Journal of Integrative Neuroscience

J. Integr. Neurosci. **2023**; 22(5): 131
https://doi.org/10.31083/j.jin2205131

Systematic Review

Efficacy and Safety of Repetitive Transcranial Magnetic Stimulation for Poststroke Memory Disorder: A Meta-Analysis and Systematic Review

Haihua Xie[1,2], Shiyang Luo[2], Dan Xiong[1,2], Pan Zhu[1,2], Jie Chen[1], Xin Tang[1], Jie Tan[1,*], Ning Zhao[2,*]

[1]College of Acupuncture & Tuina and Rehabilitation, Hunan University of Chinese Medicine, 410208 Changsha, Hunan, China
[2]Department of Rehabilitation, Shenzhen Nanshan People's Hospital and the 6th Affiliated Hospital of Shenzhen University Medical School, 518052 Shenzhen, Guangdong, China
*Correspondence: 86869454@qq.com (Jie Tan); zhaoning2018@email.szu.edu.cn (Ning Zhao)
Academic Editor: Yoshihiro Noda
Submitted: 1 March 2023 Revised: 8 June 2023 Accepted: 13 June 2023 Published: 5 September 2023

Abstract

Background: Patients with post-stroke memory disorder (PSMD) have poor quality of life and it is necessary to identify more beneficial stimulation protocols for treatment with repetitive transcranial magnetic stimulation (rTMS). This meta-analysis was conducted to investigate the efficacy and safety of rTMS for improving memory performance, global cognition, and activities of daily living (ADL) among patients with PSMD. **Methods**: The PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Chinese Biomedical Literature Database, Chinese National Knowledge Infrastructure, China Science and Technology Journal Database, and Wanfang databases were screened to identify relevant randomized controlled trials. The primary outcome was memory performance; secondary outcomes included global cognition, ADL, and adverse events. STATA software was used to perform data synthesis. **Results**: Five articles with a total of 192 participants were included. The results indicated that rTMS was superior to control treatments for improving memory performance (mean difference [MD] = 1.73, 95% CI [Confidence Interval] [0.85, 2.60], $p < 0.001$), global cognition (MD = 2.44, 95% CI [0.96, 3.93], $p < 0.001$), and ADL (MD = 10.29, 95% CI [5.10, 15.48], $p < 0.001$). No significant differences were found between the low-frequency (LF) and high-frequency (HF) rTMS subgroups ($p = 0.47$, $I^2 = 0.00\%$) or between the sham rTMS and non-rTMS subgroups ($p = 0.94$, $I^2 = 0.00\%$). Four studies did not reported adverse events. **Conclusions**: rTMS may improve memory function, global cognition, and the ability to perform ADL in patients with PSMD. LF-rTMS and HF-rTMS may have equal efficacy for treatment of PSMD. Future studies should consider extending the follow-up period to explore the safety and long-term efficacy of rTMS for treatment of PSMD and the appropriate choice of placebo for clinical trials of this treatment.

Keywords: repetitive transcranial magnetic stimulation; memory disorders; stroke; meta-analysis

1. Introduction

Poststroke memory disorder (PSMD) is a common outcome following a stroke [1,2]. PSMD is associated with memory loss and the inability to learn and use skills [3]. A previous systematic review indicated that approximately 23–55% of poststroke patients without dementia experience PSMD after three months [4]. This disorder has a detrimental effect on daily life [5], cognitive function [6], and speech motor learning [7]. Regular cognitive rehabilitation (e.g., internal and external memory aids) has limited efficacy for treating PSMD [2]. Several studies have indicated that repetitive transcranial magnetic stimulation (rTMS) is useful for restoring memory function [8–14]. This technique modulates the excitability of the brain through stimulation at different frequencies. Low-frequency rTMS (LF-rTMS, 0.2–1 Hz) decreases brain excitability and high-frequency rTMS (HF-rTMS) (≥5 Hz) increases brain excitability [15].

Nonetheless, the clinical efficacy of rTMS for improving memory function in patients with PSMD has yet to be fully elucidated and study results have been inconsistent. Rektorova *et al.* [16] revealed that 10-Hz rTMS of the left dorsolateral prefrontal cortex (DLPFC) in an randomized clinical trial (RCT) with a crossover design had no effect on memory function compared to baseline or controls. Sedlackova *et al.* [17] found that both 1-Hz and 10-Hz rTMS of the left DLPFC failed to improve memory performance on various subtests of the Wechsler Memory Scale (WMS). Two previous descriptive reviews stated that additional high-quality RCTs and sufficient data were still needed to demonstrate the efficacy of rTMS for treatment of PSMD [18,19].

Additionally, studies have found that rTMS effectively enhanced memory in patients with poststroke cognitive impairment (PSCI) [20–24]. Li W *et al.* [24] reported a beneficial effect of intermittent theta burst stimulation (left DLPFC, 50 Hz repeated at 5 Hz, 100% resting motor threshold (RMT), 600 pulses) on memory performance in patients with PSCI by using the Oxford Cognitive Screen (OCS) in a double-blind RCT. A systematic review also suggested that rTMS improved Mini-Mental State Examination (MMSE) scores in patients with PSCI [20]. However the efficacy of rTMS for treating PSMD is still unclear. While memory

Table 1. Inclusion and exclusion criteria.

Inclusion criteria	
Design	RCTs reported in English or Chinese with complete data available
Participants	Diagnosed with PSMD with disease course more than two weeks
Intervention	Active rTMS alone or combined with other treatments (drug therapy, cognition training, or others) in the intervention group
Comparators	Sham rTMS or non-rTMS
Outcomes	Including RBMT or WMS
Exclusion criteria	
Design	Conference papers, quasi-experimental studies, or editorials
Participants	History of psychiatric or neurological disorders or memory disorders
	Metal dentures, pacemakers, intracranial metal implants, or cranial defects
Data	Derived from the same trial

RCTs, randomized controlled trials; PSMD, patients with post-stroke memory disorder; rTMS, repetitive transcranial magnetic stimulation; RBMT, rivermead behavioral memory test; WMS, wechsler memory scale.

function is an aspect of cognition, patients with PSCI do not all necessarily have memory dysfunction. Moreover, both the OCS and MMSE are suited for assessing cognitive function but do not focus on memory [25,26]. Special scales are needed, such as the WMS [27] and the Rivermead Behavioral Memory Test (RBMT), to test memory performance specifically [28]. Furthermore, the stimulation parameters are often different across studies (e.g., stimulation frequency, sham rTMS, or non-rTMS in the control) [8,10,21]. The optimal rTMS stimulation protocol for PSMD remains unclear.

Therefore, the current quantitative meta-analysis was conducted to evaluate the effect of rTMS on PSMD. The objectives were as follows: (1) to explore the effect of rTMS on memory performance, (2) to assess differences in LF-rTMS and HF-rTMS, and (3) to evaluate the impact of sham rTMS versus non-rTMS controls on the apparent efficacy of therapeutic rTMS.

2. Materials and Methods

This study was conducted in accordance with the PRISMA guidelines [29] and its protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42021282439). PRISMA checklist is shown in **Supplementary Material 1**.

2.1 Search Strategy and Selection Criteria

Seven databases (PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Chinese Biomedical Literature Database (CBM), Chinese National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (VIP), and Wanfang) were searched from inception to August 2021 using explicit search strategies combining MeSH terms and free text. The search strategy for all databases is described in detail in **Supplementary Material 2**. Inclusion and exclusion criteria are shown in Table 1.

2.2 Data Selection and Extraction

The initial selection was conducted independently by two researchers (DX and PZ) through independent screening and analysis of the titles and abstracts of the imported studies. Another two researchers (JC and XT) read the full text of the potentially eligible papers and conducted a second round of selection. Additionally, the reasons for excluding papers were recorded and a third researcher (SYL) was consulted to resolve disagreements during the screening process. Note Express 3.5.0 software (Beijing Aegean Music Technology, Beijng, China) was used to manage all the imported search records.

Data extraction was conducted by two researchers (PZ and XT) using a standardized form. The following data were extracted: study characteristics, trial methodologies, participant information, the stimulation parameters of rTMS, sham or non-rTMS control, and outcomes. Further details on data extraction are described in **Supplementary Material 3**.

