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Comparative efficacy of different repetitive transcranial magnetic stimulation protocols for lower extremity motor function in stroke patients: a network meta-analysis

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Background: Lower extremity motor dysfunction is one of the most severe consequences after stroke, restricting functional mobility and impairing daily activities. Growing evidence suggests that repetitive transcranial magnetic stimulation (rTMS) can improve stroke patients' lower extremity motor function. However, there is still controversy about the optimal rTMS protocol. Therefore, we compared and analyzed the effects of different rTMS protocols on lower extremity motor function in stroke patients using network meta-analysis (NMA).

Methods: We systematically searched CNKI, WanFang, VIP, CBM, PubMed, Embase, Web of Science, and Cochrane Library databases (from origin to 31 December 2023). Randomized controlled trials (RCTs) or crossover RCTs on rTMS improving lower extremity motor function in stroke patients were included. Two authors independently completed article screening, data extraction, and quality assessment. RevMan (version 5.4) and Stata (version 17.0) were used to analyze the data.

Results: A total of 38 studies with 2,022 patients were eligible for the NMA. The interventions included HFrTMS-M1, LFrTMS-M1, iTBS-Cerebellum, iTBS-M1, dTMS-M1, and Placebo. The results of NMA showed that LFrTMS-M1 ranked first in FMA-LE and speed, and HFrTMS-M1 ranked first in BBS, TUGT, and MEP amplitude. The subgroup analysis of FMA-LE showed that HFrTMS-M1 was the best stimulation protocol for post-stroke time >1 month, and LFrTMS-M1 was the best stimulation protocol for post-stroke time ≤1 month.

Conclusion: Considering the impact of the stroke phase on the lower extremity motor function, the current research evidence shows that HFrTMS-M1 may be the preferred stimulation protocol to improve the lower extremity motor function of patients for post-stroke time >1 month, and LFrTMS-M1 for post-stroke time ≤1 month. However, the above conclusion needs further analysis and validation by more high-quality RCTs.

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KEYWORDS

stroke, lower extremity, motor function, repetitive transcranial magnetic stimulation, network meta-analysis

1 Introduction

Stroke is a local brain dysfunction caused by acute cerebrovascular disease (Park et al., 2011). By 2019, the proportion of stroke patients had increased to 2.58% among residents aged ≥ 40 years in China (Wang et al., 2022). Stroke is the leading cause of adult death and disability in China, with the five characteristics of high incidence, high disability rate, high mortality rate, high recurrence rate, and high economic burden, which has seriously endangered the health of Chinese people. With the development of medical technology, the mortality rate of stroke has decreased year by year, but 72% of the survivors still have lower extremity dysfunction (Ng and Hui-Chan, 2010), which affects the walking function of patients. Walking dysfunction is one of the most severe consequences of stroke. Nearly 30% of stroke patients are unable to walk even in the chronic recovery stage (Park et al., 2011), which significantly affects the patients' social interactions and can lead to lifelong disability in severe cases (Park and An, 2016). Therefore, improving the motor function of the lower extremity, restoring independent walking as soon as possible, and improving activities of daily living (ADL) are the problems that many stroke patients are eager to solve urgently. However, pharmacological therapy (Mead et al., 2013) and traditional rehabilitation therapies [e.g., neurodevelopmental therapy (Langhammer and Stanghelle, 2011), proprioceptive neuromuscular facilitation (Eng and Tang, 2007), and electromyography biofeedback (Woodford and Price, 2007)] seem to have limited effects on improving motor function of the lower extremity after stroke. Therefore, a more effective treatment is needed.

Repetitive transcranial magnetic stimulation (rTMS), one of the brain stimulation techniques without any trauma, can induce neuroplastic changes and promote brain function restoration (Nathou et al., 2018). At present, the interhemispheric competition (IHC) model is the primary theoretical basis for applying rTMS in stroke rehabilitation. This model suggests that stroke destroys the balance of mutual inhibition of the bilateral cerebral hemispheres through the corpus callosum, resulting in the decreased inhibition of the ipsilateral hemisphere to the contralateral hemisphere and the increased inhibition of the contralateral hemisphere to the ipsilateral hemisphere (Di Pino et al., 2014). Therefore, in clinical practice, there are two main ways to use rTMS to promote functional recovery after stroke. One is to reduce the excitability of the contralateral hemisphere through low-frequency (≤ 1 Hz) rTMS to reduce the inhibitory effect of the contralateral hemisphere on the ipsilateral hemisphere. The other is to restore the balance of competitive inhibition between the bilateral cerebral hemispheres by stimulating the ipsilateral hemisphere with high-frequency (≥ 5 Hz) rTMS to increase its excitability (George and Aston-Jones, 2010). Both stimulation modes have been used to treat motor/non-motor dysfunction after stroke.

Theta burst stimulation (TBS), a novel mode of rTMS, saves time in the rehabilitation of motor function after stroke (Huang et al., 2005). There are two types of TBS: intermittent TBS (iTBS) and continuous TBS (cTBS), which generate excitatory and inhibitory effects, respectively (Larson et al., 1986; Huang et al., 2011). Compared

with conventional rTMS protocols, TBS provides significant advantages due to its reduced stimulation time (Chung et al., 2015) and long-lasting effects with lower-intensity stimulation (Cárdenas-Morales et al., 2010). Deep transcranial magnetic stimulation (dTMS) is a new non-invasive neuromodulation technique based on rTMS technology, which uses a different coil type (Hesed coil). dTMS has the advantages of deeper and wider stimulation, more precise localization, and less damage to the superficial cortex than conventional TMS (Roth et al., 2014). The primary motor cortex (M1) is typically the target of rTMS. However, some studies have shown that the cerebellum is one of the alternative targets of M1, and rTMS targeting the cerebellum can also improve motor function in stroke patients (Wessel and Hummel, 2018). In conclusion, rTMS can regulate the asymmetry of excitability between the bilateral cerebral hemispheres by changing the stimulation mode, stimulation target, stimulation frequency, and coil type to promote the recovery of lower extremity motor dysfunction after stroke (Kesikburun, 2022).

The effect of rTMS on lower extremity motor function in stroke patients has been demonstrated in previous meta-analysis (Li et al., 2018; Tung et al., 2019). However, an important drawback is that conventional meta-analysis can only compare two interventions simultaneously. At the same time, in these studies, the intervention protocols of the experimental group were roughly classified, and the effects of different stimulation frequencies, stimulation targets, stimulation modes, and post-stroke times on treatment effects were not comprehensively considered. Although Fan et al. (2021) conducted a detailed systematic review of rTMS to improve lower extremity motor function in stroke patients, this study did not consider the new stimulation mode-iTBS, the new stimulation target-cerebellum, and the effect of stroke phase on the efficacy of rTMS.

