not be obtained because some studies did not report exact numbers of certain side effects, and these data could not be acquired by contacting the authors. Hence, descriptive results were presented in our study. Among studies that reported adverse events, pain, including scalp pain, neck pain, and eye pain, was the most commonly observed event. It was reported in 47 patients from 3 available studies (Bloch et al., 2008, MacMaster et al., 2019, Croarkin et al., 2021) and referred to in two other studies (Rosenich et al., 2019; Zhang et al., 2019). Gastrointestinal problems such as nausea and vomiting were reported in 13 patients from 2 studies (MacMaster et al., 2019, Croarkin et al., 2021); muscle twitching and muscle aches were reported in 18 patients from 2 studies (MacMaster et al., 2019, Croarkin et al., 2021); psychiatric problems such as Insomnia, panic attacks and suicidal ideation were reported in 6 patients from 1 studies (Croarkin et al., 2021); infection was reported by only 2 patients in a single study (Croarkin et al., 2021), and psychiatric disorders were reported by 6 patients in one study: insomnia (2), panic attacks (2) and suicide ideation (2).

4. Discussion

Repetitive TMS has been approved as an alternative and add-on therapy for adults with MDD since 2008 and it has gained much attraction in recent years (Mutz et al., 2019). Whether this form of non-invasive neuromodulation could benefit children and adolescents or not is unknown. Our study for the first time quantitatively validated that the youth achieved improvement in symptoms after unilateral (high-frequency left-side) or bilateral (high-frequency left-side and low-frequency right-side) rTMS was applied to the prefrontal cortex as an add-on therapy. Furthermore, response rate for studies included in our meta-analysis ranges from 33 % to 56 % (Bloch et al., 2008, MacMaster et al., 2019, Rosenich et al., 2019, Croarkin et al., 2021), which was similar to that in adults (29 %–60 %) (Berlim et al., 2014; Cao et al., 2018; Lacroix et al., 2021); And remission rate varies from 13 % to 44 % (Bloch et al., 2008, MacMaster et al., 2019, Rosenich et al., 2019, Croarkin et al., 2021), which seems better in children and adolescents than that in adults (18 %–22 % respectively) (Berlim et al., 2014; Cao et al., 2018). This result indicated rTMS is effective on young people affected by depression, but future studies with larger sample size and different rTMS strategies are needed to validate the results given the small number of primary studies in current meta-analysis.

Our present analysis displayed an overall promising result of rTMS on treating children and adolescents with MDD, opposite opinions from some single studies also deserve discussion. Croarkin et al. showed differences of symptom severity alteration between the TMS group and the sham control group were not significant and they attributed it to a large placebo effect (Croarkin et al., 2021). Placebo effect, refers to any changes (usually beneficial) that occur within a group 'treated' with a placebo, has been deliberately applied, demonstrated and measured by our medical forebears (Thompson, 2000; Hernández et al., 2014). For instance, Baeken et al. reported significant benefits of sham rTMS for adult MDD, attributing them to the placebo effect (Baeken et al., 2019); Razza et al. drew a similar conclusion in their rTMS depression trials among young people (Razza et al., 2018), and Jay et al. demonstrated the superiority of antidepressant medication over placebo may be minimal or non-existent, on average, in patients with mild or moderate depression (Fournier et al., 2010). As the placebo effect introduces a great deal of heterogeneity across individuals in various trials, future studies need sham control groups to exclude the placebo effect and further explore its mechanism.