2.3 Quality Assessment

The Cochrane risk-of-bias tool from the Cochrane Handbook for Systematic Reviews of Interventions was applied using Review Manager to evaluate the risk of bias for each study [30]. The risk-of-bias tool consisted of seven items, each of which was rated on a three-level scale. The risk of bias was evaluated independently by two researchers (PZ and JC), and a separate researcher (SYL) made the final decision in the event of a disagreement. The quality of the data was assessed by the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) [31], which contained four criteria (inconsistency, indirectness, imprecision, and publication bias). Each of these four criteria were rated on a four-level scale: high, moderate, low, or extremely low.

Table 2. Characteristics of eligible studies.

Studies	Sample size	Participants					Intervention				Outcomes	Adverse events
		Mean age (T/C)	Sex (M/F)	Type of stroke (I/H)	Disease course (month/day)	Educational level (year)	Stimulation parameters	Type of coil	Site of stimulation	Sham rTMS		
Huang [13] (2021)	24	T: 63.87 ± 6.31 C: 61.48 ± 9.08	T: 12/0 C: 10/2	UC	T: 96.25 ± 29.11 d C: 105.83 ± 44.20 d	T: 10.15 ± 2.96 C: 11.85 ± 4.91	80%–120% RMT, 5 Hz, 20 min, 1 time/d, 5 d/week, 4 weeks	O-coil	Left DLPFC	No	①②③④	No
Wen *et al*. [14] (2020)	50	T: 58.52 ± 10.61 C: 55.08 ± 10.05	T: 14/11 C: 13/12	T: 16/9 C: 14/11	T: 1.07 ± 0.58 m C: 1.13 ± 0.66 m	T: 9.52 ± 3.49 C: 10.96 ± 4.03	80% RMT, 1 Hz, 30 min, 1 time/d, 5 d/week, 4 weeks	'8' coil	Contralesional DLPFC	Yes	①②③④⑤	Unreported
Zhou [12] (2017)	40	T: 52.57 ± 8.53 C: 55.32 ± 7.58	T: 14/7 C: 9/10	UC	T: 1.43 ± 0.68 m C: 1.63 ± 0.76 m	T: 9.48 ± 2.34 C: 9.05 ± 2.59	80%–120% RMT, 10 Hz, 15 min, 1 time/d, 5 d/week, 4 weeks	O-coil	Bilateral DLPFC	Yes	①③④⑥	Unreported
Lu *et al*. [11] (2015)	40	T: 42.5 ± 12.3 C: 47.3 ± 11.8	T: 12/7 C: 13/8	T: 8/11 C: 10/11	T: 67 (30, 365) d C: 56 (30, 296) d	T: 12.8 ± 3.8 C: 11.5 ± 4.5	100% RMT, 1 Hz, 20 pulses/session, 30 sessions, 1 time/d, 5 d/week, 4 weeks	'8'coil	Right DLPFC	Yes	①③⑦	Unreported
Ou *et al*. [10] (2014)	38	T: 68.3 ± 2.30 C: 69.2 ± 2.49	T: 11/7 C: 13/7	T: 13/5 C: 14/6	T: 127.30 ± 34.93 d C: 155.55 ± 63.89 d	UC	60% RMT, 20 Hz, 30 pulses/session, 1 session, 1 time/d, 5 d/week, 4 weeks	UC	Ipsilesional frontal cortex	No	①⑥	Unreported

T/C, treatment group/ control group; UC: Unclear; I/H, Ischemic/ Hemorrhage; RMT, resting motor threshold; DLPFC, dorsolateral prefrontal cortex; MoCA, Montreal Cognitive Assessment; MBI, Modified Barthel Index; MMSE, Mini-Mental State Examination; CAMPROMPT, Cambridge Prospective Memory Test Scale; LOTCA, Lovingston Homework Therapy Cognitive Assessment. ①, RBMT; ②, P300; ③, MoCA; ④, MBI; ⑤, MMSE; ⑥, CAMPROMPT; ⑦, LOTCA. Location of lesion and quality of outcomes reporting are not mentioned in original papers. Pulses of per session and number of session are not mentioned in Huang, Wen *et al*, and Zhou.

2.4 Baseline Differences

To reduce heterogeneity and improve comparability between rTMS groups across studies, we extracted the preintervention means and standard deviation of each study to conduct baseline difference testing.

2.5 Heterogeneity and Publication Bias

Heterogeneity between eligible studies was measured using I^2 statistics and Galbraith plots. I^2 statistics were calculated to determine the magnitude of study heterogeneity and Galbraith plots were used to reflect the extent of heterogeneity. To confirm the robustness of the conclusions and measure publication bias, Egger's test and Begg's test were conducted.

2.6 Data Synthesis

Data was analyzed using STATA 17 (StataCorp LLC4905 Lakeway Drive, College Station, TX, USA) to determine whether rTMS can improve memory performance, global cognition, and activities of daily living (ADL). All data analyses were performed using postintervention data from both the rTMS group and control group, and the results are presented as the mean difference (MD) and 95% confidence interval (CI). A random-effect model or a fixed-effect model was applied to determine effect sizes. When I^2 = 0.00%, the fixed-effect model was employed; otherwise, the random-effect model was applied.

2.7 Subgroup Analysis and Sensitivity Analysis

We performed subgroup analysis based on stimulation frequency (low frequency or high frequency), age (greater or less than 60), sex (male or female), stimulation intensity, duration of intervention (greater or less than 1 month), and intervention in the control group (sham rTMS or non-rTMS). Sensitivity analysis was performed to reduce the level of heterogeneity. The leave-one-out method was used to increase the reliability and credibility of the results.

3. Results

3.1 Study Identification

The databases initially yielded 1230 studies, 42 of which were potentially eligible for the final selection. Thirty-seven papers were subsequently excluded as a result of participants not being diagnosed with memory dysfunction, data from multiple studies being derived from the same trial, lack of appropriate memory assessment scale, and ineligible article types. The remaining five articles were included in the final analysis. The process of study selection is presented in Fig. 1.

3.2 Study Characteristics

The relevant features of eligible papers are presented in Table 2 (Ref. [10–14]). A total of 192 patients were included in the meta-analysis, including 121 males (63.0%) and 71 females (37.0%). The number of subjects in the eligible studies varied from 24 to 50 per study. The mean age range of the participants was 42.5 to 68.3 in the rTMS group and 47.3 to 69.2 in the control group. Three studies reported the prevalence rates of ischemic and hemorrhagic stroke; the number of ischemic strokes was 75 (58.6%) [10,11,14]. Participants' average number of years of education ranged from 9.48 to 12.8 in the rTMS group and from 9.05 to 11.85 in the control group [11–14].

The stimulation parameters are shown in Table 2. A figure-eight coil was applied in two studies [11,14], an O-coil was used in two studies [12,13], and the coil type was not reported in the fifth study [10]. Two studies employed 1-Hz low-frequency stimulation [11,14], and the other three employed 5-, 10-, or 20-Hz high-frequency stimulation [10,12,13]. The stimulation intensity in all the studies ranged from 60% to 120% of the resting motor threshold (five sessions per week for four consecutive weeks). The stimulation sites for rTMS included the left DLPFC [13], the contralesional DLPFC [14], bilateral DLPFC [12], the right DLPFC [11], and ipsilesional frontal cortex [10]. Regarding the interventions in the control group, three studies employed sham rTMS using three different approaches. These included a sham coil, a real coil placed perpendicular to the scalp that was not active, or stimulation stopped after 15 seconds. [11,12,14]. Non-rTMS interventions (drugs and regular cognitive rehabilitations) were used in the other two studies [10,13].

All papers that were included assessed memory function using the RBMT [10–14]. One study used the Cambridge Prospective Memory Test Scale (CAMPROMPT) in addition to the RBMT to evaluate memory performance [10]. To assess global cognition, the Montreal Cognitive Assessment (MoCA) was administered in four studies [11–14], one of which used a combination of the MoCA and the MMSE [14]. Ou *et al*. [10] did not assess global cognition. The Modified Barthel Index (MBI) was utilized to assess ADL in three studies [12–14]. Ou *et al*. [10] and Lu *et al.* [11] did not assess ADL. No adverse events were reported in these studies, except for Huang [13].

3.3 Quality Assessment

Three papers used a random number method to divide participants into treatment groups [11,12,14]. One paper used a computerized randomization method [13]. The method of randomization was not specified in the fifth paper [10]. In regard to allocation concealment, one paper used sealed opaque envelopes [13] and the remaining four papers did not report the details of allocation concealment [10–12,14]. Regarding blinding, three papers were considered to have a low risk of bias as both the patients and examiners were blinded [11–13]. Two papers had potential risk of performance and detection bias; only patients were blinded in the study by Wen *et al*. [14], and the blinding method was unspecified in the study by Ou *et al.* [10]. All of the included studies had complete data (Fig. 2).