Network meta-analysis (NMA) is developed from conventional meta-analysis, and its primary function is to comprehensively evaluate and rank multiple interventions simultaneously (Rouse et al., 2017). Therefore, we took the stimulation mode, stimulation frequency, and stimulation target of rTMS into account and summarized the following five different rTMS protocols: high-frequency rTMS-M1 (HFrTMS-M1), low-frequency rTMS-M1 (LFrTMS-M1), iTBS-Cerebellum, iTBS-M1, and dTMS-M1. Then, we compared and analyzed the effects of different protocols on lower extremity motor dysfunction in stroke patients by NMA. In addition, considering the effects of the stroke phase on the efficacy of rTMS at different protocols, we also carried out a subgroup analysis for FMA-LE according to the phase of the stroke to provide sufficient evidence for future clinical practice.

2 Materials and methods

2.1 Study enrollment and reporting

Our NMA was conducted using the Cochrane Handbook for Systematic Reviews of Interventions, and the findings were reported according to the Preferred Reporting Items for Systematic Reviews

and Meta-Analyses (PRISMA) statement (Page et al., 2021). This NMA was prospectively registered in PROSPERO (registration ID: CRD42023474215).

2.2 Search strategy

Two authors separately searched for randomized controlled trials (RCTs) and crossover RCTs about rTMS improving lower extremity motor function in stroke patients from China National Knowledge Infrastructure (CNKI), Wanfang database, VIP database, China Biomedical Literature Database (CBM), PubMed, Embase, Web of Science, and Cochrane Library. The search time limit was from the establishment of the database to 31 December 2023. By combining medical subject headings (MeSH) with free words using Boolean logic operators, we integrated the following terms for a comprehensive search: “Stroke,” “cerebrovascular accident,” “CVA,” “Brain Vascular Accident,” “hemiplegia,” “apoplexy,” “hemiparesis,” “repetitive transcranial magnetic stimulation,” “Transcranial Magnetic Stimulation,” “TMS,” “rTMS,” “Theta burst stimulation,” “θ-brust stimulation,” “random,” “randomized controlled trial,” “RCT.” In addition, we also reviewed meta-analysis, reviews, and references of the included studies to supplement the search. PubMed was used as an example, and the specific search strategy was provided in [Supplementary Table 1](#).

2.3 Eligibility criteria

Eligibility criteria were defined in accordance with the PICOS framework (Hutton et al., 2015).

2.3.1 Inclusion criteria

1. Populations: Stroke patients with lower extremity dysfunction who were diagnosed according to the stroke diagnostic criteria formulated by The Fourth National Cerebrovascular Disease Conference in 1995.
2. Interventions: HFrTMS-M1, LFrTMS-M1, iTBS-Cerebellum, iTBS-M1, and dTMS-M1.
3. Comparators: The placebo included conventional rehabilitation and sham rTMS (or conventional rehabilitation alone). Sham rTMS refers to the analog sound without any effective magnetic stimulation. Conventional rehabilitation, such as physiotherapy, occupational therapy, physical therapy, treadmill training, motor imagery practice, task-oriented training, and mirror therapy, was acceptable as cointervention.
4. Outcomes: The primary outcome indicator was the Fugl-Meyer Assessment of Lower Extremity (FMA-LE). The secondary outcome indicators included the Berg Balance Scale (BBS), Timed Up and Go Test (TUGT), Motor Evoked Potential amplitude (MEP amplitude), and speed.
5. Study designs: RCTs or crossover RCTs.

2.3.2 Exclusion criteria

1. Patients with lower extremity motor dysfunction were not caused by stroke but by traumatic brain injury, cerebral palsy, Parkinson’s disease, and other diseases.

2. Conference abstracts, researcher protocols, reviews, meta-analysis, dissertations, and non-RCTs (e.g., case reports, observational studies, cross-sectional studies, and studies without a control group).
3. Lack of outcome indicators related to the lower extremity motor function.
4. Studies with more patients withdrawing midway.
5. Studies that could not be downloaded.
6. Studies with incomplete outcome data and contacting the authors three times without response.
7. Repeatedly published studies.

2.4 Study selection

First, two authors (CSW and QZ) used EndnoteX9 software to eliminate duplicate articles. Then, they screened out articles that did not meet the criteria by reading their titles and abstracts. Finally, they browsed the full text to select articles that met the criteria. In case of any disagreement during the review process, the decision was made by consultation between the two authors or by joint decision with the third author (LLZ).

2.5 Data extraction

Two authors (DYZ and YNX) independently reviewed all articles and extracted data. The extracted data included basic published information: first author’s name, year of publication, country of origin, participant characteristics (age and sample size), intervention characteristics (intervention protocol, coil type, rTMS target, rTMS frequency, rTMS intensity, No. of pulses, and duration of intervention), and outcome indicators (FMA-LE, BBS, TUGT, MEP amplitude, and speed) at baseline and at last observation to obtain their change scores. The collected data were put into an Excel spreadsheet and cross-checked by two authors (DYZ and YNX). In case of disagreement during data extraction, the third author (ZJL) participated in discussion and decision-making.

2.6 Quality assessment

Two authors (CLW and SZW) independently assessed the risk of bias for the included articles through the Cochrane Risk of Bias Tool (Savović et al., 2014), which mainly included seven indicators: (I) Random sequence generation; (II) Allocation concealment; (III) Blinding of participants and personnel; (IV) Blinding of outcome assessment; (V) Incomplete outcome data; (VI) Selective reporting; (VII) Other bias. Assessment indicators were rated “low risk,” “unclear,” or “high risk” based on the available information. If there was any dispute during the evaluation, the third author (ZJL) would participate in the discussion and make decisions together.

2.7 Statistical analysis

Odds ratio (OR) for binary variables and mean difference (MD) for continuous variables were used as the effect indicators, and the

95% confidence interval (CI) was provided for each effect size. If a particular study used different methods or scales to measure the same outcome, standardized MD (SMD) was calculated instead of MD. We calculated the difference before and after treatment for continuous variable indicators and the standard deviation (SD) according to the method provided in 16.1.3.2 of Cochrane Handbook 5.0.2 and then performed the statistical analysis. We used RevMan (version 5.4) for pairwise meta-analysis. The p -value of the chi-square test and the I^2 index from the heterogeneity test were used to express the level of statistical heterogeneity. Different effect models were selected according to the test data's heterogeneity level. When the level of heterogeneity was low ($p \geq 0.1$, $I^2 \leq 50\%$), we selected the fixed effect model for analysis. Otherwise, a random effect model ($p < 0.1$, $I^2 > 50\%$) was used (Higgins et al., 2003; Tufanaru et al., 2015).

