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REVIEW

The Effects of Repetitive Transcranial Magnetic Stimulation on Post-Traumatic Stress Disorder and Parameter Discussion: A Meta-Analysis Based on Randomized Controlled Trials

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Background: Recovery from posttraumatic stress disorder (PTSD) is an urgent clinical issue. Repetitive transcranial magnetic stimulation (rTMS) has shown advantages in treating PTSD. However, the quality of existing evidence is low. This review aims to evaluate the efficacy and safety of rTMS for PTSD and to explore the key parameters that influence its therapeutic effects.

Methods: We searched five electronic databases from their inception through September 22, 2024. Eligible studies were screened and data were extracted; the methodological quality of the included trials was assessed. Meta-analysis was performed using RevMan 5.3, and dose–response analysis was conducted with Stata 18.0.

Results: Fifteen studies involving 760 patients were included. There was no statistically significant difference between high-frequency rTMS (HF-rTMS) and low-frequency rTMS (LF-rTMS) ($p = 0.24$). Neither the >80% motor threshold (MT) group nor the >10-day treatment group differed significantly from their respective control groups (80% MT and ≤10 days; $p > 0.05$). The dose-response analysis showed no linear relationship between MT and PTSD Checklist (PCL) (nonlinearity test $P=0.008< 0.05$), whereas a linear relationship was observed between treatment sessions and PCL scores (linearity test $P=0.001< 0.05$, nonlinearity test $P=0.631> 0.05$). As the treatment sessions increased, the PCL scores decreased in a dose-dependent manner.

Conclusion: rTMS is an effective and noninvasive treatment for PTSD. However, study findings suggest that there are no statistically significant differences between HF-rTMS and LF-rTMS, or between >80% MT and <80% MT groups. Dose–response analysis indicates a positive correlation between increased number of sessions and symptom improvement. Despite limitations such as small sample sizes and high heterogeneity that may affect the robustness and generalizability of the results, this study still recommends prioritizing high-frequency rTMS and increased treatment sessions to enhance therapeutic outcomes.

Keywords: post-traumatic stress disorder, repetitive transcranial magnetic stimulation, non-invasive neuromodulation

Introduction

Post-traumatic stress disorder (PTSD) is a mental health disorder that persists after a significant traumatic event.[1] Epidemiological studies show that 70% of the population experiences at least one traumatic event in their lifetime[2], with approximately 4–9% of individuals developing PTSD.[3,4] Currently, guidelines recommend pharmacotherapy and psychotherapy as first-line treatments for PTSD symptoms.[5] Commonly used anxiolytics, antidepressants, and sedatives have limited efficacy and carry risks of drug dependence and avoidance behaviors in patients.[6–9] Psychotherapy faces

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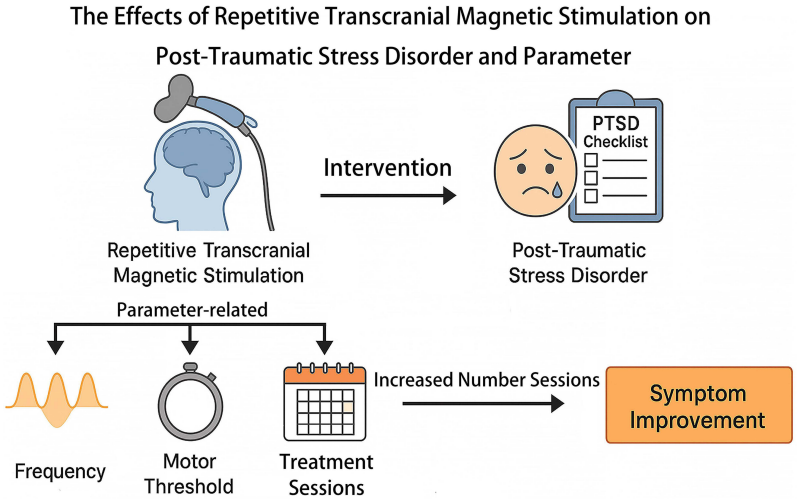
Graphical Abstract



challenges such as individual variability in treatment response, limited resources of therapists, and high economic costs.[10] Repetitive Transcranial Magnetic Stimulation (rTMS), first introduced in 1985, is a non-invasive neuromodulation technique,[11] it works by placing a coil on the head, and the magnetic field within the coil generates an induced current in specific brain regions, modulating the bioelectrical activity of neural tissue, thereby influencing brain function.[12] Low-frequency rTMS (LF rTMS, ≤1 Hz) can decrease cortical excitability, whereas high-frequency rTMS (HF rTMS, >1 Hz) can increase cortical excitability.[13] Theta-burst stimulation (TBS) is generally considered a mode of high-frequency rTMS, delivering very high-frequency stimulation in a short period of time, typically divided into intermittent TBS (iTBS) and continuous TBS (cTBS). rTMS has advantages such as being non-invasive, good tolerance and cost-effective, and has been used to treat psychiatric disorders like depression and obsessive-compulsive disorder with significant effects.[14,15] It has also received a Level B recommendation in clinical guidelines for the treatment of PTSD.[16]

rTMS involves multiple parameters, such as stimulation target, stimulation frequency, stimulation intensity, and treatment duration.[17–19] The efficacy varies with different parameters and their combinations, leading to inconsistent study conclusions.[20,21] Although existing research has demonstrated that rTMS is an effective treatment for PTSD,[9,13,22–27] no study has compared efficacy and acceptability based on different intervention targets and specific parameter protocols. Therefore, standardized treatment for PTSD patients remains unavailable, and key variables influencing treatment outcomes have not been identified. Additionally, previous studies have overlooked a large number of PTSD samples from China.

This study aims to expand inclusion criteria based on existing research to increase the number of eligible studies. Furthermore, to better identify rTMS variables related to PTSD treatment, this study conducts subgroup and dose-response analyses not only on the commonly used stimulation frequency but also on pulse intensity measured as a percentage of the Motor Threshold (MT) and treatment duration, aiming to provide more comprehensive and scientific evidence for the clinical treatment of PTSD.

Methods

Data Sources and Literature Search

This review was conducted according to the Cochrane Handbook version 5.3. A total of five electronic databases were searched (PubMed, Embase, Web of Science, China National Knowledge Infrastructure (CNKI), and SinoMed), with the search period from database inception to September 22, 2024. The search terms included Medical Subject Headings (MeSH) and text keywords and their combinations, such as "Transcranial Magnetic Stimulation", "Post-Traumatic Stress

Disorder", and others. Additional articles were identified from the reference lists of the studies found and personal reference collections. The specific search strategy can be found in Table S1——Summary of search strategy.

Inclusion and Exclusion Criteria

Inclusion criteria: The inclusion criteria are as follows: (1) Randomized controlled trials (RCTs) evaluating the efficacy of therapeutic TMS in treating PTSD, excluding review articles, systematic reviews, and qualitative studies; (2) Participants must be adults, diagnosed with PTSD based on DSM-IV (APA, 1994), DSM-V (APA, 2013), or other valid psychiatric classification standards; (3) The experimental group receives rTMS treatment, and the control group receives sham treatment; (4) The primary outcome measure is the PTSD checklist (Posttraumatic Stress Disorder Checklist, PCL); (5) Articles published in English or Chinese.

Exclusion criteria include: studies that did not use therapeutic TMS as a treatment for PTSD, non-randomized controlled trials, lack of full-text publications, studies that included conference abstracts, incomplete information, or those that did not measure the primary outcome, as well as studies published in languages other than English or Chinese.

Quality Assessment and Data Extraction

The data were extracted by two researchers (L and Z) from eligible studies, with a third researcher (W) conducting a final assessment of any inconsistencies to reach a consensus. The following data were included: publication information (study authors, year of publication), participant characteristics (age, sample size, gender), treatment parameters (stimulation site, frequency, pulse count, number of treatments, motor threshold (MT)), treatment outcomes, and adverse effects.

The methodological quality of the included studies was independently assessed by two researchers. Any differences in the results were recorded and resolved by a third researcher. Since all studies were randomized controlled trials, the Cochrane Collaboration's Risk of Bias tool was used to assess bias risk, including factors such as random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias.[28,29]

Statistical Analysis

Statistical analysis in this study was performed using RevMan 5.3.5 software, and dose-response analysis was conducted using Stata 18.0. For continuous variables such as the PTSD Checklist (PCL), results were expressed as Standardized Mean Differences (SMD) with 95% Confidence Intervals (CIs). If the mean change scores and standard deviations (SD) were unavailable, but pre- and post-intervention assessment results were provided, the study followed the Cochrane Intervention Systematic Review Handbook recommendations to convert pre/post scores into mean change scores and SD. Effect sizes were categorized as large (SMD > 0.8), moderate ($0.5 \leq SMD \leq 0.8$), or small ($0.2 \leq SMD < 0.5$).

Given the clinical and methodological differences between trials, heterogeneity in the intervention effects was inevitable. The I^2 statistic was used to assess heterogeneity, representing the percentage of total variability in effect size due to differences between studies.[30] When I^2 values were 25%, 50%, and 75%, they indicated low, moderate, and high heterogeneity, respectively. If I^2 was less than 50%, a fixed-effect model was used to combine the data, suggesting that the heterogeneity between studies was within an acceptable range. If I^2 exceeded 50%, a random-effects model was applied, followed by subgroup analysis or sensitivity analysis to explore the sources of heterogeneity.