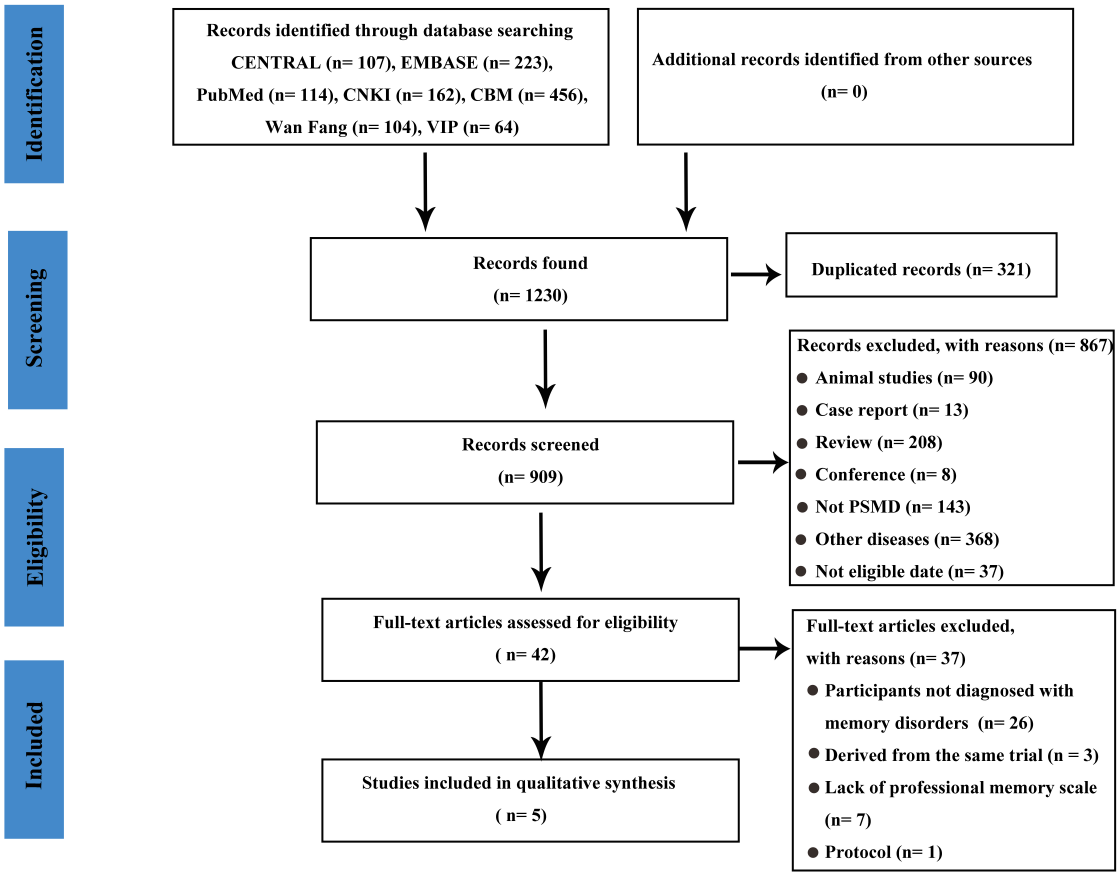

Fig. 1. Flow diagram of study selection.

According to the GRADE, the level of evidence for the primary (RBMT) and secondary outcomes (MoCA and MBI) was moderate. The quality of this outcome was downgraded because the method of allocation concealment was unclear (**Supplementary Material 4**).

3.4 Baseline Difference

The results of data synthesis based on the baseline data indicated no significant difference between the rTMS and control groups in scores on the RBMT (MD = –0.76, 95% CI [Confidence Interval] [–1.68, 0.15], $p = 0.10$, $I^2 = 0.00\%$, Fig. 3A), MoCA (MD = –0.65, 95% CI [–2.07, 0.77], $p = 0.37$, $I^2 = 0.00\%$, Fig. 3B), and MBI (MD = –0.73, 95% CI [–8.27, 6.80], $p = 0.85$, $I^2 = 37.93\%$, Fig. 3C).

3.5 Heterogeneity and Publication Bias

The Galbraith plot also did not indicate heterogeneity, as all dots were distributed between the two regression lines (Fig. 4A). There was no significant heterogeneity among the studies on memory performance (Q = 3.94, $p = 0.41$, $I^2 = 0.00\%$, Fig. 5A). Neither Begg's test (t = 0.73, $p = 0.462$, Fig. 4B) nor Egger's test (t = 1.00, $p = 0.393$, Fig. 4B) revealed evidence of publication bias.

3.6 Meta-Analyses

As mentioned in the Methods and published protocol section [32], a random-effect model or a fixed-effect model was applied to determine effect sizes. When $I^2 = 0.00\%$, the fixed-effect model was employed; otherwise, the random-effect model was applied.

3.6.1 Primary Outcome

The RBMT contains 12 sub scores consisting of 10 retrospective memory tasks and 2 prospective memory tasks. This scale was used to evaluate memory for details. All included papers used the RBMT to assess the impact of rTMS on memory function. The results based on the fixed-effect model indicated that the RBMT scores of the rTMS group were significantly greater than those of the control group (MD = 1.73, 95% CI [0.85, 2.60], $p < 0.001$, $I^2 = 0.00\%$, Fig. 5A).

As shown in Fig. 6A, subgroup analysis revealed no significant difference between the effects of the LF-rTMS and HF-rTMS on memory performance (Q = 0.52, $p = 0.47$, $I^2 = 0.00\%$). Regarding low-frequency versus control, subgroup analysis demonstrated that the effect of LF-rTMS on memory function in participants with PSMD was significantly greater than that of control treatment (MD = 2.12,

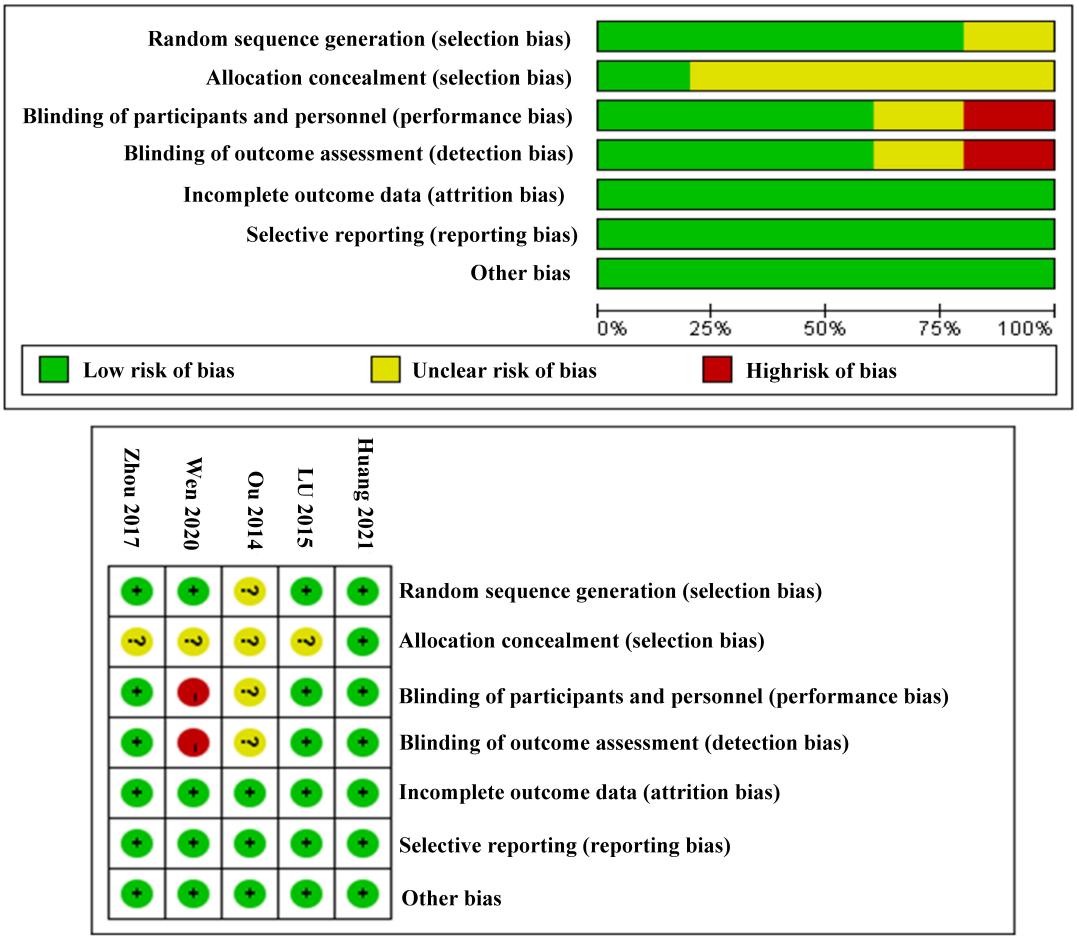

Fig. 2. Risk-of-bias graph and summary of the included studies.