We used Stata (version 17.0) to perform the NMA and produce various charts, such as network meta-analysis diagrams of eligible comparisons, surface under the cumulative ranking area (SUCRA), funnel plot of publication bias, etc (Shim et al., 2017). When there were closed loops between interventions, we first needed to assess global inconsistency. If $p > 0.05$, the inconsistent model was not significant, and the consistent model was selected (White et al., 2012). We used a node-splitting approach to assess local inconsistency (Dias et al., 2010). At the same time, it was also necessary to evaluate the loop inconsistency and calculate the inconsistency factors (IF) and 95% CI for each closed loop. If the lower limit of 95% CI included or was close to 0, the consistency between the direct and indirect comparison results was good; otherwise, the closed loop was considered to have apparent inconsistency. If no closed loops existed between interventions, the consistency model was used directly for analysis. We used the SUCRA to rank interventions. The closer SUCRA was to 100%, the better the effect of the intervention. Finally, the publication bias of the included articles was evaluated using the funnel plot of publication bias and Egger's test. Asymmetry in the funnel plot of publication bias and $p < 0.05$ in Egger's test indicated publication bias in the included articles (Fleiss, 1993).

3 Results

3.1 Search results

We strictly searched the above 8 databases according to the inclusion and exclusion criteria and preliminarily obtained 12,814 articles. After the duplicate articles were removed, 10,166 articles remained in the database. By reading the titles and abstracts of the articles, we excluded articles that did not meet the inclusion criteria, leaving 176 remaining in the database. By reading the full text, we again excluded 138 articles. Ultimately, 38 articles met our study requirements. Figure 1 shows the article search process and results.

3.2 Characteristics of the included studies

Characteristics of studies adopted are shown in Table 1, published between 2012 and 2023. We finally included 38 studies with a total of 2,022 patients. 4 studies were crossover RCTs, and 34 studies were RCTs. Among the included studies, most of them were carried out in

China (28/38), and the others were conducted in Korea (5/38), Italy (2/38), Egypt (1/38), India (1/38), and Japan (1/38). Outcome indicators included FMA-LE (29 studies), BBS (11 studies), TUGT (8 studies), MEP amplitude (8 studies), and speed (13 studies). Interventions included HFrTMS-M1 (16 studies), LFrTMS-M1 (18 studies), iTBS-Cerebellum (5 studies), iTBS-M1 (1 study), and dTMS-M1 (2 studies).

3.3 Quality evaluation

25 studies (65.8%) had a low risk of bias concerning random sequence generation. 9 studies (23.7%) had a low risk of bias concerning allocation concealment. 24 studies (63.2%) had a low risk of bias concerning blinding of participants and personnel. 27 studies (71.1%) had a low risk of bias concerning blinding of outcome assessment. 37 studies (97.4%) had a low risk of bias concerning incomplete outcome data. 38 studies (100.0%) had a low risk of bias concerning selective reporting. Other biases were not known. Details of the evaluation of bias results for the included articles are shown in Figure 2.

3.4 Pairwise meta-analysis

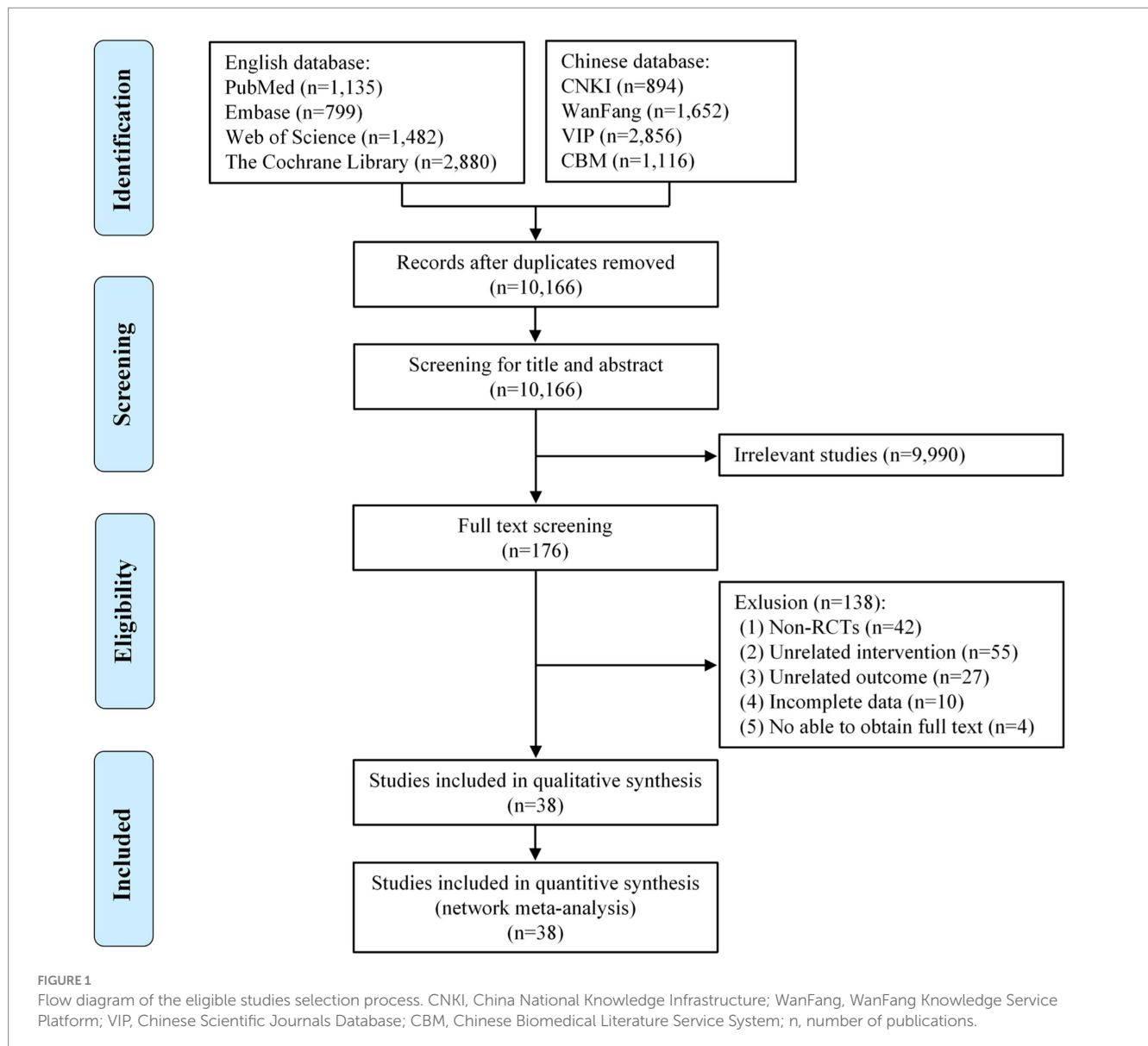
A pairwise meta-analysis was used to compare the two interventions comprehensively. We carried out 6 pairwise meta-analysis to compare FMA-LE, 6 to compare FMA-LE (post-stroke time > 1 month), 3 to compare FMA-LE (post-stroke time \leq 1 month), 5 to compare BBS, 4 to compare TUGT, 4 to compare MEP amplitude, and 2 to compare speed, respectively, which can be summarily seen in Table 2. The detailed results of pairwise meta-analysis are shown in Supplementary Figures 1–7.