The differences between subgroups were assessed using a Z-test, calculating the Z-value and p-value for the difference in SMDs between the two groups, as shown in the following formula: $Z= (SMD_1-SMD_2) / (SE_1^2+SE_2^2)^{1/2}$, Where SMD_1 and SMD_2 are the effect sizes for the subgroups, and SE_1 and SE_2 are their standard errors, which were derived from the confidence intervals (CI) using the formula SE = (CI upper limit - CI lower limit) / 3.92. In addition, a one-stage robust error meta-regression (REMR) model based on inverse variance-weighted least squares regression and clustered robust variance was used to analyze the dose–response relationships between the number of treatments and MT with PCL scores, respectively.[31]

Results

Literature Search Results

A total of 313 articles were identified in this study. After removing 35 duplicate articles, 222 articles were excluded based on a careful review of the titles and abstracts. After a full-text review, 42 additional studies were excluded based on the inclusion and exclusion criteria. Ultimately, 15 studies were included in the analysis, all meeting the inclusion criteria (See Figure 1 for the search flow diagram).

This meta-analysis includes 15 randomized controlled trials published between 2004 and 2023, comprising a total of 760 PTSD patients (sample sizes ranged from 20 to 96).[17,18,32–44] The average age of the participants ranged from 30.09 ± 6.30 years to 57.8 ± 11.8 years. Fourteen studies included female participants, while one study only included male participants, specifically male veterans.[33] Each study targeted the right dorsolateral prefrontal cortex (DLPFC) as the stimulation site. One study also investigated the effects of stimulating the left DLPFC,[32] while another explored bilateral DLPFC stimulation.[33] The stimulation frequency varied from 0.5 Hz to 20 Hz, and some studies used the iTBS mode.[34,36] Motor threshold (MT) ranged from 80% to 120%, and the number of treatment sessions varied from 10 to 20 (See Table 1 at the end of the article).

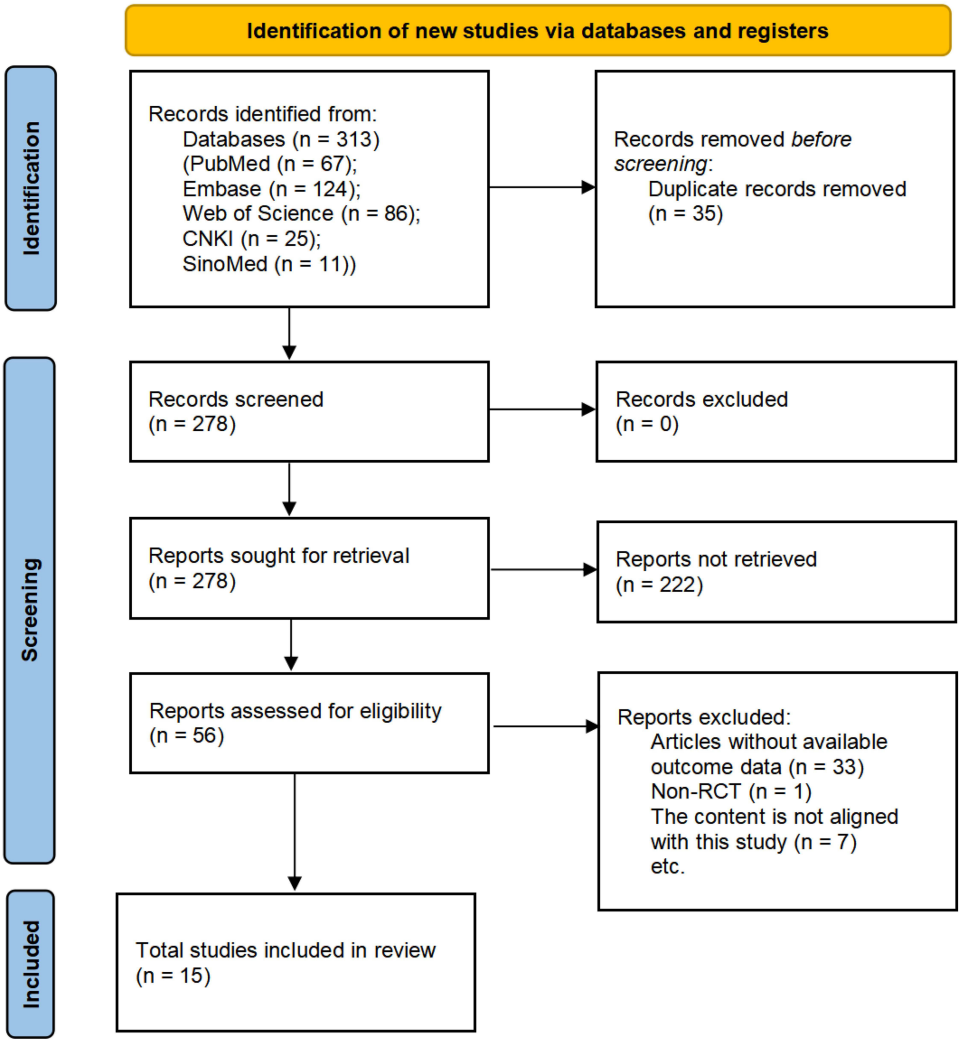


Figure 1 Literature Search Flowchart and Application of Inclusion and Exclusion Criteria.

Table 1 | Characteristics of Randomized Controlled Trials

Author(s)	Year	Country	Age	Sample	Gender		Stimulus Site (DLPFC)	Method (rTMS)	Duration of Single Stimulus (min)	Number of Treatment Sessions	MT (%)	PCL		Adverse Reactions
					M	F						Baseline	Study Endpoint	
Cohen et.al[17]	2004	Israel	40.8 (9.9)	8	7	1	R	1Hz	20	10	80%	62.5 (7.8)	56.0 (9.5)	Manic Episode(n=1)
			41.8 (11.4)	10	6	4	R	10Hz				63.2 (13.1)	43.5 (8.3)	Dizziness(n=1), Neck Pain(n=2), Manic Episode(n=1)
			42.8 (14.8)	6	4	2	Sham	Sham				56.8 (3.6)	55 (4.9)	/
Boggio et.al[32]	2010	Brazil	40.7 (13.65)	10	4	6	R	20Hz	20	10	80%		35.2(4.4)	/
			47.1 (12.13)	10	3	7	L	20Hz					47.6(5.6)	
			45.9 (11.45)	10	2	8	Sham	Sham					48.4(4)	
Bie et.al[37]	2011	China	37.1 (11.4)	18	5	13	R	10Hz	20	10	80%	78.13(3.84)	55.21 (5.39)	Mild Headache(n=2)
			39.4 (9.6)	18	6	12	Sham	Sham				77.16(3.94)	64.14 (3.14)	/
Watts et.al[18]	2012	The United States	54 (12.3)	10	9	1	R	1Hz	20	10	90%	64.9 (6.5)	48.7 (9.9)	/
			57.8 (11.8)	10	9	1	Sham	Sham				57.3 (3.7)	54.8 (5.0)	
Wang et.al[38]	2014	China	35.40 (12.41)	20	9	11	R	20Hz	15	10	80%	49.50 (9.37)	33.90 (5.88)	/
			34.50 (11.22)	10	7	3	Sham	Sham				49.20 (6.65)	45.00 (4.99)	
Wu et.al[39]	2014	China		28	5	23	R	10Hz	20	20	80%	62.93 (9.15)	36.68 (5.83)	Headache(n=2), Excessive Sedation(n=4), Fatigue(n=5),
				29	9	20	Sham	Sham				65.59 (8.85)	47.72 (9.28)	Nausea(n=3), Thirst(n=6), Constipation(n=6), Diarrhea (n=1), Agitation(n=1)
Zhou et.al[40]	2016	China	30.57 (10.26)	26	9	17	R	10Hz	20	20	80%	65.14(7.26)	37.63 (5.75)	Thirst(n=2), Nausea(n=2), Fatigue(n=1), Headache(n=1), Constipation(n=1)
			31.24 (11.06)	25	9	16	Sham	Sham				64.32(5.74)	43.58(7.22)	Nausea(n=2), Fatigue(n=1), Hand Tremors (n=1), Agitation(n=1), Urinary Retention(n=1)
Sun et.al[41]	2017	China		20	9	11	R	10Hz	20	20	80%	64.10 (6.46)	42.93(6.20)	/
				18	9	9	Sham	Sham				63.70(6.05)	46.23(4.34)	
Zhang et.al[42]	2017	China	50.25 (6.42)	43	17	26	R	10Hz	20	15	85%	78.91(3.65)	54.09(6.21)	/
			50.25 (6.42)	43	19	24	Sham	Sham				78.35(3.85)	61.89(3.25)	
Ahmadizadeh et.al[33]	2018	Iran	52.10 (7.62)	19	19		B	20Hz	30	10	100%	71.26 (7.65)	45.81 (4.67)	Mild Headache(n=2); Discomfort (n=1)
			51.89 (7.93)	19	19		R	20Hz				70.57 (9.00)	49.41 (6.53)	Warm Sensation (n=1)
			51.89 (7.93)	20	20		Sham	Sham				70.55 (9.04)	66.93 (10.34)	/
Li et.al[44]	2018	China	32.1 (12.8)	40	21	19	R	10Hz	20	20	80%	65.5(8.5)	37(2.1)	/
			32.3 (13.9)	40	22	18	Sham	Sham				64.3(8.9)	43.84(4.1)	
Philip et.al[34]	2019	the United States	48 (13)	25	20	5	R	iTBS	9.5	10	80%	49.4 (9.4)	35.5 (13.9)	Headache(n=6)
			53 (12)	25	22	3	Sham	Sham				50.0 (11.4)	39.4 (16.8)	/
Leong et.al[35]	2020	Canada	39.2 (13.5)	11	1	10	R	1Hz	37.5	10	120%	59.4 (16.44)	48.1 (23.54)	Suicidal Thoughts(n=1)
			43.5 (12.4)	9	2	7	R	10Hz				65.33 (11.4)	53.44 (22.8)	/
			49.5 (6.9)	9	2	7	Sham	Sham				61.62 (7.96)	52.14 (10.05)	/
Li et.al[43]	2020	China	45.35 (6.42)	32	14	18	R	0.5Hz	25	15	80%	57.45(8.91)	47.49(6.64)	/
			43.76 (5.24)	32	16	16	R	10Hz				59.21(7.56)	48.85(9.35)	Facial Flushing(n=2)
			46.27 (5.36)	32	13	19	Sham	Sham				61.57(9.42)	58.28(7.53)	/
Yuan et.al[36]	2023	China	36.87 (8.37)	25	9	16	R	iTBS	9.5	15	80%	67.86 (11.46)	39.68 (11.80)	/
			37.16 (9.22)	25	5	20	R	10Hz			120%	65.21 (10.73)	39.13 (10.84)	
			30.09 (6.30)	25	6	19	Sham	Sham				67.66 (7.86)	59.09 (7.02)	