95% CI [0.90, 3.33], $p < 0.001$, $I^2 = 0.00\%$). Regarding high-frequency versus control treatment, there was no significant difference in memory performance between these two conditions (MD = 1.42, 95% CI [–0.07, 2.90], $p = 0.06$, $I^2 = 18.87\%$, Fig. 6A).

As shown in Fig. 6B, the sham rTMS group and the non-rTMS did not significantly differ according to subgroup analysis (Q = 0.01, $p = 0.94$, $I^2 = 0.00\%$). Regarding sham rTMS versus rTMS, an analysis with three studies [11,12,14] indicated rTMS group was superior to the sham rTMS group in RBMT (MD = 1.96, 95% CI [0.84, 3.07], $p < 0.001$, $I^2 = 0.00\%$). Regarding non-rTMS versus rTMS, the analysis with two studies [10,13] reported that there was no significant difference between the non-rTMS and rTMS groups (MD = 1.85, 95% CI [–0.80, 4.50], $p = 0.17$, $I^2 = 58.96\%$, Fig. 6B).

Regarding the duration of intervention, a subgroup analysis could not be conducted because all the interventions examined herein lasted for one month. Regarding sex, all included studies recruited both males and females and did not assess the data separately by sex. Regarding stimulation intensity, two studies had the same stimulation intensity but the intensity was different in the remaining three studies. Regarding age, both younger and older patients were simultaneously included in four studies. Therefore, subgroup analyses could not be performed based on the duration of intervention, age, sex, or stimulation intensity (**Supplementary Material 5**).

3.6.2 Secondary Outcomes

The MoCA is a rapid screening tool for cognitive abnormalities and tests eight cognitive domains, including delayed memory, visuospatial function, executive function, attention, numeracy, language function, temporal orientation, and place orientation. By including these domains, the MoCA is thought to measure overall cognitive function [33]. The MBI is an 11-item scale used to evaluate the ability to perform basic ADL [34].

The results showed that rTMS was superior to control treatments for improving global cognition (MD = 2.44, 95% CI [0.96, 3.93], $p < 0.001$, $I^2 = 20.23\%$, Fig. 5B) and ADL (MD = 10.29, 95% CI [5.10, 15.48], $p < 0.001$, $I^2 = 0.00\%$, Fig. 5C). According to subgroup analysis, the LF-rTMS and HF-rTMS group did not significantly differ in either MoCA (Q = 1.41, $p = 0.23$, $I^2 = 20.23\%$, **Supplementary Material 6**) or MBI scores (Q = 0.26, $p = 0.61$,

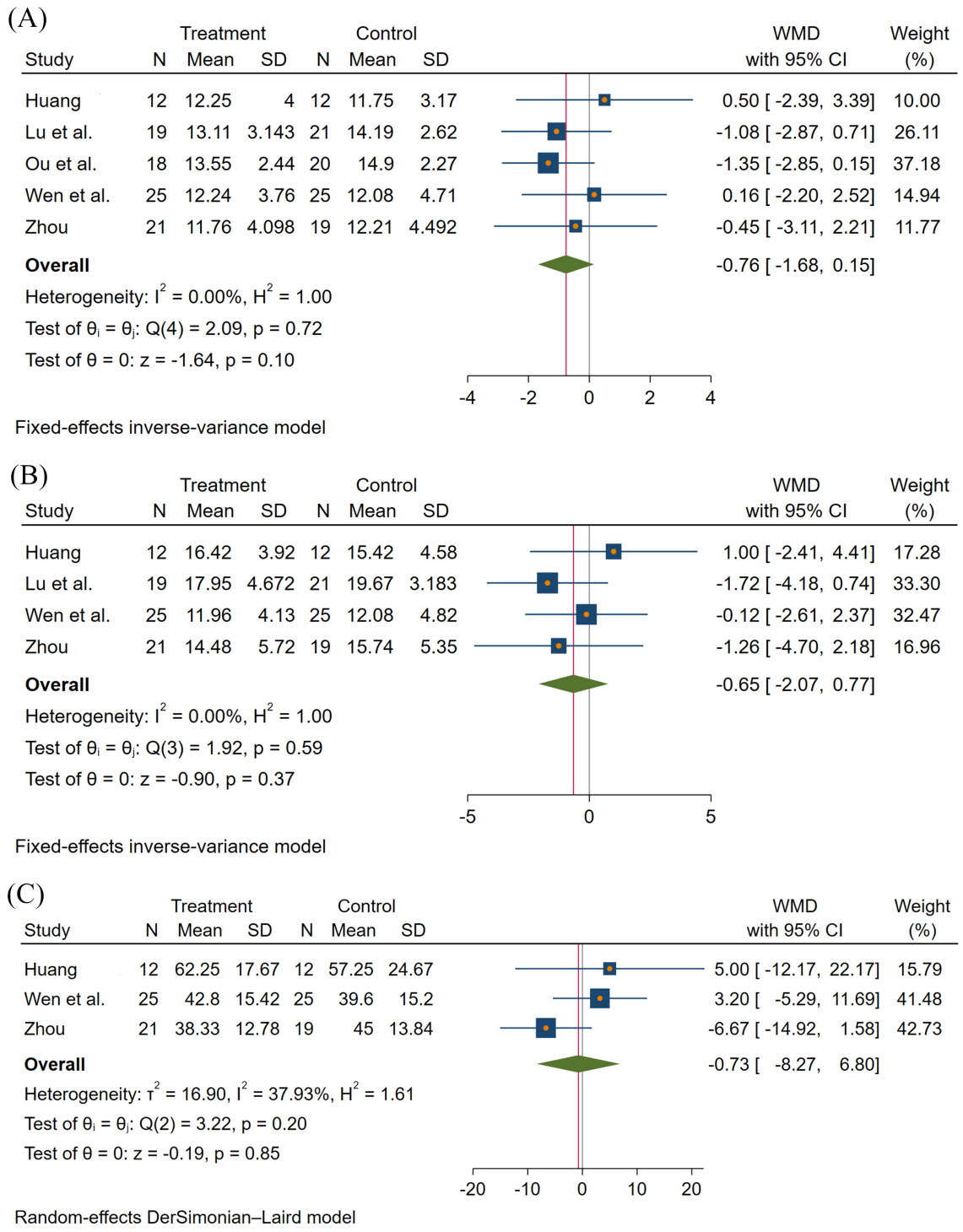

Fig. 3. Comparison of pre-intervention clinical data between the rTMS and control groups. (A) Comparison of differences in RBMT between the rTMS and control groups. (B) Comparison of differences in MoCA between the rTMS and control groups. (C) Comparison of differences in MBI between the rTMS and control groups. rTMS, repetitive transcranial magnetic stimulation; RBMT, Rivermead Behavioral Memory Test; MoCA, Montreal Cognitive Assessment; MBI, Modified Barthel Index; WMD, Weighted Mean Difference; 95% CI, 95% Confidence Interval.