3.5 Network of evidence

Figure 3 shows the network meta-analysis diagrams of eligible comparisons, where the blue circles represent the different interventions. The circle size represents the sample size. The straight line between the two circles represents a direct comparison between the two different interventions. The thicker the solid line, the greater the number of studies in that pairwise comparison.

3.5.1 FMA-LE

A total of 29 included studies evaluated FMA-LE, involving 6 intervention protocols: HFrTMS-M1, LFrTMS-M1, iTBS-Cerebellum, iTBS-M1, dTMS-M1, and Placebo. A total of 1,685 patients were included. The inconsistency model evaluated global inconsistency, which showed $p = 0.0772$ (> 0.05 ; Supplementary Figure 8A). The inconsistency test was not significant, so we used the consistency model. The node-splitting approach was used to evaluate local inconsistency. The test of local inconsistency from the node-splitting model showed a small percentage of inconsistency (1 of 6 comparisons), as detailed in Supplementary Table 2. 1 closed loop was formed for the 3 interventions, so we assessed the inconsistency of the



closed loop. The results showed that the 95% CI included 0, and IF was close to 0, indicating that our NMA was highly credible (Supplementary Figure 9A).

The NMA results showed that FMA-LE generated a total of 15 pairwise comparisons. Compared with Placebo, LFrTMS-M1 (MD = 2.83, 95% CI: 1.96 to 3.70) and HFrTMS-M1 (MD = 2.74, 95% CI: 1.60 to 3.87) significantly improved FMA-LE in stroke patients. There was no statistically significant difference between the other two interventions ($p > 0.05$; Figure 4). Figure 5A and Table 3 show the SUCRA rankings for all interventions. According to the analysis, LFrTMS-M1 (SUCRA, 84.6%) may be the most effective intervention to improve FMA-LE in stroke patients.

Different phases of stroke may lead to different therapeutic effects of rTMS. Therefore, we performed a subgroup analysis for FMA-LE according to the phase of stroke, including post-stroke time > 1 month and post-stroke time ≤ 1 month (Brunelli et al., 2019). The global consistency model of FMA-LE (post-stroke time > 1 month) and FMA-LE (post-stroke time ≤ 1 month) showed

that the inconsistency test was not significant (Supplementary Figures 8B,C). There was a small percentage of inconsistency (1 of 3 comparisons) only for the local inconsistency test of FMA-LE (post-stroke time ≤ 1 month), details of which are provided in Supplementary Tables 3, 4.

For post-stroke time > 1 month, Figure 4 demonstrated that HFrTMS-M1 significantly improved FMA-LE (post-stroke time > 1 month) compared to iTBS-M1 (MD = 3.84, 95% CI: 0.52 to 7.16) and Placebo (MD = 3.94, 95% CI: 2.50 to 5.38). Figure 5B and Table 3 showed that the HFrTMS-M1 (SUCRA, 95.8%) was the best protocol. For post-stroke time ≤ 1 month, Figure 4 demonstrated that compared with the placebo, the LFrTMS-M1 (MD = 1.49, 95% CI: 0.05 to 2.93) and HFrTMS-M1 (MD = 2.47, 95% CI: 1.41 to 3.53) had better curative effects, with a statistically significant difference ($p < 0.05$). Figure 5C and Table 3 showed that the LFrTMS-M1 (SUCRA, 98.9%) was the best protocol. We found no publication bias by the funnel plot of publication bias and Egger's test (Supplementary Figures 10B,C).

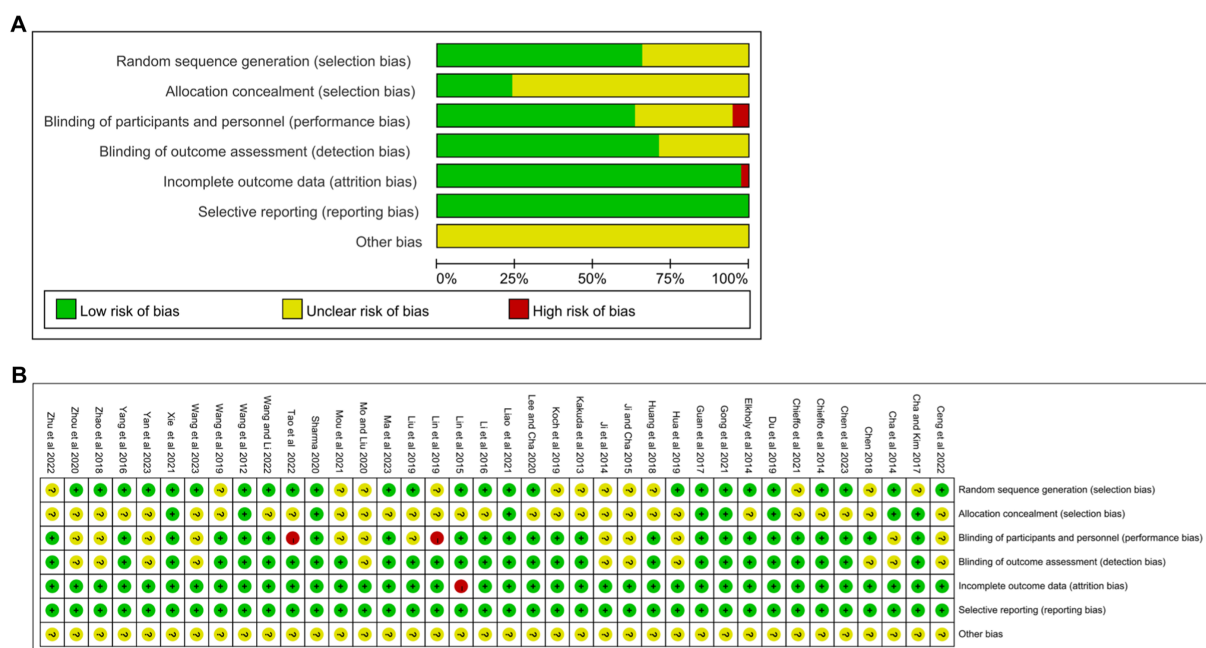


FIGURE 2 Quality assessment of selected studies by the Cochrane Risk Of Bias Tool. (A) Risk of bias graph: review authors' judgments about each risk of bias item presents as percentages across all included studies. (B) Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