Aside from relieving depression severity, TMS had also been proposed to reduce suicidality in children and adolescents with MDD. Croarkin et al. found adolescents with treatment-resistant depression got improvement in suicidal ideation across 30 sessions and though this effect was attenuated when adjusting for illness severity (Croarkin et al., 2018), the outcome might not have been solid owing to the small sample size. This study implied it was nonetheless of great importance for rTMS is a promising approach to treating suicidal ideation among adolescents. Now, the youth have the highest prevalence of suicidal ideation and depression, and suicide is the second leading cause of death for people

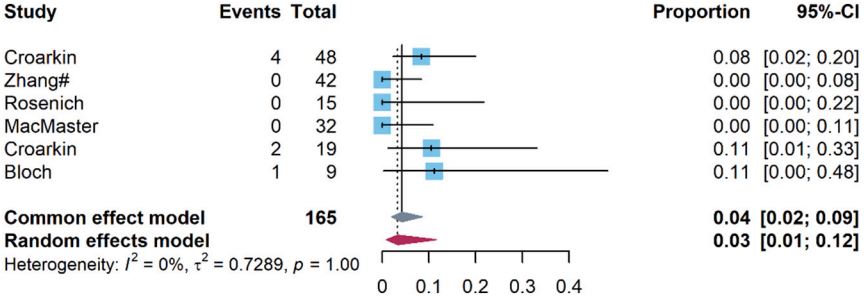

Fig. 4. Withdrawal rate of repetitive transcranial magnetic stimulation treated children and adolescents with depression.
Six studies provided data on withdrawals during repetitive transcranial magnetic stimulation treatment. Error bars show 95 % confidence intervals.

aged 10–24 years (Milliman et al., 2020). Behind the phenomenon is the incomplete neurodevelopment of children and adolescents, which means immature inhibitory control systems and sharpened reward systems that contribute to high responsivity to emotional stimuli (Spear, 2013). Since rTMS is an effective method to regulate certain brain regions, it might be fruitful to explore the efficacy of rTMS against suicidal ideation in children and adolescents with depression in a larger population.

Besides, our result demonstrated a low patient dropped out rate (4 %) during treatment which adds favorable evidence for the safety of rTMS. Zewdie et al. conducted several studies before to assess the safety and tolerability of various non-invasive brain stimulation in children, including rTMS treatment in children with MDD (King et al., 2019; Zewdie et al., 2020; Kahl et al., 2021) and showed no serious adverse events. His another study, focusing on rTMS treatment in 10 children with Tourette syndrome, also found no serious adverse events (Kahl et al., 2021). Hence, we speculate that the commonly used rTMS stimulation modalities and paradigms were relatively safe and tolerable in the pediatric population.

However, we also revealed side effects of rTMS on children and adolescents during treatment. Among 165 patients in our meta-analysis, 63 % reported treatment-related pain and it was consistent with previous research (Krishnan et al., 2015). The uncomfortableness experienced during treatment might be caused by incidental stimulation of the facial nerve, and the severity depends on individual susceptibility, scalp location, stimulation frequency, stimulation intensity, and coil design (Borckardt et al., 2006; Rossi et al., 2009). Studies aimed at the adult population estimated that pain risk is elevated when stimulation intensities are higher than 100 % of the motor threshold and stimulation frequencies higher than 1 Hz (Milev et al., 2016; Lefaucheur et al., 2020). Since children and adolescents showed hyper-excitability signs, extremely short recovery cycles and non-attenuated cortical responses to repetitive stimulation when compared with adults (Zanini et al., 2016), parameters applicable to the adult may not fit for children and adolescents. In addition, an interesting phenomenon we observed in our analysis was that when children and adolescents received stimulation under 100 % RMT, they were more unlikely to drop out because of pain. As a result, we would advocate individualized parameters.

The most severe and concerning potential side effect, seizure, was not reported in our results for only articles meet our criteria were included. But other studies had offered some evidence on this problem, Debra et al. reported that the risk of rTMS-induced seizures in children and adolescents was similar to that of adults (<0.1 % per acute treatment course) and Croarkin et al. illustrated roughly the same possible incidence of seizures (limited to 0.1 %–0.6 % of adolescent patients with depression) (Carpenter et al., 2012; Croarkin and MacMaster, 2019; Stultz et al., 2020). Since studies focused on exploring rTMS-induced seizures in children and adolescents were not enough, we can only infer risk factors for this special group through experience learned from adults. In one possible mechanism, high frequencies and short intervals between trains of stimulation could induce hypersynchronous discharges of groups of neurons in the grey matter and thus cause seizures. In another mechanism, direct stimulation of the motor cortex or stimulation of adjacent brain areas with a spread of neuronal excitation to the motor cortex can induce seizures (Wassermann, 1998; Rossi et al., 2009). Since children and adolescents showed hyper-excitability signs in the cortex, choosing proper frequencies and intervals and localizing the target sites with higher accuracy may aid in decreasing seizures.