I^2 = 0.00%, **Supplementary Material 7**). Furthermore, there was no significant difference in effect size observed between the sham rTMS group and the control group without sham rTMS in either MoCA (Q = 0.52, p = 0.47, I^2 = 20.23%, **Supplementary Material 8**) or MBI scores (Q = 0.22, p = 0.64, I^2 = 0.00%, **Supplementary Material**

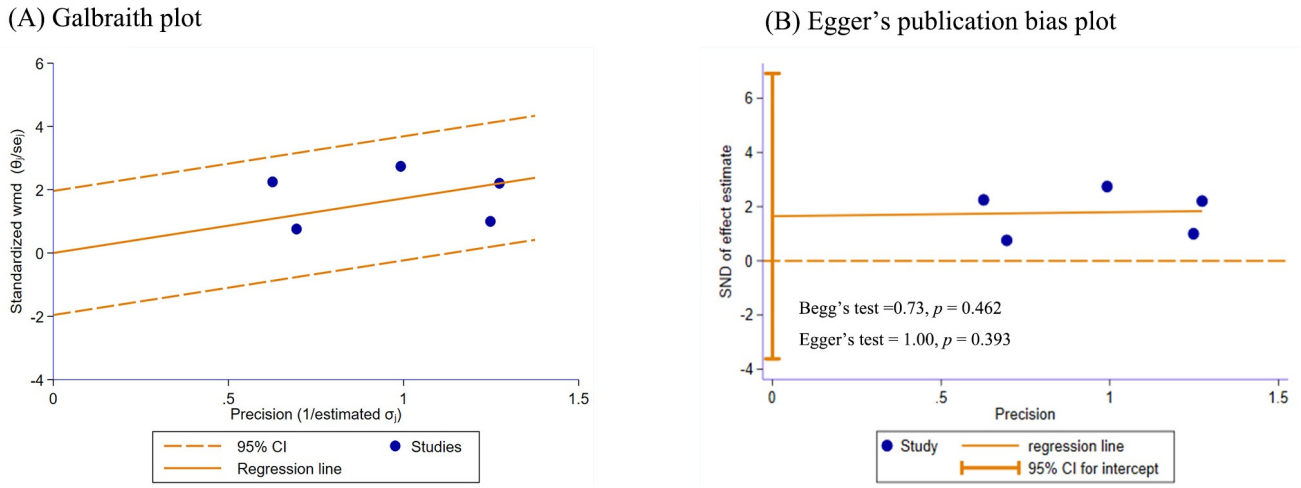

Fig. 4. Series assessments for heterogeneity and publication bias for the effect of rTMS on memory function. (A) Galbraith plot indicating no heterogeneity. (B) Begg's test and Egger's test suggesting no publication bias.

9). One study stated that there were no adverse effects after rTMS intervention [13]; the other studies did not mention adverse events [10–12,14]. As we were unable to analyze the data quantitatively, a descriptive analysis was conducted for adverse events.

3.7 Sensitivity Assessment

The leave-one-out method revealed that the effect sizes fell within the original confidence interval regardless of which study was left out. This result suggested that the assessment of memory evaluation is stable and reliable (Fig. 7).

4. Discussion

To our knowledge, this is the first meta-analysis to explore the efficacy of rTMS for treatment of patients with PSMD. Our results revealed that the impact of rTMS on memory performance in patients with PSMD was superior to that of control treatment. Additionally, we found that rTMS enhanced general cognition and ADL scores. Furthermore, subgroup analysis revealed that LF-rTMS and HF-rTMS may have similar efficacy for treating PSMD. Finally, there was no impact of sham rTMS and non-rTMS on efficacy. Based on these results, our study strongly supports the application of rTMS to treat PSMD in clinical settings.

4.1 Efficacy of rTMS on Memory Performance

rTMS is a noninvasive technique used to modulate cortical activity. Its effects on memory performance among stroke patients may be associated with its influence on long-term depression (LTD) and long-term potentiation (LTP), processes that are required for memory formation [35]. LF-rTMS decreases cortical excitability by influencing LTD, while HF-rTMS facilitates cortical excitability through LTP [36]. Studies have demonstrated that the effectiveness of TMS is related to the activation of brain regions such as the prefrontal cortex (PFC) [37,38]. and hippocampus [39]. Additionally, rTMS was shown to promote the recovery of damaged nerves and the production of new neurons through upregulation of brain-derived neurotrophic factors [40].

Our findings that rTMS treatment was effective at improving memory performance in patients with PSMD is consistent with previous studies [8,21,23,41]. Conversely, it differs from the studies of Sedlackova *et al*. [17] and Rektorova *et al*. [16], that found rTMS to have no effect on memory performance. There are several tenable reasons for these inconsistent findings. It may be associated with differences in sample size between studies. Their studies included 7 participants [16,17], whereas our study included 192 patients. Additionally, their studies compared baseline and post-intervention data, while we compared the performance of the two groups after the intervention in the absence of differences at baseline. The latter approach may be more appropriate for demonstrating the efficacy of rTMS. Stimulation parameters also varied across different studies, possibly affecting the clinical efficacy of rTMS.

Subgroup analyses revealed that the LF-rTMS condition was superior to the control condition, whereas HF-rTMS was not different from the control condition. These findings contradict those of other studies [21,42,43] that have reported HF-rTMS as being superior to control treatments. This inconsistency may be a result of different stimulation sites, frequency, and intensity. There was also heterogeneity detected, which may affect the final effect size. Therefore, additional studies are required to investigate the efficacy of HF-rTMS on memory performance.

In addition, stimulation frequency indicated similar efficacy between LF-rTMS and HF-rTMS subgroups, results that are consistent with previous studies [42,44–46]. For instance, Ying-Hui Chou and coworkers reported that both LF-rTMS and HF-rTMS over the right DLPFC and the left DLPFC, respectively, were effective at enhanc-

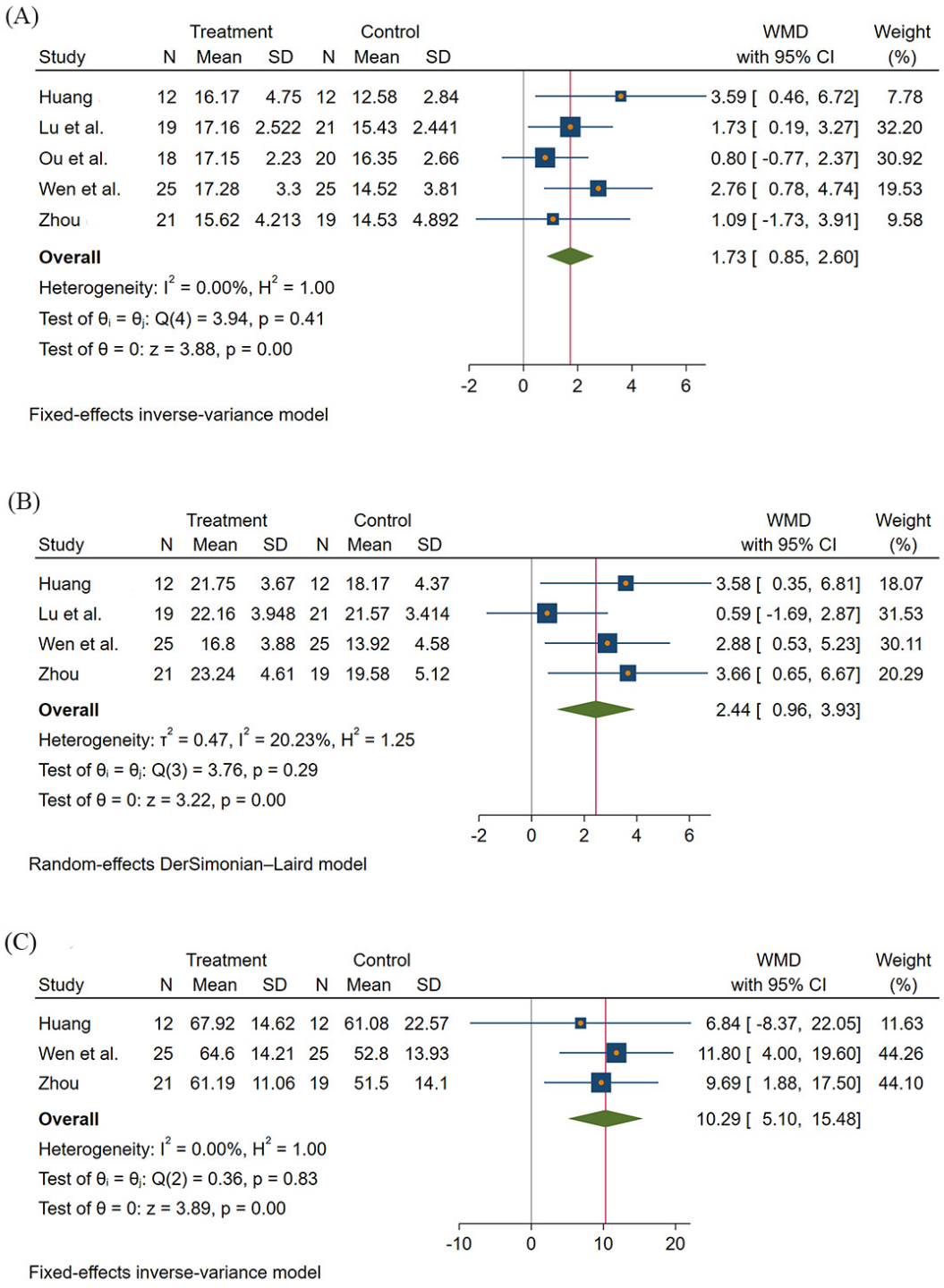

Fig. 5. Comparison of postintervention clinical data between the rTMS and control groups. (A) Comparison of differences in RBMT between the rTMS and control groups. (B) Comparison of differences in MoCA between the rTMS and control groups. (C) Comparison of differences in MBI between the rTMS and control groups.