Abbreviations: M, male; F, female; B, bilateral; min, minutes; PTSD, Post-traumatic stress disorder; DLPFC, Dorsolateral Prefrontal Cortex; MT, Motor Threshold; PCL, Posttraumatic Stress Disorder Checklist.

Quality Assessment of Included Studies

To assess the risk of bias for the 15 studies included in this meta-analysis, we used the Cochrane Handbook's recommended RevMan 5.3 software. The quality evaluation for the included RCTs is shown in Figures 2 and 3. The results indicate that all 15 included studies demonstrated good quality with regard to bias risk.

Meta-Analysis of Treatment Effects

In RevMan 5.3 software, the default event type for analysis is "adverse event", with the default forest plot labels being "Favors experimental" on the left side and "Favors control" on the right. However, this study focuses on "favorable events", so we modified the forest plot labels accordingly: "Favors control" on the left side and "Favors experimental" on the right.

All included studies used the PCL as the outcome measure for PTSD symptoms. Fifteen studies involving a total of 760 PTSD patients assessed the effects of therapeutic TMS on PCL. Some studies included multiple intervention groups,[17,32,33,35,36,43] and the studies were merged/split according to the Cochrane Handbook. The heterogeneity of the included studies was high ($I^2 = 72\%$), so a random-effects model was used for the meta-analysis. The funnel plot showed significant symmetry (See Figure 4). The results indicated that therapeutic TMS significantly improved the core symptoms of PTSD compared to the control group (standardized mean difference (SMD) = 1.29; 95% confidence interval (CI) 0.96 to 1.62, $p < 0.0001$). (See Figure 5).

Subgroup Analysis

To further investigate the optimal parameters for rTMS treatment of PTSD, we conducted a subgroup analysis based on stimulation frequency (low-frequency vs high-frequency), MT (80% vs >80%), and treatment sessions (10 sessions vs >10 sessions).

Stimulation Frequency

Specifically, a subgroup analysis based on stimulation frequency (LF-rTMS and HF-rTMS) included 15 studies with 18 datasets involving 760 PTSD patients. The subgroup analysis showed that the SMD for LF-rTMS was 0.71 (95% CI −0.04 to 1.46), indicating a moderate effect on improving PTSD symptoms, but the confidence interval includes zero, suggesting high uncertainty. The study on HF-rTMS showed an SMD of 1.24 (95% CI 0.78 to 1.70), indicating a large effect on PTSD symptom improvement, with a confidence interval that does not include zero, suggesting more robust results (See Figure 6). A Z-test was conducted to further assess the difference between the two groups. The results showed that the point estimate of the effect size for HF-rTMS was higher than that for LF-rTMS (SMDdifference = 0.53), but the difference did not reach statistical significance ($Z = 1.15$, $p = 0.25$).

To further investigate the optimal treatment frequency, this study conducted a subgroup analysis of rTMS frequencies, including 14 studies with 19 data sets, involving a total of 672 PTSD patients. The patients were divided into four groups: ≤1 Hz, 10 Hz, 20 Hz, and iTBS (See Figure 7). The subgroup analysis showed that the standardized mean difference

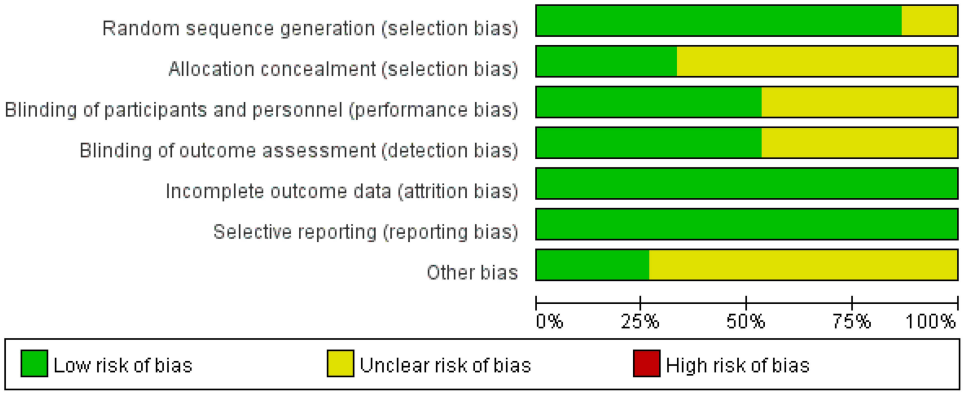


Figure 2 Bias display for each type of bias in all studies.
Note: +, Low risk; ?, Unclear risk; -, High risk.

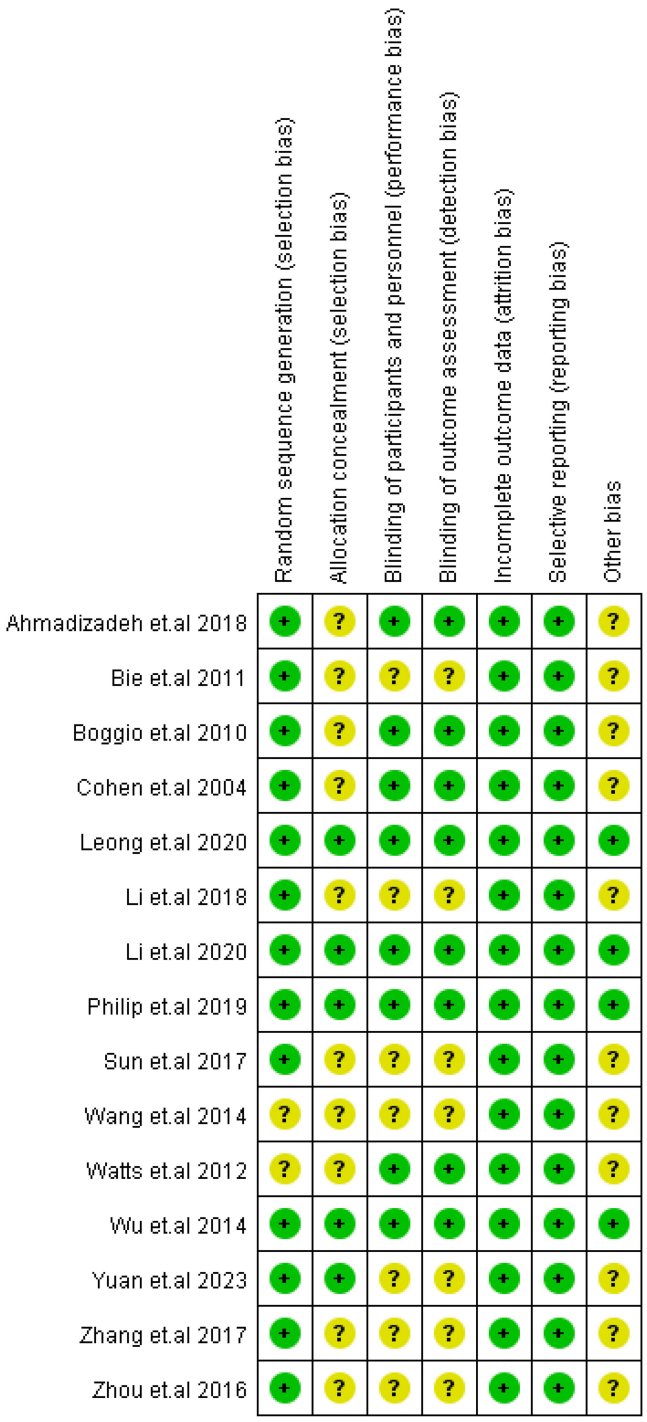


Figure 3 The summary bias plot of all studies.