3.5.2 BBS

A total of 11 included studies evaluated BBS, involving 5 intervention protocols: HFrTMS-M1, LFrTMS-M1, iTBS-Cerebellum, iTBS-M1, and Placebo. A total of 820 patients were included. The inconsistency model evaluated global inconsistency, which showed $p = 0.2800$ (>0.05 ; Supplementary Figure 8D). The inconsistency test was not significant, so we used the consistency model. The node-splitting approach was used to evaluate local inconsistency. The measured p -values were all greater than 0.05, indicating good local consistency (Supplementary Table 5). 1 closed loop was formed for the 3 interventions, so we assessed the inconsistency of the closed loop. The results showed that the 95% CI included 0, and IF was close to 0, indicating that our NMA was highly credible (Supplementary Figure 9D).

The NMA results showed that BBS generated a total of 10 pairwise comparisons. Compared with Placebo, HFrTMS-M1 (MD = 6.97, 95% CI: 3.95 to 9.98), LFrTMS-M1 (MD = 4.36, 95% CI: 2.00 to 6.72), and iTBS-Cerebellum (MD = 3.29, 95% CI: 0.63 to 5.95) significantly improved BBS in stroke patients. In addition, HFrTMS-M1 (MD = 6.36, 95% CI: 0.65 to 12.07) was significantly better than iTBS-M1 in improving BBS. Other pairwise comparisons showed no statistically significant differences ($p > 0.05$; Figure 4). Figure 5D and Table 3 show the SUCRA rankings for all interventions. According to the results of SUCRA analysis, HFrTMS-M1 (SUCRA, 96.8%) may be the most effective intervention to improve BBS in stroke patients.

3.5.3 TUGT

A total of 8 included studies evaluated TUGT, involving 5 intervention protocols: HFrTMS-M1, LFrTMS-M1, iTBS-Cerebellum, iTBS-M1, and Placebo. A total of 382 patients were included. There

was no closed loop, so we did not need to perform a consistency check. The NMA results showed that TUGT generated a total of 10 pairwise comparisons.

Compared with Placebo, HFrTMS-M1 (MD = -3.25, 95% CI: -5.19 to -1.30) and LFrTMS-M1 (MD = -2.72, 95% CI: -3.95 to -1.49) significantly improved TUGT in stroke patients. There was no statistically significant difference between the other two interventions ($p > 0.05$; Figure 4). Figure 5E and Table 3 show the SUCRA rankings for all interventions. According to the analysis, HFrTMS-M1 (SUCRA, 80.3%) may be the most effective intervention to improve TUGT in stroke patients.

3.5.4 MEP amplitude

A total of 8 included studies evaluated MEP amplitude, involving 4 intervention protocols: HFrTMS-M1, LFrTMS-M1, iTBS-Cerebellum, and Placebo. A total of 246 patients were included. The inconsistency model evaluated global inconsistency, which showed $p = 0.5656$ (>0.05 ; Supplementary Figure 8E). The inconsistency test was not significant, so we used the consistency model. The node-splitting approach was used to evaluate local inconsistency. The measured p -values were all greater than 0.05, indicating good local consistency (Supplementary Table 3). 1 closed loop was formed for the 3 interventions, so we assessed the inconsistency of the closed loop. The results showed that the 95% CI included 0, and IF was close to 0, indicating that our NMA was highly credible (Supplementary Figure 9E).

The NMA results showed that MEP amplitude generated a total of 6 pairwise comparisons. Compared with Placebo, HFrTMS-M1 (SMD = 0.99, 95% CI: 0.17 to 1.82) significantly improved MEP amplitude in stroke patients. There was no statistically significant

TABLE 1 Characteristics of included studies.