ing memory performance in patients with mild cognitive impairment (MCI) and Alzheimer's disease (AD) [42]. Another meta-analysis showed that both low- and high-frequency rTMS could significantly enhance memory performance [44]. Additionally, several studies have shown that low-frequency and high-frequency rTMS have similar effects in the treatment of poststroke motor disorder [45,46]. Xiang H *et al.* [46] conducted a meta-analysis to investigate how the adjustable parameters of rTMS influence its efficacy as a treatment for poststroke motor disorder and found that stimulation frequency did not have an effect on the efficacy of rTMS. Du J *et al.* [45] reported that

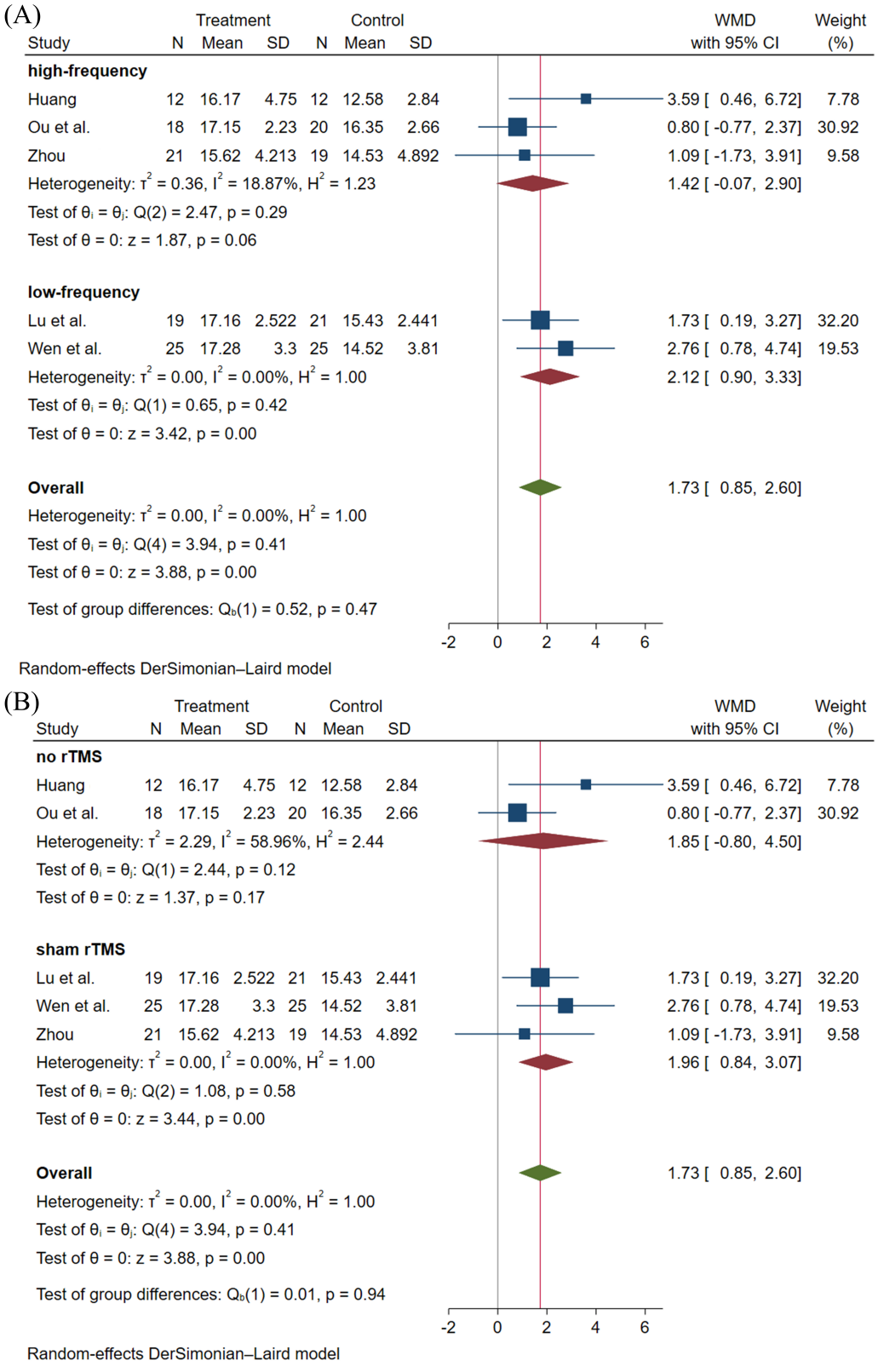

Fig. 6. Forest plots of subgroup analysis. (A) Stimulation frequency (low frequency or high frequency). (B) Intervention in the control group (sham rTMS or non-rTMS).

both 10 Hz HF-rTMS and 1 Hz LH-rTMS were superior to sham rTMS for poststroke motor disorder as measured by the Fugl–Meyer Assessment (FMA), while similar efficacy was observed between HF-rTMS and LH-rTMS.

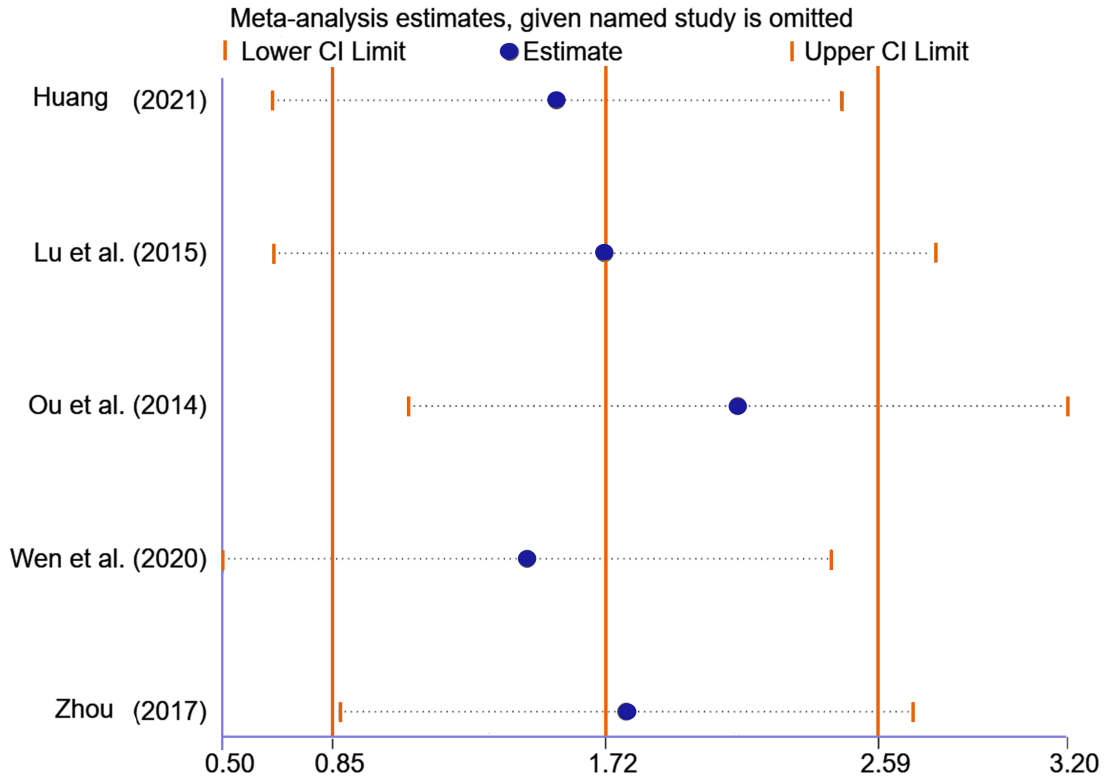

Fig. 7. Sensitivity analysis for the RBMT.