(SMD) for ≤1 Hz rTMS was 0.71 (95% CI: –0.04 to 1.46), for 10 Hz rTMS was 1.19 (95% CI: 0.65 to 1.73), for 20 Hz rTMS was 1.95 (95% CI: 1.00 to 2.91), and for iTBS was 1.01 (95% CI: –0.53 to 2.54). The confidence intervals for the ≤1 Hz and iTBS groups both included zero, indicating high uncertainty in their efficacy. Although the confidence intervals of the 20 Hz and 10 Hz groups overlapped, the point estimate for the 20 Hz group was the highest, suggesting that it may be the optimal treatment frequency.

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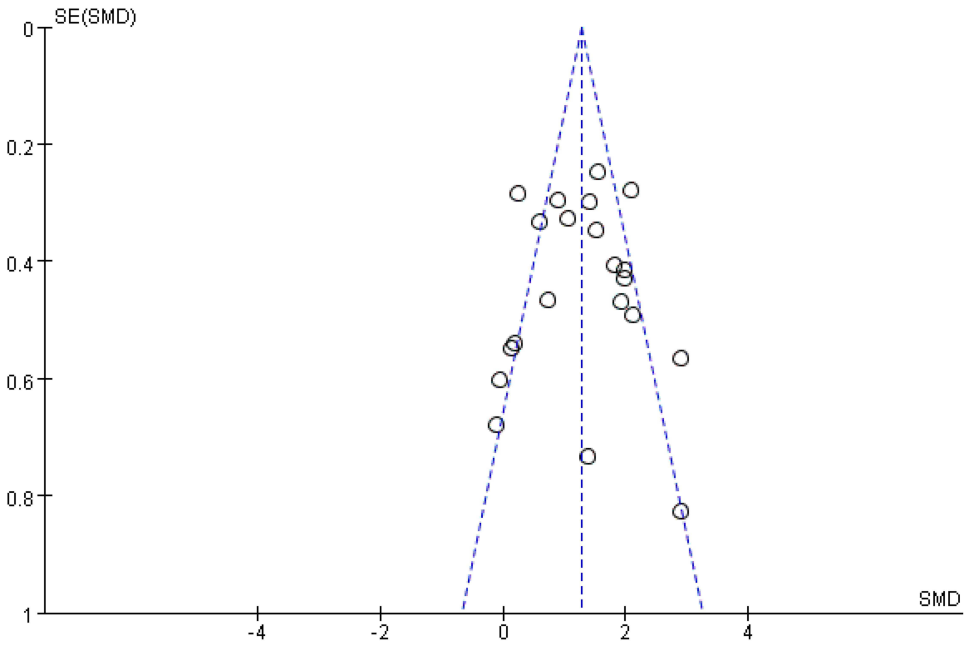

Figure 4 PTSD Symptoms Funnel Plot.
Note: In some studies, there are three groups. For example, in the study by Leong et al, they designed three groups: 1 Hz, 10 Hz, and sham stimulation. We compared 1 Hz and 10 Hz with sham stimulation separately; therefore, some studies are divided into parts a and b.

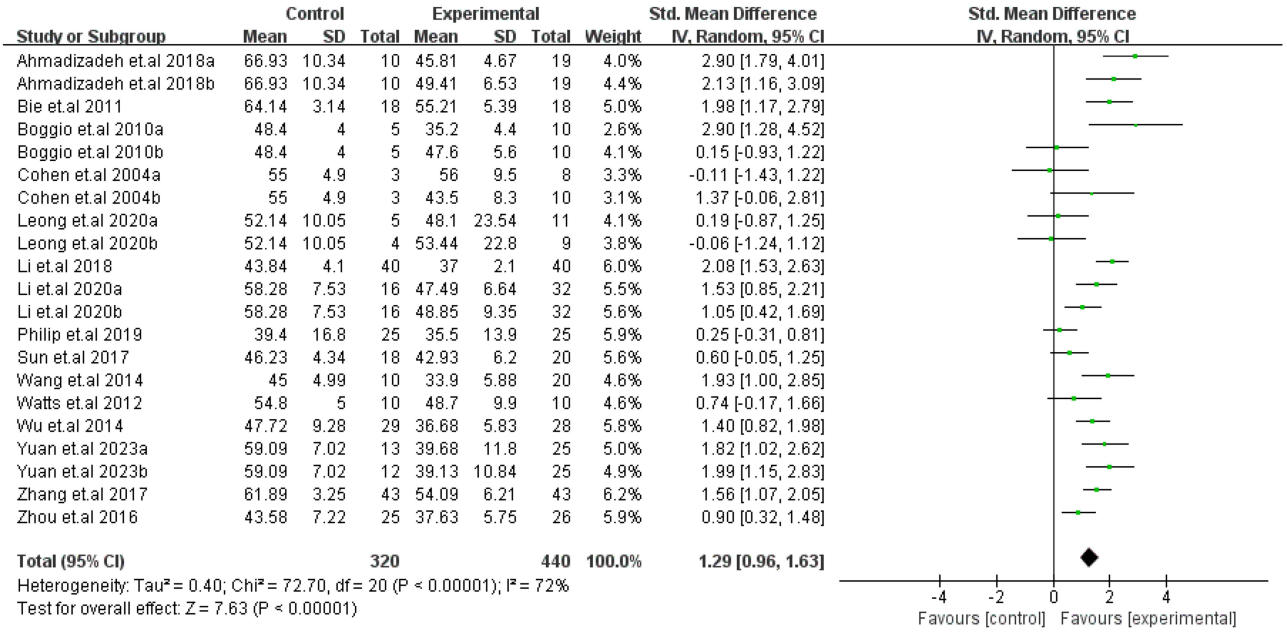

Figure 5 PTSD Symptoms Forest Plot.
Note: Some studies included three groups. For example, in the study by Leong et al, three groups were designed: 1 Hz, 10 Hz, and sham stimulation. We compared 1 Hz and 10 Hz separately with sham stimulation; therefore, in Leong's study, group a represents LF-rTMS (1 Hz) and group b represents HF-rTMS (10 Hz).

MT%

Subgroup analysis was conducted based on MT% (80% vs >80%). The results showed no significant difference in PCL scores between the two groups (80% MT: SMD = 1.27; 95% CI (0.92, 1.61); >80% MT: SMD = 1.34; 95% CI (0.22, 2.47)) (See Figure 8). Although the point estimate for the >80% MT group was slightly higher (SMD = 1.34 vs 1.27), the Z-test indicated

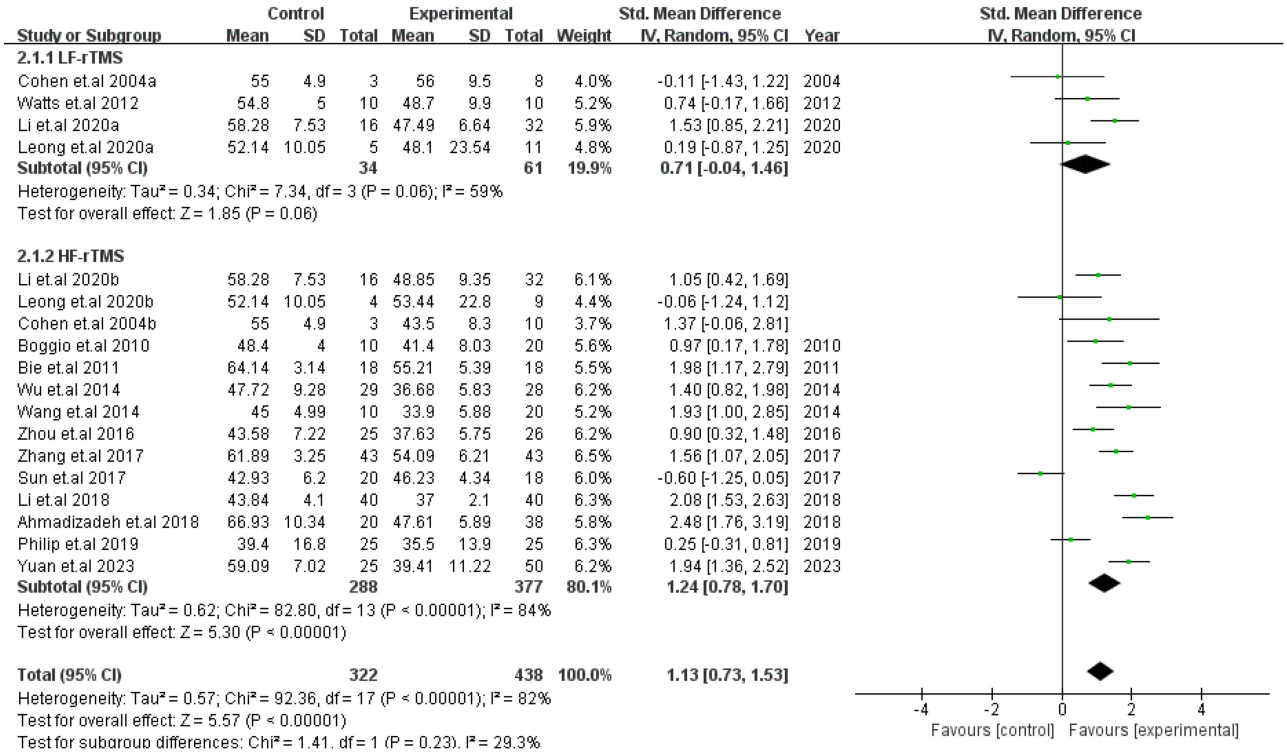

Figure 6 Forest Plot of Subgroup Analysis for PTSD Symptoms: LF-rTMS and HF-rTMS.
Note: Some studies have three groups, such as the study by Leong et al, which designed three groups with 1Hz, 10Hz, and placebo stimulation. We compared the efficacy between 1Hz/10Hz and placebo, so there is a distinction between "a" and "b" in the study, representing different stimulation parameters in this figure.

that the difference between the two groups was not statistically significant (Z = 0.10, p = 0.92). The wider confidence interval for the >80% MT group (0.22–2.47) may reflect insufficient sample size or high heterogeneity in intervention responses.