Study	Country	Age (E/C, year)	Sample size (E/C)	Intervention							Outcomes
				Intervention protocol (E/C)	Coil type	rTMS target	rTMS frequency (Hz)	rTMS intensity (%)	No. of pulses	Duration of intervention	
Yang et al. (2016)	China	56.4 ± 7.8/57.5 ± 9.2	14/14	HFrTMS-M1/Placebo	75-mm figure-of-8 coil	Ipsi-M1	10 Hz	90% RMT	2,000	6 times per week for 4 weeks	①③
Ma et al. (2023)	China	56.75 ± 7.07/54.85 ± 5.65	20/20	HFrTMS-M1/Placebo	NR	Ipsi-M1	10 Hz	80% RMT	1,200	5 times per week for 4 weeks	①③④
Mo and Liu (2020)	China	56.68 ± 3.12/57.75 ± 2.86	53/52	HFrTMS-M1/Placebo	Figure-of-8 coil	Ipsi-M1	10 Hz	90% RMT	2,000	7 times per week for 4 weeks	①②③
Cha et al. (2014)	Korea	54.83 ± 6.32/51.33 ± 8.71	12/12	HFrTMS-M1/LF-ZrTMS	70-mm figure-of-8 coil	Ipsi-M1/ Contra-M1	10 Hz/1 Hz	90% RMT	2,000/1,200	5 times per week for 4 weeks	②④
Cha and Kim (2017)	Korea	53.80 ± 13.28/55.80 ± 16.40	10/10	HFrTMS-M1/Placebo	70-mm figure-of-8 coil	Ipsi-M1	10 Hz	90% RMT	1,000	5 times per week for 8 weeks	④⑤
Wang et al. (2019)	China	53.5 ± 13.7/54.7 ± 12.2	8/6	HFrTMS-M1/Placebo	Figure-of-8 coil	Ipsi-M1	5 Hz	90% RMT	900	3 times per week for 3 weeks	①④⑤
Lee and Cha (2020)	Korea	66.85 ± 4.05/64.00 ± 3.57	7/6	HFrTMS-M1/Placebo	70-mm figure-of-8 coil	Ipsi-M1	5 Hz	90% RMT	900	5 times per week for 3 weeks	③
Ji et al. (2014)	Korea	49.00 ± 11.01/44.28 ± 8.52	15/15	HFrTMS-M1/Placebo	70-mm figure-of-8 coil	Ipsi-M1	10 Hz	NR	NR	3 times per week for 6 weeks	⑤
Ji and Kim (2015)	Korea	55.65 ± 8.95/56.36 ± 10.44	20/19	HFrTMS-M1/Placebo	70-mm figure-of-8 coil	Ipsi-M1	10 Hz	NR	2,000	5 times per week for 4 weeks	⑤
Ceng et al. (2022)	China	60.22 ± 2.73/61.41 ± 2.24	40/40	HFrTMS-M1/Placebo	NR	Ipsi-M1	10 Hz	80% RMT	NR	5 times per week for 8 weeks	①
Kakuda et al. (2013)	Japan	52.1 ± 11.9	9/9	HFrTMS-M1/Placebo	80-mm double-cone coil	Bi-M1	10 Hz	90% RMT	2,000	1 time	⑤
Guan et al. (2017)	China	59.7 ± 6.8/57.4 ± 14.0	21/21	HFrTMS-M1/Placebo	Figure-of-8 coil	Ipsi-M1	5 Hz	120% RMT	1,000	10 consecutive weekdays	①
Wang et al. (2023)	China	63.85 ± 9.54/63.92 ± 10.28/ 64.10 ± 9.96	80/80/80	HFrTMS-M1/ LFrTMS-M1/Placebo	NR	Ipsi-M1/ Contra-M1	10 Hz/0.5 Hz	NR	NR	6 times per week for 3 weeks	①
Hua et al. (2019)	China	63.2 ± 9.5/63.4 ± 10.7/65.4 ± 10.8	15/15/15	HFrTMS-M1/ LFrTMS-M1/Placebo	Figure-of-8 coil	Ipsi-M1/ Contra-M1	10 Hz/0.5 Hz	80% RMT	1,290/1,090	6 times per week for 3 weeks	①②
Liu et al. (2019)	China	58.78 ± 6.97/60.78 ± 6.73/58.44 ± 5.94	18/18/18	HFrTMS-M1/ LFrTMS-M1/Placebo	NR	Ipsi-M1/ Contra-M1	10 Hz/0.5 Hz	90% MT	NR	5 times per week for 3 weeks	①

(Continued)

TABLE 1 (Continued)

Study	Country	Age (E/C, year)	Sample size (E/C)	Intervention							Outcomes
				Intervention protocol (E/C)	Coil type	rTMS target	rTMS frequency (Hz)	rTMS intensity (%)	No. of pulses	Duration of intervention	
Du et al. (2019)	China	54 ± 12/56 ± 9/56 ± 11	20/20/20	HFrTMS-M1/ LFrTMS-M1/Placebo	90-mm figure-of-8 coil	Ipsi-M1/ Contra-M1	10 Hz/1 Hz	100% RMT	1,200/1,200	5 consecutive weekdays	④
Sharma et al. (2020)	India	54.85 ± 13.39/ 52.89 ± 14.95	47/49	LFrTMS-M1/Placebo	70-mm figure-of-8 coil	Contra-M1	1 Hz	110% RMT	750	5 times per week for 2 weeks	①
Zhao et al. (2018)	China	56.2 ± 12.7/54.0 ± 11.4	36/39	LFrTMS-M1/Placebo	Circular coil	Contra-M1	1 Hz	80–120% RMT	1,000	20 consecutive weekdays	①②
Zhou et al. (2020)	China	58.80 ± 7.58/58.32 ± 7.61	50/50	LFrTMS-M1/Placebo	70-mm double-cone coil	Contra-M1	1 Hz	70% RMT	1,200	5 times per week for 3 weeks	①
Li et al. (2016)	China	56.7 ± 6.0/58.0 ± 6.5	30/30	LFrTMS-M1/Placebo	70-mm figure-of-8 coil	Contra-M1	1 Hz	90% RMT	NR	5 times per week for 4 weeks	①③
Yan et al. (2023)	China	67.82 ± 9.97/69.11 ± 10.03	88/88	LFrTMS-M1/Placebo	Circular coil	Contra-M1	1 Hz	70% RMT	NR	5 times per week for 6 weeks	①②③
Mou et al. (2021)	China	52.10 ± 14.96/48.40 ± 15.58	20/20	LFrTMS-M1/Placebo	Circular coil	Contra-M1	1 Hz	90% RMT	1,000	6 times per week for 6 weeks	①
Huang et al. (2018)	China	62.2 ± 10.4/61.2 ± 9.4	18/20	LFrTMS-M1/Placebo	110-mm double-cone coil	Contra-M1	1 Hz	120% RMT	900	15 consecutive weekdays	①③④
Lin et al. (2015)	China	58.3 ± 10.8/62.3 ± 11.7	16/16	LFrTMS-M1/Placebo	70-mm figure-of-8 coil	Contra-M1	1 Hz	130% MT	900	15 consecutive weekdays	①
Chen (2018)	China	55.2 ± 11.5/51.3 ± 12.1	70/70	LFrTMS-M1/Placebo	90-mm figure-of-8 coil	Contra-M1	1 Hz	90% RMT	1,000	5 times per week for 1 week	①②③
Wang et al. (2012)	China	64.90 ± 12.37/62.98 ± 10.88	14/14	LFrTMS-M1/Placebo	Figure-of-8 coil	Contra-M1	1 Hz	90% RMT	600	5 times per week for 2 weeks	①④⑤
Elkholy et al. (2014)	Egypt	44.06 ± 3.71/45.66 ± 4.27	30/15	LFrTMS-M1/Placebo	NR	Contra-M1	1 Hz	2 G	NR	3 times per week for 6 weeks	③⑤
Zhu et al. (2022)	China	59.48 ± 7.04/58.36 ± 5.38	25/25	LFrTMS-M1/Placebo	NR	Contra-M1	1 Hz	90% RMT	NR	5 times per week for 4 weeks	①③⑤
Tao et al. (2022)	China	57.5 ± 6.4/58.2 ± 4.8	20/20	LFrTMS-M1/Placebo	Figure-of-8 coil	Contra-M1	1 Hz	80% RMT	600	5 times per week for 4 weeks	①②
Gong et al. (2021)	China	63.40 ± 10.37/59.66 ± 14.31	16/16	LFrTMS-M1/Placebo	NR	Contra-M1	1 Hz	NR	NR	5 times per week for 4 weeks	①④