Furthermore, our findings revealed no significant difference between the effects of the sham and non-rTMS control conditions on memory function. This suggests that rTMS does not have a placebo effect on memory rehabilitation. Accordingly, Jelić MB *et al.* [47], also did not report a placebo effect of rTMS on motor learning. This supports our conclusion as memory function is essential for motor learning. However, the placebo effect was not confirmed due to the considerable heterogeneity. Thus, further studies are required to explore the placebo effect of sham rTMS.

4.2 Efficacy of rTMS on Secondary Outcomes

The comparison of the rTMS group versus the control group revealed that rTMS was effective at enhancing global cognition and ADL in patients with PSMD. These results are consistent with those reported in previous publications [20,24,38,41]. For instance, Mengting Liu and colleagues reported positive effects of rTMS on cognitive function among stroke patients [20]. Another study found that intermittent theta-burst stimulation significantly enhanced cognition and quality of life among patients with PSCI [38]. Additionally, studies have shown that rTMS improves quality of daily life and general cognition among patients with AD [48], Parkinson's disease [49], and MCI [42]. Nevertheless, our results should be followed up with additional evidence as there was mild heterogeneity in our meta-analysis.

Only one article included in our review reported that there were no adverse effects, while the others did not mention them. Thus, no firm conclusions can be drawn from our meta-analysis regarding possible adverse events. Previously studies have reported that rTMS is safe for treating both poststroke motor disorder and aphasia [50,51]. However, several articles have reported that patients experienced dizziness [52], headache [45], anxiety [53], and other discomforts after rTMS treatment. These adverse events may be related to the high stimulation intensity of rTMS and individual participant differences. Therefore, it is necessary to conduct additional studies to determine the safety of rTMS for treatment of patients with PSMD.

4.3 Limitations and Future Perspectives

One limitation of our study was the small number of eligible papers on patients with PSMD. As a result, we did not examine funnel plots to evaluate publication bias. While our findings support the use of rTMS in clinical practice for improving memory performance, MoCA and MBI scores among patients with PSMD, the duration of its efficacy is still unknown as long-term follow-up studies are limited. Future studies should extend the follow-up observation period to explore the time point at which the best long-term outcomes can be obtained and to provide new insights into the long-term benefits of rTMS treatment for PSMD. Additionally, mechanical embolectomy is closely associated with stroke outcomes and future analyses should

control for the impact of this factor on results. Future clinical trials should control for confounding factors and stratify patients according to the type of PSMD to improve data quality and determine the best stimulation strategy. Furthermore, future studies need to improve clarity of methodological details regarding trial design by including information about allocation concealment and blinding to decrease the risk of bias.

5. Conclusions

In conclusion, the results of our meta-analysis suggest that rTMS is effective for improving memory performance, global cognition, and ADL in patients with PSMD. LF-rTMS and HF-rTMS may have similar efficacy in treatment of PSMD. Additional studies are required to explore the safety, placebo effect, and long-term effect of rTMS.

Abbreviations

PSMD, poststroke memory disorder; RCT, randomized controlled trial; rTMS, repetitive transcranial magnetic stimulation; RBMT, Rivermead Behavioral Memory Test; MoCA, Montreal Cognitive Assessment; MBI, Modified Barthel Index.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article.

Author Contributions

HHX, NZ and JT designed the research. SYL and DX, PZ, JC and XT completed data selection and extraction. HHX, SYL and DX, PZ, JC and XT contributed to participated in data analysis. HHX and SYL participated in writing original draft. HHX, NZ and JT were responsible for revising manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

The National Natural Science Foundation of China (Grant No. 81874499) and Hunan University of Chinese Medicine Postgraduate Innovation Project (Grant No. 2022CX106).

Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/j.jin2205131.

References

[1] Kalaria RN, Ballard C. Stroke and cognition. Current Atherosclerosis Reports. 2001; 3: 334–339.

[2] das Nair R, Cogger H, Worthington E, Lincoln NB. Cognitive rehabilitation for memory deficits after stroke. The Cochrane Database of Systematic Reviews. 2016; 9: CD002293.

[3] de Lima Ferreira G, de Oliveira Lopes MV, Montoril MH, Diniz CM, Santana RF. Clinical validation of the nursing diagnosis of impaired memory in patients with a stroke. Japan Journal of Nursing Science: JJNS. 2019; 16: 136–144.

[4] Snaphaan L, de Leeuw FE. Poststroke memory function in nondemented patients: a systematic review on frequency and neuroimaging correlates. Stroke. 2007; 38: 198–203.

[5] Lamb F, Anderson J, Saling M, Dewey H. Predictors of subjective cognitive complaint in postacute older adult stroke patients. Archives of Physical Medicine and Rehabilitation. 2013; 94: 1747–1752.

[6] van Rijsbergen MWA, Mark RE, de Kort PLM, Sitskoorn MM. Subjective cognitive complaints after stroke: a systematic review. Journal of Stroke and Cerebrovascular Diseases: the Official Journal of National Stroke Association. 2014; 23: 408–420.

[7] van Zelst AL, Earle FS. A case for the role of memory consolidation in speech-motor learning. Psychonomic Bulletin & Review. 2021; 28: 81–95.

[8] Lu H, Zhang T, Wen M, Sun L. Impact of repetitive transcranial magnetic stimulation on post-stroke dysmnesia and the role of BDNF Val66Met SNP. Medical Science Monitor: International Medical Journal of Experimental and Clinical Research. 2015; 21: 761–768.

[9] Hu DM, Cheng XR, Zhou WX, Zhang YX, Zhou LC. Treatment of post stroke cognitive impairment by rTMS. Sheng Li Ke Xue Jin Zhan. 2012; 43: 411–416. (In Chinese)

[10] Ou H, Gan Y, Nong W, Lu W, Liu Y. Effect of Chifukang Oral Liquid and Repetitive Transcranial Magnetic Stimulation on Prospective Memory Impairment after Stroke. Chinese Journal of Integrative Medicine on Cardio. 2014; 12: 799–801. (In Chinese)

[11] Lu H, Sun L, Guo H, Zhang T. Effect of Low-frequency Repetitive Transcranial Magnetic Stimulation on Memory and Cognition Impairment after Stroke. Chinese Journal of Rehabilitation Theory and Practice. 2015; 21: 1074–1077. (In Chinese)

[12] Zhou Q. Effect of Repetitive Transcranial Magnetic Stimulation on prospective memory dysfunction after stroke [master's thesis]. Zhengzhou University. 2017.

[13] Huang C. Effect of rTMS combined with tDCS treatment on memory dysfunction after stroke [master's thesis]. Tianjin University of Sport. 2021.

[14] Wen W, Gong Z, Ma Z, Su C, Chen J, Wang C, *et al*. Effects of low-frequency rTMS on cognitive of post-stroke memory disorders patients and P300. Journal of Neuroscience and Mental Health. 2020; 20: 692–697.

[15] Hallett M. Transcranial magnetic stimulation: a primer. Neuron. 2007; 55: 187–199.

[16] Rektorova I, Megova S, Bares M, Rektor I. Cognitive functioning after repetitive transcranial magnetic stimulation in patients with cerebrovascular disease without dementia: a pilot study of seven patients. Journal of the Neurological Sciences. 2005; 229-230: 157–161.