Treatment Sessions

A subgroup analysis based on the number of treatment sessions (10 sessions vs > 10 sessions) was conducted. The results showed that the standardized mean difference (SMD) for the 10-session group was 1.12 (95% confidence interval [CI]: 0.47 to 1.78), while the SMD for the group with more than 10 sessions was 1.41 (95% CI: 1.04 to 1.77) (See Figure 9). The Z-test indicated that the difference between the two groups was not statistically significant (Z = 0.76, p = 0.45).

Adverse Effects

All included studies reported no serious adverse events. Eight studies reported minor adverse events, such as headache, thirst, and nausea, with headache being the most common (approximately 2%). One study did not report adverse events separately for the experimental and control groups, and after we reached out to the authors without receiving a response, we decided to exclude this study from the analysis.[39] Due to the occurrence of various adverse effects across the studies, this research used a random-effects model to analyze the data from seven studies. One participant experienced suicidal ideation after the first 1Hz rTMS treatment and subsequently withdrew from the trial. This participant had exhibited flu-like symptoms prior to starting rTMS.[23] The random-effects model results showed that the risk of adverse events in the experimental group was slightly higher than in the control group (RR = 1.87, 95% CI 0.89–3.92, p = 0.10), but the difference did not reach statistical significance (p = 0.10) (See Figure 10).

Dose-Response Analysis

We used a one-stage robust error meta-regression (REMR) model to perform a nonlinear dose–response analysis between the number of rTMS treatment sessions and PCL scores. The overall dose–response trend was significant (P = 0.0001 < 0.05), and no nonlinear dose-response relationship was found (P NonLinearity= 0.631 > 0.05), indicating a linear relationship between

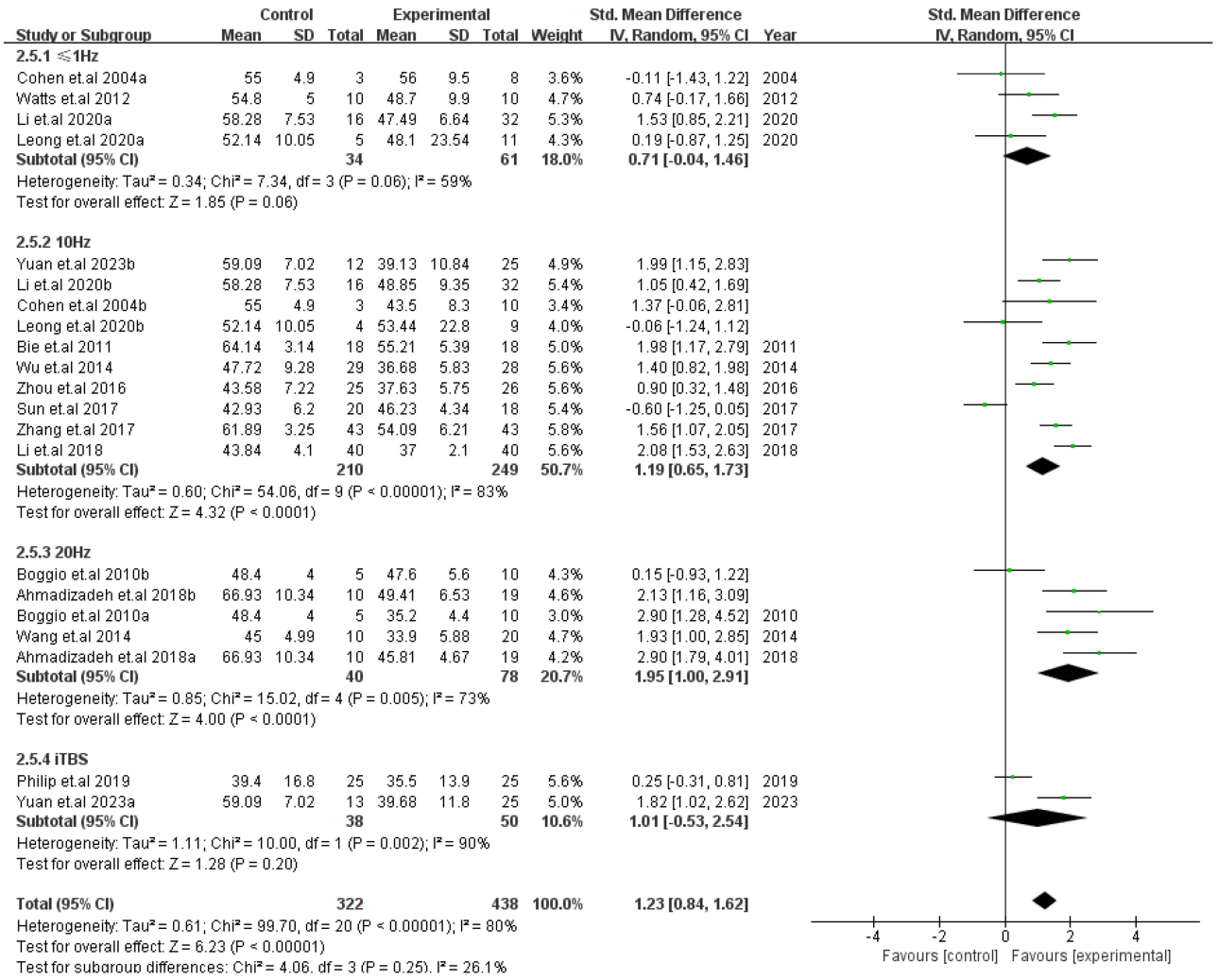

Figure 7 Forest Plot of Subgroup Analysis for PTSD Symptoms: different frequencies.
Note: In Yuan et al's study, two MT values were used, with "a" representing the 80% MT group and "b" representing the >80% MT group.

the two variables (Figure 11). Therefore, we fitted a linear model. Figure 12 shows that the linear dose-response model was overall significant ($P < 0.001$). The dual validation results from both models demonstrate that increasing the number of rTMS treatment sessions can better reduce PCL scores, thus achieving improved therapeutic outcomes.

The REMR model showed that the overall effect of MT was significant ($P = 0.0145 < 0.05$), with a significant nonlinear trend observed (P NonLinearity = $0.008 < 0.05$) (Figure 13). This indicates that the relationship between the rTMS parameter MT and PCL scores is not a simple linear one; the effect of increasing MT on PCL scores varies at different MT levels, exhibiting a complex nonlinear pattern.

Discussion

This meta-analysis included 15 studies, with a total of 760 PTSD patients, of whom 440 received 10 to 20 sessions of therapeutic TMS, and 320 received sham stimulation. Overall, the results of this meta-analysis support the benefits of therapeutic TMS for overall PTSD symptoms. Therapeutic TMS is a safe intervention for PTSD patients, with no reports of severe adverse effects.