(Continued)

TABLE 1 (Continued)

Study	Country	Age (E/C, year)	Sample size (E/C)	Intervention							Outcomes
				Intervention protocol (E/C)	Coil type	rTMS target	rTMS frequency (Hz)	rTMS intensity (%)	No. of pulses	Duration of intervention	
Koch et al. (2019)	China	63 ± 11/65 ± 12	18/18	iTBS-Cerebellum/Placebo	70-mm figure-of-8 coil	Contra-cerebellar	iTBS	80% RMT	1,200	3 weeks	ⓀⓂ
Chen et al. (2023)	China	58.88 ± 15.79/62.38 ± 12.66	16/16	iTBS-Cerebellum/Placebo	Figure-of-8 coil	Contra-cerebellar	iTBS	80% RMT	600	6 times per week for 3 weeks	Ⓚ
Wang and Li (2022)	China	52.62 ± 8.61/54.62 ± 7.85	21/21	iTBS-Cerebellum/Placebo	70-mm figure-of-8 coil	Contra-cerebellar	iTBS	80% RMT	600	5 times per week for 4 weeks	ⓀⓂ
Liao et al. (2021)	China	51.53 ± 9.22/55.40 ± 8.10	15/15	iTBS-Cerebellum/Placebo	70-mm figure-of-8 coil	Contra-cerebellar	iTBS	90% AMT	600	5 times per week for 2 weeks	ⓂⓀ
Xie et al. (2021b)	China	52.35 ± 8.62/54.41 ± 7.01	18/18	iTBS-Cerebellum/Placebo	70-mm figure-of-8 coil	Contra-cerebellar	iTBS	90% AMT	600	10 consecutive weekdays	ⓀⓂ
Lin et al. (2019)	China	60.8 ± 8.1/61.1 ± 9.7	10/10	iTBS-M1/Placebo	70-mm figure-of-8 coil	Bi-M1	iTBS	100% RMT	1,200	2 times per week for 5 weeks	ⓀⓂⓀ
Chieffo et al. (2014)	Italy	62.20 ± 10.23	5/5	dTMS-M1/Placebo	H-coil	Bi-M1	20 Hz	90% RMT	1,500	11 times for 3 weeks	Ⓚ
Chieffo et al. (2021)	Italy	58.67 ± 10.33/61.17 ± 8.70	6/6	dTMS-M1/Placebo	H-coil	Bi-M1	20 Hz	80–90% RMT	1,600	11 times for 3 weeks	Ⓚ

E, experimental group; C, control group; HFrTMS, high-frequency repetitive transcranial magnetic stimulation; LFrTMS, low-frequency repetitive transcranial magnetic stimulation; iTBS, intermittent theta-burst stimulation; dTMS, deep transcranial magnetic stimulation; M1, primary motor cortex; Ipsi, ipsilateral; Contra, contralateral; Bi, bilateral; NR, not reported; MT, motor threshold; RMT, resting motor threshold; AMT, active motor threshold. Ⓚ: FMA-LE; Ⓜ: BBS; Ⓚ: TUGT; Ⓚ: MEP amplitude; Ⓚ: Speed.

TABLE 2 Pairwise meta-analysis.

Comparison	Number of studies	MD/SMD (95% CI)	Heterogeneity test	
			I ² (%)	p-value
FMA-LE				
HFrTMS-M1/Placebo	9	3.36 (2.01, 4.72)	81	<0.00001
LFrTMS-M1/Placebo	16	2.62 (1.71, 3.54)	81	<0.00001
iTBS-Cerebellum/Placebo	4	0.41 (-0.74, 1.56)	0	0.88
iTBS-M1/Placebo	1	0.10 (-1.29, 1.49)	NR	NR
dTMS-M1/Placebo	2	1.60 (0.59, 2.61)	0	1
LFrTMS-M1/HFrTMS-M1	3	2.37 (1.35, 3.38)	12	32
FMA-LE (post-stroke time > 1 month)				
HFrTMS-M1/Placebo	6	4.52 (2.85, 6.19)	76	0.001
LFrTMS-M1/Placebo	9	2.84 (1.56, 4.12)	88	<0.00001
iTBS-Cerebellum/Placebo	4	0.41 (-0.74, 1.56)	0	0.88
iTBS-M1/Placebo	1	0.10 (-1.29, 1.49)	NR	NR
dTMS-M1/Placebo	2	1.60 (0.59, 2.61)	0	1
LFrTMS-M1/HFrTMS-M1	1	0.89 (-3.16, 4.94)	NR	NR
FMA-LE (post-stroke time ≤ 1 month)				
HFrTMS-M1/Placebo	3	1.25 (0.44, 2.06)	0	0.82
LFrTMS-M1/Placebo	7	2.39 (1.16, 3.63)	52	0.05
LFrTMS-M1/HFrTMS-M1	2	2.47 (1.41, 3.52)	42	0.19
BBS				
HFrTMS-M1/Placebo	2	6.64 (4.37, 8.91)	75	0.05
LFrTMS-M1/Placebo	4	4.49 (1.75, 7.24)	90	<0.00001
iTBS-Cerebellum/Placebo	4	3.23 (0.99, 5.47)	57	0.07
iTBS-M1/Placebo	1	0.60 (-1.68, 2.88)	NR	NR
HFrTMS-M1/LFrTMS-M1	2	4.34 (-5.73, 14.41)	84	0.01
TUGT				
HFrTMS-M1/Placebo	2	-3.25 (-5.19, -1.30)	37	0.21
LFrTMS-M1/Placebo	4	-2.72 (-3.95, -1.49)	0	0.94
iTBS-Cerebellum/Placebo	1	-0.38 (-12.70, 11.94)	NR	NR
iTBS-M1/Placebo	1	-0.70 (-4.63, 3.23)	NR	NR
MEP amplitude				
HFrTMS-M1/Placebo	3	0.92 (0.08, 1.77)	61	0.08
LFrTMS-M1/Placebo	3	0.36 (-0.48, 1.21)	78	0.01
iTBS-Cerebellum/Placebo	1	-0.10 (-0.81, 0.62)	NR	NR
HFrTMS-M1/LFrTMS-M1	2	0.71 (-0.99, 2.41)	89	0.003
Speed				
HFrTMS-M1/Placebo	8	0.91 (0.68, 1.13)	26	0.21
LFrTMS-M1/Placebo	5	1.04 (0.81, 1.26)	46	0.12

Red and bold numbers are statistically significant. HFrTMS, high-frequency repetitive transcranial magnetic stimulation; LFrTMS, low-frequency repetitive transcranial magnetic stimulation; iTBS, intermittent theta-burst stimulation; dTMS, deep transcranial magnetic stimulation; M1, primary motor cortex; NR, not reported.

difference between the other two interventions ($p > 0.05$; Figure 4). Figure 5F and Table 3 show the SUCRA rankings for all interventions. According to the analysis, HFrTMS-M1 (SUCRA, 93.7%) may be the most effective intervention to improve MEP amplitude in stroke patients.