[17] Sedlackova S, Rektorova I, Fanfrdlova Z, Rektor I. Neurocogni-

tive Effects of Repetitive Transcranial Magnetic Stimulation in Patients with Cerebrovascular Disease Without Dementia. Journal of Psychophysiology. 2008; 22: 14–19.
[18] Hillis AE. Developments in treating the nonmotor symptoms of stroke. Expert Review of Neurotherapeutics. 2020; 20: 567–576.
[19] Fisicaro F, Lanza G, Grasso AA, Pennisi G, Bella R, Paulus W, *et al*. Repetitive transcranial magnetic stimulation in stroke rehabilitation: review of the current evidence and pitfalls. Therapeutic Advances in Neurological Disorders. 2019; 12: 1756286419878317.
[20] Liu M, Bao G, Bai L, Yu E. The role of repetitive transcranial magnetic stimulation in the treatment of cognitive impairment in stroke patients: A systematic review and meta-analysis. Science Progress. 2021; 104: 368504211004266.
[21] Tsai PY, Lin WS, Tsai KT, Kuo CY, Lin PH. High-frequency versus theta burst transcranial magnetic stimulation for the treatment of poststroke cognitive impairment in humans. Journal of Psychiatry & Neuroscience: JPN. 2020; 45: 262–270.
[22] Sun D, Liu J, Song T, Zhang C. Effects of low frequency repetitive transcranial magnetic stimulation on memory function of patients with memory dysfunction after cerebral stroke. Hebei Medical Journal. 2020; 42: 2565–2570. (In Chinese)
[23] Yin M, Liu Y, Zhang L, Zheng H, Peng L, Ai Y, *et al*. Effects of rTMS Treatment on Cognitive Impairment and Resting-State Brain Activity in Stroke Patients: A Randomized Clinical Trial. Frontiers in Neural Circuits. 2020; 14: 563777.
[24] Li W, Wen Q, Xie YH, Hu AL, Wu Q, Wang YX. Improvement of poststroke cognitive impairment by intermittent theta bursts: A double-blind randomized controlled trial. Brain and Behavior. 2022; 12: e2569.
[25] Demeyere N, Riddoch MJ, Slavkova ED, Bickerton WL, Humphreys GW. The Oxford Cognitive Screen (OCS): validation of a stroke-specific short cognitive screening tool. Psychological Assessment. 2015; 27: 883–894.
[26] Lomholt RK, Jürgensen KS. The mini-mental state examination in screening of cognitive dysfunction and dementia. Ugeskrift for Laeger. 1998; 160: 7251–7254.
[27] Elwood RW. The Wechsler Memory Scale-Revised: psychometric characteristics and clinical application. Neuropsychology Review. 1991; 2: 179–201.
[28] Wilson B, Cockburn J, Baddeley A, Hiorns R. The development and validation of a test battery for detecting and monitoring everyday memory problems. Journal of Clinical and Experimental Neuropsychology. 1989; 11: 855–870.
[29] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. British Medical Journal (Clinical Research Edition). 2021; 372: n71.
[30] Cumpston M, Li T, Page MJ, Chandler J, Welch VA, Higgins JP, *et al*. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. The Cochrane Database of Systematic Reviews. 2019; 10: ED000142.
[31] Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, *et al*. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. Journal of Clinical Epidemiology. 2011; 64: 383–394.
[32] Xie H, Xiong D, Zhu P, Li H, Zhang H, Tan J, *et al*. Effectiveness and safety of repetitive transcranial magnetic stimulation on memory disorder in stroke: A protocol for systematic review and meta-analysis. Medicine. 2022; 101: e30933.
[33] Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, *et al*. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. Journal of the American Geriatrics Society. 2005; 53: 695–699.
[34] Ohura T, Hase K, Nakajima Y, Nakayama T. Validity and reliability of a performance evaluation tool based on the modified Barthel Index for stroke patients. BMC Medical Research Methodology. 2017; 17: 131.
[35] Stanton PK. LTD, LTP, and the sliding threshold for long-term synaptic plasticity. Hippocampus. 1996; 6: 35–42.
[36] Hoogendam JM, Ramakers GMJ, Di Lazzaro V. Physiology of repetitive transcranial magnetic stimulation of the human brain. Brain Stimulation. 2010; 3: 95–118.
[37] Barbosa J, Stein H, Martinez RL, Galan-Gadea A, Li S, Dalmau J, *et al*. Interplay between persistent activity and activity-silent dynamics in the prefrontal cortex underlies serial biases in working memory. Nature Neuroscience. 2020; 23: 1016–1024.
[38] Chu M, Zhang Y, Chen J, Chen W, Hong Z, Zhang Y, *et al*. Efficacy of Intermittent Theta-Burst Stimulation and Transcranial Direct Current Stimulation in Treatment of Post-Stroke Cognitive Impairment. Journal of Integrative Neuroscience. 2022; 21: 130.
[39] Wang JX, Voss JL. Long-lasting enhancements of memory and hippocampal-cortical functional connectivity following multiple-day targeted noninvasive stimulation. Hippocampus. 2015; 25: 877–883.
[40] Fu R, Xu G, Zhu H, Ding C. Research progress on the effect of transcranial magnetic stimulation on learning, memory and plasticity of brain synaptic. Sheng Wu Yi Xue Gong Cheng Xue Za Zhi. 2021; 38: 783–789. (In Chinese)
[41] Li H, Ma J, Zhang J, Shi WY, Mei HN, Xing Y. Repetitive Transcranial Magnetic Stimulation (rTMS) Modulates Thyroid Hormones Level and Cognition in the Recovery Stage of Stroke Patients with Cognitive Dysfunction. Medical Science Monitor: International Medical Journal of Experimental and Clinical Research. 2021; 27: e931914.
[42] Chou YH, Ton That V, Sundman M. A systematic review and meta-analysis of rTMS effects on cognitive enhancement in mild cognitive impairment and Alzheimer's disease. Neurobiology of Aging. 2020; 86: 1–10.
[43] Drumond Marra HL, Myczkowski ML, Maia Memória C, Arnaut D, Leite Ribeiro P, Sardinha Mansur CG, *et al*. Transcranial Magnetic Stimulation to Address Mild Cognitive Impairment in the Elderly: A Randomized Controlled Study. Behavioural Neurology. 2015; 2015: 287843.
[44] Wang T, Guo Z, Du Y, Xiong M, Yang Z, Ren L, *et al*. Effects of Noninvasive Brain Stimulation (NIBS) on Cognitive Impairment in Mild Cognitive Impairment and Alzheimer Disease: A Meta-analysis. Alzheimer Disease and Associated Disorders. 2021; 35: 278–288.
[45] Du J, Yang F, Hu J, Hu J, Xu Q, Cong N, *et al*. Effects of high- and low-frequency repetitive transcranial magnetic stimulation on motor recovery in early stroke patients: Evidence from a randomized controlled trial with clinical, neurophysiological and functional imaging assessments. NeuroImage. Clinical. 2019; 21: 101620.
[46] Xiang H, Sun J, Tang X, Zeng K, Wu X. The effect and optimal parameters of repetitive transcranial magnetic stimulation on motor recovery in stroke patients: a systematic review and meta-analysis of randomized controlled trials. Clinical Rehabilitation. 2019; 33: 847–864.
[47] Jelić MB, Stevanović VB, Milanović SD, Ljubisavljević MR, Filipović SR. Transcranial magnetic stimulation has no placebo effect on motor learning. Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology. 2013; 124: 1646–1651.
[48] Li X, Qi G, Yu C, Lian G, Zheng H, Wu S, *et al*. Cortical plasticity is correlated with cognitive improvement in Alzheimer's disease patients after rTMS treatment. Brain Stimulation. 2021; 14: 503–510.

[49] Khedr EM, Mohamed KO, Ali AM, Hasan AM. The effect of repetitive transcranial magnetic stimulation on cognitive impairment in Parkinson's disease with dementia: Pilot study. Restorative Neurology and Neuroscience. 2020; 38: 55–66.
[50] Tung YC, Lai CH, Liao CD, Huang SW, Liou TH, Chen HC. Repetitive transcranial magnetic stimulation of lower limb motor function in patients with stroke: a systematic review and meta-analysis of randomized controlled trials. Clinical Rehabilitation. 2019; 33: 1102–1112.
[51] Zhang J, Zhong D, Xiao X, Yuan L, Li Y, Zheng Y, *et al*. Effects of repetitive transcranial magnetic stimulation (rTMS) on aphasia in stroke patients: A systematic review and meta-analysis. Clinical Rehabilitation. 2021; 35: 1103–1116.
[52] Chieffo R, Giatsidis F, Santangelo R, Alyagon U, Comola M, Zangen A, *et al*. Repetitive Transcranial Magnetic Stimulation with H-Coil Coupled with Cycling for Improving Lower Limb Motor Function After Stroke: An Exploratory Study. Neuromodulation: Journal of the International Neuromodulation Society. 2021; 24: 916–922.
[53] Fregni F, Boggio PS, Valle AC, Rocha RR, Duarte J, Ferreira MJL, *et al*. A sham-controlled trial of a 5-day course of repetitive transcranial magnetic stimulation of the unaffected hemisphere in stroke patients. Stroke. 2006; 37: 2115–2122.