This study demonstrates that therapeutic TMS improves the overall symptoms of PTSD, with moderate heterogeneity in the outcome measures ($I^2 = 72\%$). This heterogeneity may arise from methodological differences between studies, variations in sample characteristics, or differences in treatment parameters. Despite the heterogeneity, the symmetry of

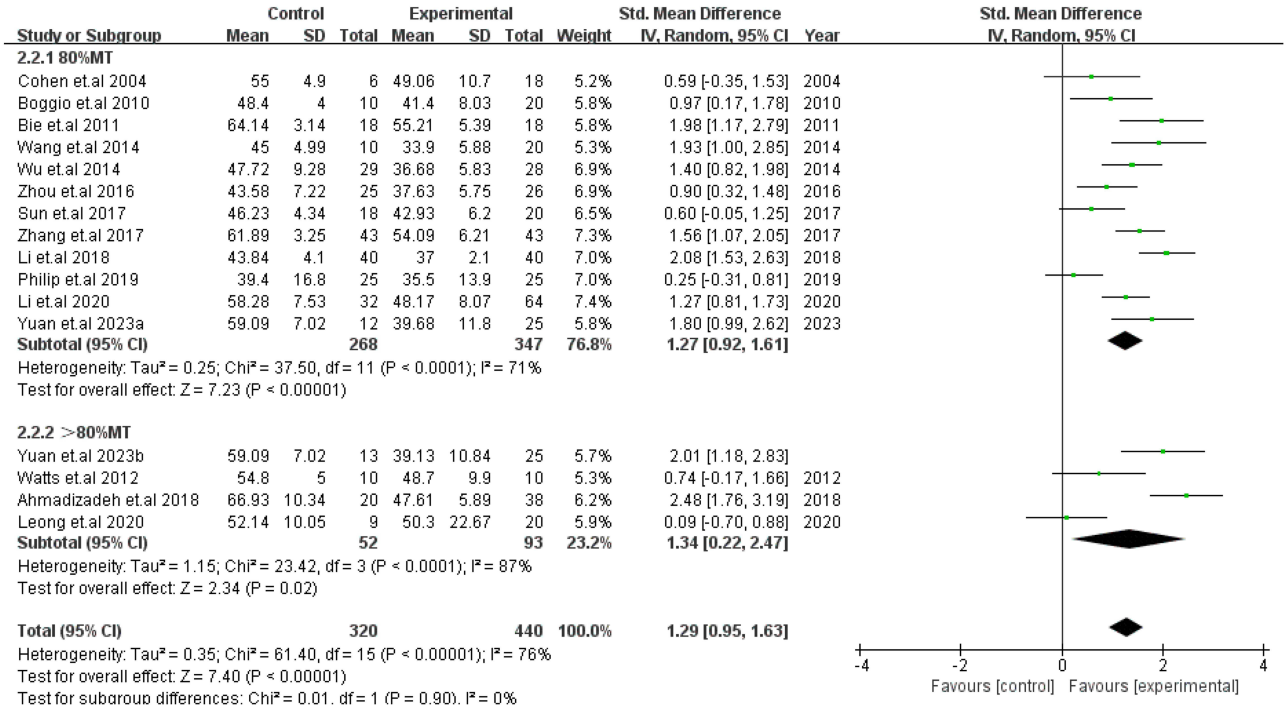

Figure 8 Forest plot of PTSD symptom subgroup analysis: 80% MT vs >80% MT.

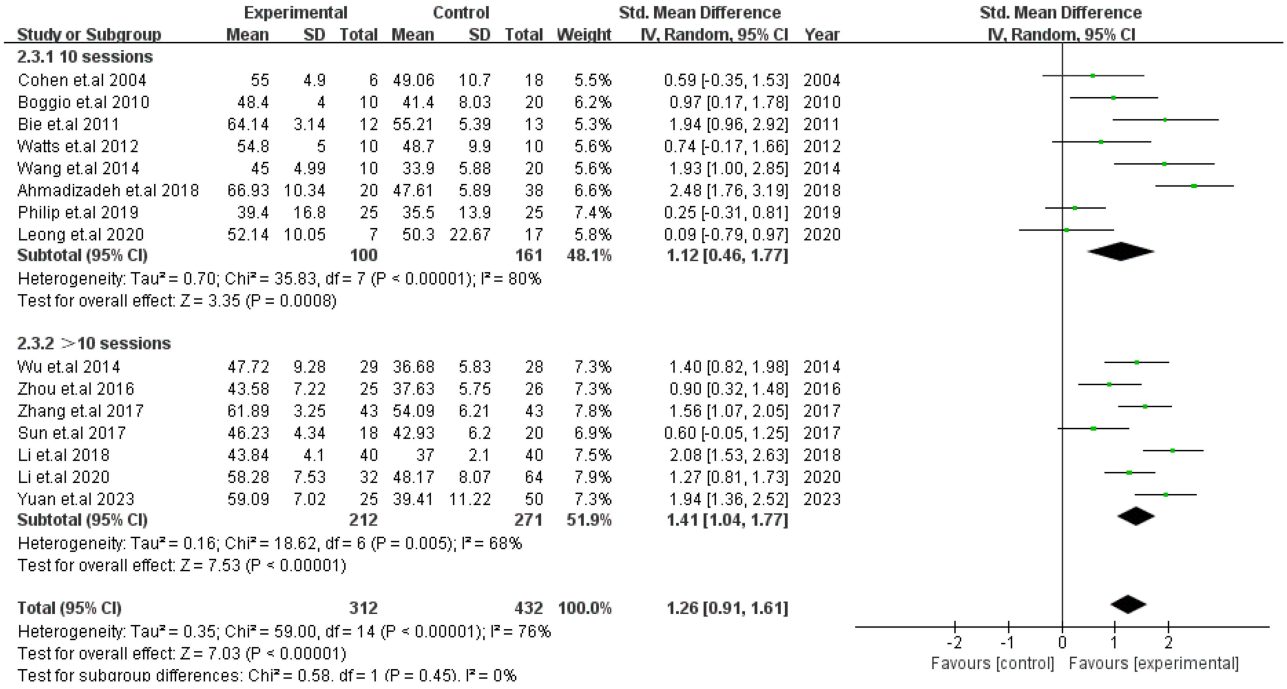

Figure 9 Forest plot of PTSD symptom subgroup analysis: 10 sessions vs >10 sessions.
Note: Individual randomized clinical trials (RCTs) are represented by circles, with the size of each circle corresponding to its weight in the overall analysis. The solid line represents the estimated dose-response relationship between the number of treatment sessions and PCL scores. The dashed lines indicate the 95% confidence interval (CI).
Abbreviation: REMR, Robust Error Meta-Regression.

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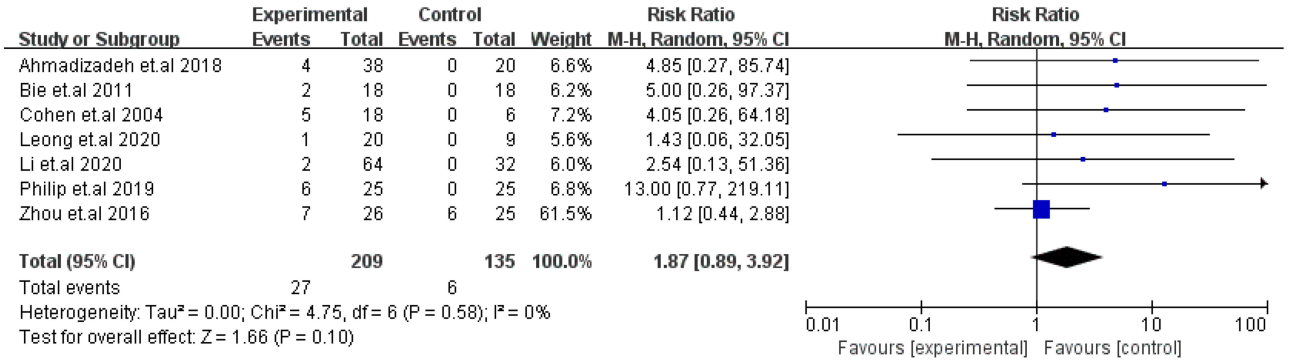

Figure 10 Forest plot of adverse effects.

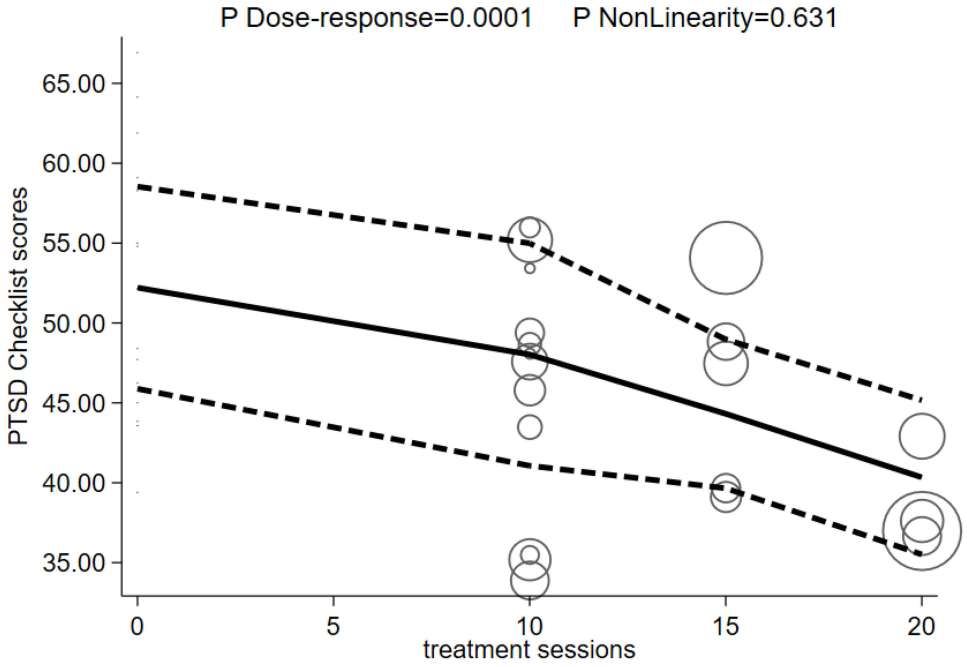

Figure 11 Nonlinear dose-response relationship between treatment sessions and PCL scores (mean response).
Note: Individual randomized clinical trials (RCTs) are represented by circles, with the size of each circle corresponding to its weight in the overall analysis. The solid line represents the estimated dose-response relationship between the number of treatment sessions and PCL scores.

the funnel plot indicates that the included studies show no obvious publication bias, which strengthens the credibility of our findings. Our summary results are consistent with previous reviews,[13,23,25] which reported the positive impact of therapeutic TMS on PTSD recovery. However, compared to existing studies, this research differs in the following ways: (1) This study only included randomized controlled trials comparing therapeutic TMS with sham stimulation, excluding the effects of other types of non-invasive brain stimulation (NIBS) on PTSD. (2) Based on existing research findings, this study further validated the effectiveness of TMS as a treatment for PTSD and explored the relationship between other potential moderating factors in the TMS treatment protocol and treatment outcomes. In addition to TMS frequency, this study also analyzed several potential moderating factors, including motor threshold (MT%), treatment duration, and the number of treatments. (3) A dose-response analysis was conducted on the number of treatment sessions, and the results showed a linear relationship between the number of sessions and PCL scores. As the number of treatment sessions increased, PCL scores decreased dependently, indicating a more significant improvement in PTSD symptoms.