Finally, when we discuss the efficacy and safety of rTMS in children and adolescents and before we adopt protocols that seem safe for adult population to the youth, we can hardly omit the neurobiological differences between these two groups. For example, one Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) analysis probing neuroanatomical substrates of MDD revealed that regions closely interacting with the limbic system (essential parts of limbic–cortical circuits that constitute the MDD pathophysiological model) had cortical thickness deficits in adult MDD, while reduced total surface area in adolescent patients (Schmaal et al., 2017). Another meta-analysis found adult and adolescent MDD patients' different network dysfunction was related to distinct impairments of amygdala-centered resting-state functional connectivity (Tang et al., 2018). In addition, youth is a period characterized by substantial structural and functional development; markers of excitation, inhibition and connectivity are age-dependent. Evidence from neuroendocrine studies also confirmed developmental differences between adults and youth, which might influence outcomes of therapy, including rTMS (Kaufman et al., 2001); hence, it is unclear whether the changes in their depression symptoms reflect the reality of their illness. Furthermore, the intracortical neurophysiology of depression is more difficult to discern in children than in adults (Hollis et al., 2020) because the neurobiological systems implicated in the pathophysiology of adult depression are immature in children and adolescents (Kaufman et al., 2001); thus, additional longitudinal research is needed to determine whether their treatment response reflects the real function of rTMS therapy. However, given what is known from these studies, rTMS has the potential to be a safe and effective add-on therapy for children and adolescents with MDD.

4.1. Limitations

The current study has the following limitations. First, the number of studies included in our meta-analysis and sample size for each study are both small, and this might underscore or overestimate the real efficacy of rTMS. Second, studies included used inconsistent symptom severity rating scales and though we did our best to explain the sources of high heterogeneity using meta-regression analyses regarding efficacy, we found no significant associations between the study characteristics and efficacy. The individual patient-level data would help to explore the potential effects of the characteristics. Moreover, although there was one sham-controlled study (Croarkin et al., 2021), other studies were all self-controlled studies, and our interpretation of the results was therefore impeded. Third, since different protocols have different efficacy according to a previous study (Brunoni et al., 2017), in this study we excluded novel forms of TMS, such as TBS and sTMS, and the efficacy of different protocols of rTMS will need to be examined in future research. Thus, our study is not a comprehensive assessment of TMS treatment for depression in children and adolescents and the results can only represent for rTMS in particular. Finally, almost patients in our analysis were allowed to take medications, though the heterogeneity induced by medication may reduce credibility of the results, these findings still provide evidence in favor of effectiveness and safety of rTMS in children and adolescents. Hence, more large sham-controlled studies were needed in the future.

5. Conclusion

This review and meta-analysis not only suggest that rTMS might be a useful add-on therapy for children and adolescents with depression but also showed its safety by a low withdrawal proportion and mild-moderate adverse events. However, practitioners and health professionals should be cautious with the results since we cannot exclude placebo effects and influence of medication. As most of the studies have small sample sizes and lack sham controls, sham-controlled studies with larger sample sizes are needed in the future. Furthermore, future studies exploring neurophysiology of TMS in young people might help to explain the mechanisms of this popular non-invasive stimulation on depressive symptoms in children and adolescents.

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CRediT authorship contribution statement

Xiaoqi Huang, Qiyong Gong and Haoyang Xing conceptualized and designed the study, provided methodological advice, supervised the conduct of the study and revised the manuscript.

Hui Qiu and Kaili Liang collected data, performed the data analysis and drafted the initial manuscript.

Lu Lu, Hailong Li, Yingxue Gao, and Xinyue Hu revised and proofread the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Conflict of interest

All authors report no financial interests or potential conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2022.09.060.

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