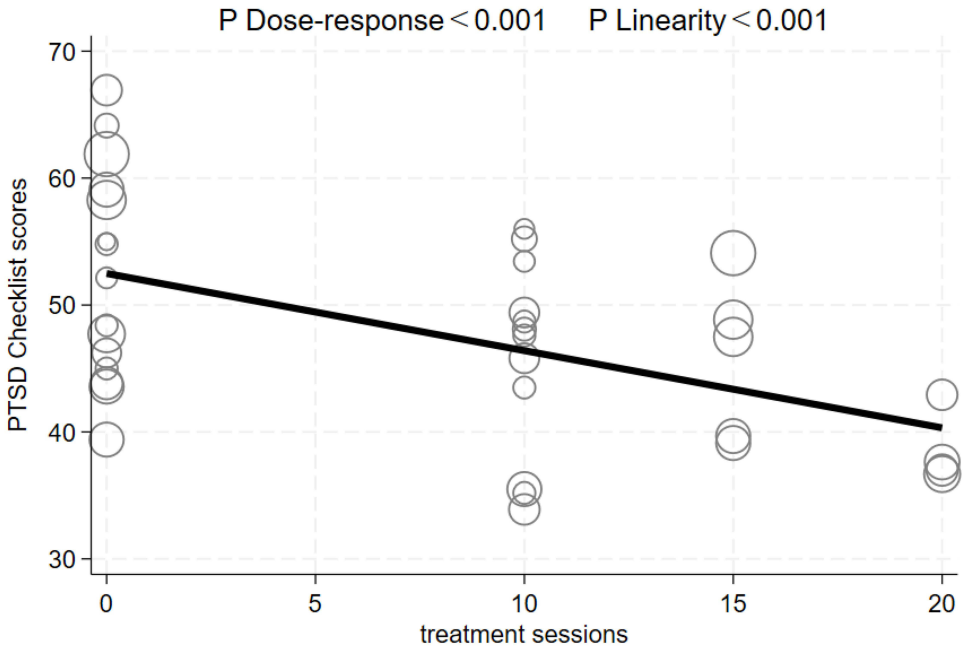

Figure 12 Linear meta-regression plot of the association between treatment sessions and PCL scores (mean response).
Note: Individual randomized clinical trials (RCTs) are represented by circles, with the size of each circle corresponding to its weight in the overall analysis. The solid line represents the estimated dose-response relationship between the number of treatment sessions and PCL scores. The dashed lines indicate the 95% confidence interval (CI).
Abbreviation: REMR, Robust Error Meta-Regression.

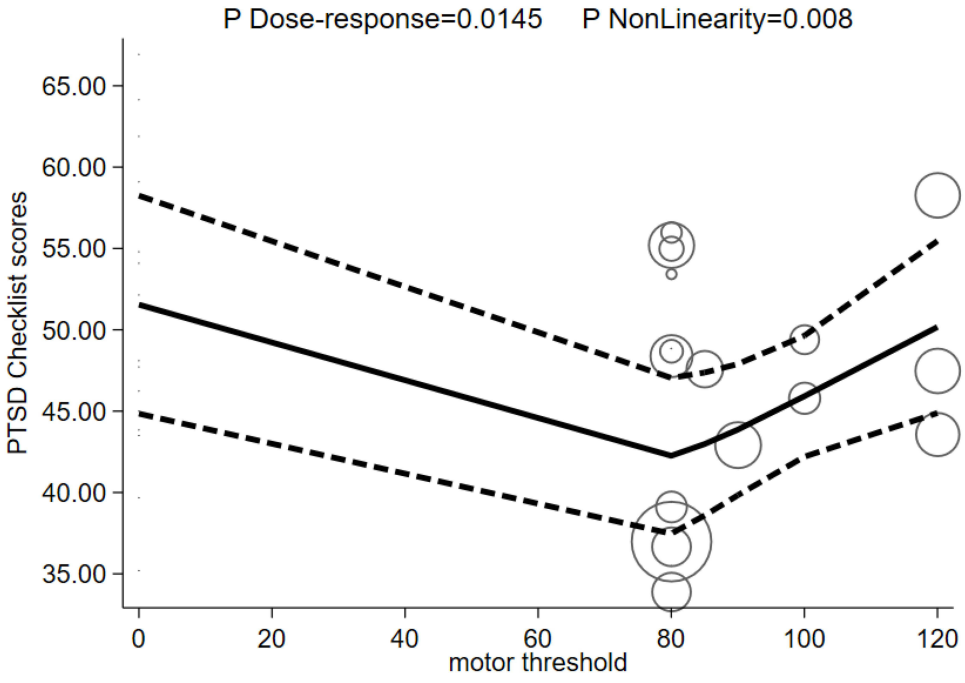

Figure 13 Nonlinear dose-response relationship between MT and PCL scores (mean response).

To reduce potential heterogeneity, this study conducted subgroup analyses based on stimulation frequency, motor threshold (MT), and treatment duration, and performed dose-response analyses on the number of treatments and MT. The subgroup analysis of stimulation frequency showed that both low-frequency rTMS (LF-rTMS) and high-frequency rTMS (HF-rTMS) significantly alleviated PTSD symptoms, with no statistically significant difference between the two ($p = 0.24$). This finding is

consistent with the results reported by McGirr et al.[25] To further investigate the effect of treatment frequency on PCL scores, this study conducted a subgroup analysis of rTMS frequencies, divided into four groups: ≤1 Hz, 10 Hz, 20 Hz, and iTBS. The subgroup analysis results showed that the SMD for ≤1 Hz rTMS was 0.71 (95% CI: −0.04 to 1.46), for 10 Hz rTMS was 1.19 (95% CI: 0.65 to 1.73), for 20 Hz rTMS was 1.95 (95% CI: 1.00 to 2.91), and for iTBS was 1.01 (95% CI: −0.53 to 2.54). The confidence intervals for the ≤1 Hz and iTBS groups both included zero, indicating a high degree of uncertainty in their efficacy. Although there was overlap in the confidence intervals between the 20 Hz and 10 Hz groups, the point estimate for the 20 Hz group was the highest, suggesting it may be the optimal treatment frequency.This trend suggests that HF-rTMS may have better efficacy, consistent with some previous research findings.[13,22–24] This difference may be related to the small sample size in this study or the high heterogeneity among the studies. Larger-sample studies are needed in the future to further verify the differences in efficacy of rTMS at different frequencies. The subgroup analysis based on MT% showed that the >80% MT group had a slightly greater improvement in PCL scores (SMD = 1.34 vs 1.27), but statistical tests did not support a significant difference between the >80% MT group and the 80% MT group ($Z = 0.10$, $p = 0.92$). The wider confidence interval for the >80% MT group (95% CI 0.22–2.47) may reflect insufficient sample size or higher heterogeneity in intervention responses. Further studies with larger samples are needed to confirm this finding.

This study also conducted a multifaceted analysis of the relationship between the number of treatments and efficacy. The subgroup analysis showed that the effect size for the >10-day treatment duration group (SMD=1.41) was higher than that of the ≤10-day treatment group (SMD=1.12). We used a one-stage robust error meta-regression (REMR) model to conduct a nonlinear dose-response analysis between the number of rTMS treatments and PCL scores. The overall dose-response trend between the two was significant ($P = 0.0001 < 0.05$), and no nonlinear dose-dependence was detected (nonlinearity test $P = 0.631 > 0.05$). The linear dose-response model was overall significant ($P < 0.001$). The dual validation results of both models indicate that increasing the number of rTMS treatments can better reduce PCL scores, thereby achieving improved therapeutic effects.[45] The REMR model showed that motor threshold (MT) had a significant overall effect on the outcome ($P = 0.0145 < 0.05$), with a significant nonlinear trend present (P Nonlinearity = 0.008 < 0.05). This suggests that the relationship between rTMS parameter MT and PCL scores is not a simple linear one; the impact of increasing MT on PCL scores varies with different MT levels, exhibiting a complex nonlinear pattern.

The results from the random-effects model indicate that the risk of adverse events in the experimental group was slightly higher than in the control group (RR=1.87, 95% CI 0.89–3.92), but the difference did not reach statistical significance (p=0.10). Although the point estimate suggests a potentially higher risk of adverse events in the experimental group, the wide confidence interval with the lower limit close to 1 indicates high uncertainty in the results. Additionally, with a p-value >0.05, it suggests that the risk of adverse events in the experimental group may not be significantly higher. Therefore, the current evidence is insufficient to support that the experimental group has a significantly higher risk of adverse events compared to the control group. Larger sample studies are needed in the future to further verify the safety of therapeutic TMS.

In summary, TMS parameters (such as stimulation frequency and number of sessions) may be key factors influencing therapeutic efficacy. However, the current evidence remains insufficient and the quality of existing studies is generally low. Therefore, large-scale, high-quality studies are still needed in the future to further validate the differences in efficacy of these parameters and their clinical significance.

The mechanisms underlying rTMS treatment for PTSD are still not fully understood, but they can be explored through brain network mechanisms, neuroimaging mechanisms, molecular mechanisms, and genetic mechanisms.

PTSD is conceptualized as involving an overactive salience network (SN), and an inhibited central executive network (CEN) and default mode network (DMN).[46] The SN plays a crucial role in sensory processing, environmental monitoring, and responding to personally significant stimuli.[47] In PTSD patients, the connectivity of the SN is enhanced and is associated with hypervigilance and anxiety symptoms.[48] rTMS has been shown to reduce SN activation, which can help alleviate PTSD symptoms.[49,50] The CEN is primarily responsible for higher cognitive processes, including emotional regulation, behavioral control, and attention.[51,52] Decreased connectivity in the CEN is associated with the severity of PTSD.[53] Therapeutic TMS can upregulate CEN connectivity, thereby improving cognitive and emotional functions in PTSD patients.[54] The DMN is a network that is active during the brain's resting state and is related to contextual memory and future imagining.[55] Studies have shown that DMN connectivity is reduced in PTSD patients, which affects emotional

regulation and memory functions.[46] Research by Philip et al indicated that after iTBS treatment, PTSD patients showed enhanced DMN connectivity,[34] and the connectivity pattern of the DMN could predict long-term treatment outcomes.[45] Thus, by modulating the connectivity of these brain networks, therapeutic TMS may positively influence the neurobiological abnormalities in PTSD patients, leading to improvements in their clinical symptoms.

PTSD can be broadly considered a disorder of fear regulation, with the most easily understood neural circuitry underlying mammalian fear behavior involving the amygdala, hippocampus, and medial prefrontal cortex.[56] Neuroimaging studies have revealed functional and structural abnormalities in specific brain regions of PTSD patients, particularly in the amygdala, prefrontal cortex, and hippocampus.[57] The amygdala plays a key role in the extinction of conditioned fear memories, and changes in its volume in PTSD are associated with emotional regulation deficits.[58,59] Research has shown that the reduced amygdala volume in PTSD patients may be linked to core symptoms such as hypervigilance and heightened emotional reactivity.[60] The prefrontal cortex is central to higher cognitive functions, influencing the extinction of fear memories by regulating the amygdala.[61] A reduction in the thickness of the prefrontal cortex in PTSD patients may be associated with dysfunctions in emotional and cognitive control.[62,63] HF-rTMS, through stimulation of the dorsolateral prefrontal cortex (DLPFC), has been shown to improve depression and anxiety symptoms, and improvements in core PTSD symptoms have been found to correlate with β-event-related potentials at the prefrontal-central electrode sites before and after treatment, suggesting that EEG could serve as a clinical biomarker for guiding PTSD treatment.[64] The hippocampus plays a crucial role in fear learning and inhibition within a safe environment, including fear conditioning, extinction, and fear updating, which are closely related to PTSD.[65,66] Several studies have found that PTSD patients have smaller hippocampal volumes, which may be related to the impaired extinction process and trauma-related memories in these patients.[67–69] LF-rTMS may reduce hippocampal neuronal damage by modulating apoptotic signaling pathways LF-rTMS,[70] while HF-rTMS may promote the recovery of hippocampal function by improving dendritic plasticity in hippocampal neurons.[71] Thus, therapeutic TMS exerts a positive impact by modulating brain regions associated with PTSD. These neuroimaging findings provide biological evidence for its effects and highlight potential therapeutic targets.

Therapeutic TMS influences the activity of specific brain regions and indirectly modulates the release and reuptake of monoamine neurotransmitters (such as dopamine and serotonin), affecting their concentrations in the synaptic cleft. It may also alter signal transmission by modifying the sensitivity or number of related receptors.[72] Dopamine is closely related to conditioned fear responses, and animal model studies have shown that the maintenance of PTSD-related contextual fear and anxiety in dopamine receptor knockout mice is significantly reduced, indicating the role of the dopamine system in the development of PTSD.[73] A reduction in dopamine levels can lead to working memory and emotional disturbances in PTSD patients.[74] Clinical studies have demonstrated that following rTMS treatment, dopamine flux increases in various brain regions,[75] which may improve memory and mood in PTSD patients. Serotonin is a neurotransmitter closely associated with mood, sleep, appetite, and cognitive functions, and its metabolic level is tightly linked to the onset of PTSD.[76] Selective serotonin reuptake inhibitors (SSRIs) are first-line treatments for PTSD, and meta-analyses have shown that SSRIs reduce the expression of contextual fear learned after acquisition and facilitate the extinction of fear, suggesting that modulating serotonin levels may benefit the alleviation of PTSD symptoms.[77] Additionally, LF-rTMS has been shown to alleviate anxiety disorders in generalized anxiety disorder patients and increase their serotonin levels,[78] while HF-rTMS can significantly raise serotonin levels in patients with depression.[79] Therefore, therapeutic TMS exerts a positive effect on PTSD symptoms by modulating the molecular mechanisms associated with PTSD.

Molecular genetics research on PTSD has revealed the critical roles of several genes in regulating stress response systems and influencing the development of PTSD.[80] Brain-derived neurotrophic factor (BDNF) is a neurotrophic protein essential for neuron development, maintenance, and synaptic plasticity. Numerous studies have shown that BDNF gene and protein expression undergo significant changes under stress,[81] and early trauma-related changes in BDNF may serve as predictive biomarkers for PTSD.[82] Animal models have shown that high-frequency rTMS can increase BDNF levels,[83] and therapeutic TMS may indirectly regulate hippocampal neurogenesis by modulating the BDNF pathway, potentially one of the mechanisms by which therapeutic TMS exerts its positive effects on PTSD patients. Additionally, studies have found that the catechol-O-methyltransferase (COMT) gene, which plays a role in dopamine degradation, has

polymorphisms that are associated with individual susceptibility to traumatic events and may also affect patients' response to therapeutic TMS treatment.[84,85] By modulating the expression and function of these genes, therapeutic TMS may impact the neurobiological pathways of PTSD, thereby improving symptoms.

Limitations

When interpreting the results of the current meta-analysis, several key limitations must be considered. First, the sample size of the studies included in this research was limited, which restricted the statistical power of detecting the effects of therapeutic TMS on PTSD symptoms. Therefore, future studies should recruit more participants to enhance statistical power and provide more reliable results. Second, there was significant heterogeneity in the trials, stemming from both clinical and methodological differences. For example, some studies focused on civilians or veterans, and the severity of PTSD symptoms may vary across these different populations. This heterogeneity could influence the aggregation and interpretation of treatment effects. Future research should standardize the design by using uniform diagnostic criteria, assessment tools, and treatment protocols to reduce heterogeneity. Third, most of the included studies adopted a two-week clinical trial design. However, dose-response analyses and previous research suggest that increasing treatment sessions could improve clinically relevant outcomes.[45] This short-term design may limit our ability to assess the long-term effects of therapeutic TMS. Therefore, future studies should consider adopting longer treatment periods to comprehensively evaluate the efficacy and durability of therapeutic TMS.

Conclusion

This study systematically investigated the efficacy of rTMS in treating PTSD and the parameters that may play key roles. The results indicate that rTMS is an effective and noninvasive treatment for PTSD; however, our findings did not reveal significant differences in therapeutic potential between HF and LF rTMS. Dose–response analysis showed a positive correlation between the number of treatment sessions and symptom improvement, suggesting that cumulative treatment sessions are a key factor in enhancing efficacy. No significant differences were observed between the >80% Motor Threshold treatment group and the control group, and the dose–response relationship for this parameter was also not statistically significant, possibly due to sample heterogeneity, especially individual variability in treatment response. Although existing studies have limitations such as small sample sizes and high heterogeneity that may affect the robustness and generalizability of the results, this study still recommends prioritizing high-frequency rTMS and increasing the number of treatment sessions to improve therapeutic outcomes. Future research should be conducted with larger and more homogeneous samples to further verify the impact of different treatment parameters on efficacy and to enhance the reliability of the conclusions.

Data Sharing Statement

The original contributions presented in this study are included in the article and the supplementary materials. For further inquiries, please contact the corresponding author, Yulei Xie.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

Yin-Xu Wang, Jing-Yi Lin, and Chun-Yu Zhang are co-first authors for this study. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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