3.5.5 Speed

A total of 13 included studies evaluated speed, involving 3 intervention protocols: HFrTMS-M1, LFrTMS-M1, and Placebo. A total of 667 patients were included. There was no closed loop, so

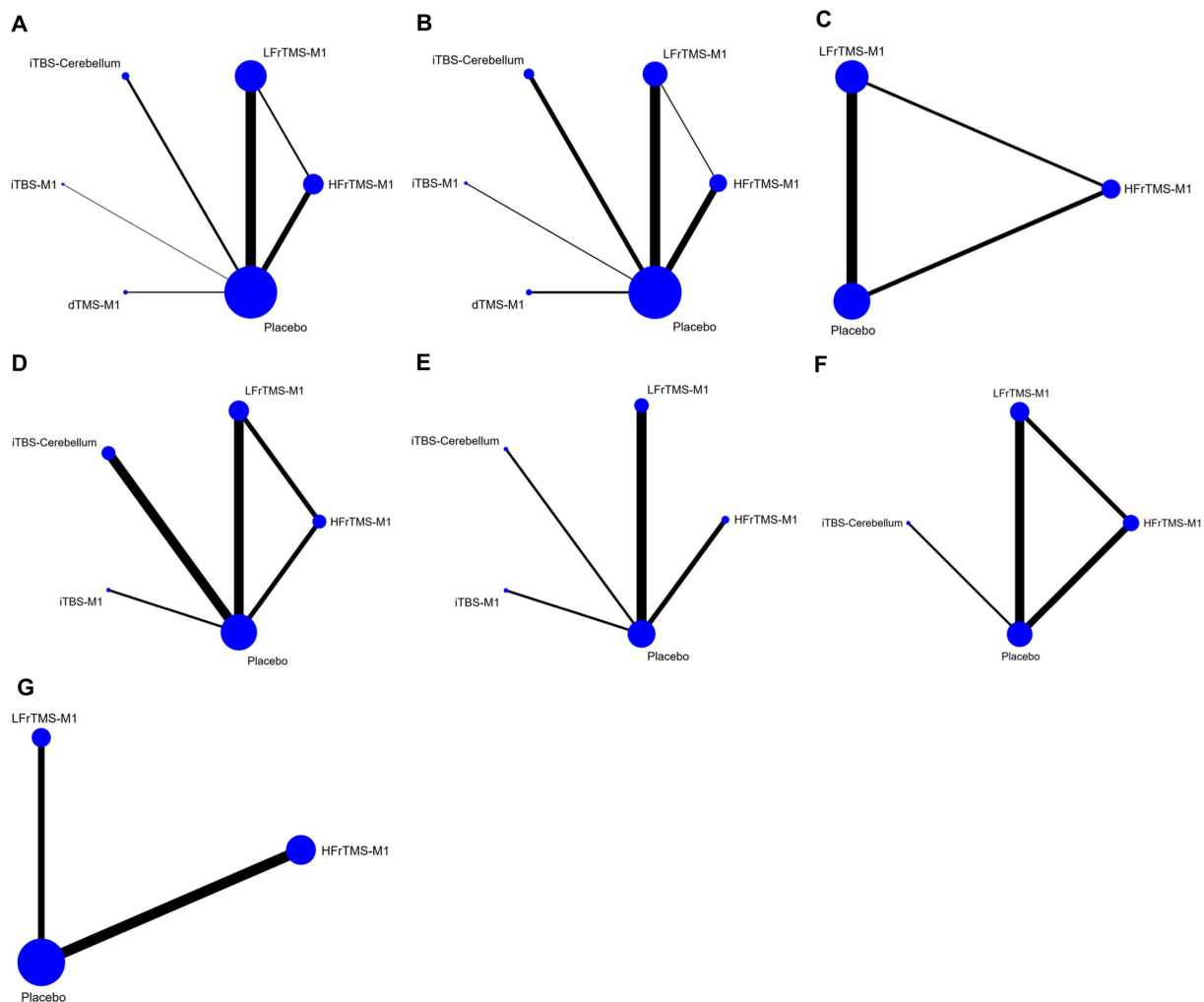


FIGURE 3
Network meta-analysis diagrams of eligible comparisons. The width of the lines is proportional to the number of trials. The size of every circle is proportional to the number of randomly assigned participants (sample size). (A) FMA-LE; (B) FMA-LE (post-stroke time > 1 month); (C) FMA-LE (post-stroke time \leq 1 month); (D) BBS; (E) TUGT; (F) MEP amplitude; (G) Speed. HFrTMS, high-frequency repetitive transcranial magnetic stimulation; LFrTMS, low-frequency repetitive transcranial magnetic stimulation; iTBS, intermittent theta-burst stimulation; dTMS, deep transcranial magnetic stimulation; M1, primary motor cortex.

we did not need to perform a consistency check. The NMA results showed that speed generated a total of 3 pairwise comparisons.

Compared with Placebo, LFrTMS-M1 (SMD = 1.01, 95% CI: 0.64 to 1.38) and HFrTMS-M1 (SMD = 0.82, 95% CI: 0.49 to 1.15) significantly improved speed in stroke patients. There was no statistically significant difference between the other two interventions ($p > 0.05$; Figure 4). Figure 5G and Table 3 show the SUCRA rankings for all interventions. According to the analysis, LFrTMS-M1 (SUCRA, 88.7%) may be the most effective intervention to improve speed in stroke patients.

3.6 Publication bias

This study evaluated publication bias for FMA-LE, FMA-LE (post-stroke time > 1 month), FMA-LE (post-stroke time \leq 1 month), BBS, TUGT, MEP amplitude, and speed using the funnel plot of publication bias (Figure 6) and Egger's test. The findings revealed that most points were evenly distributed along both sides of the midline and were

primarily focused there, indicating that our results were robust and there was no significant publication bias. In addition, we used Egger's test for secondary validation of publication bias. The results showed FMA-LE (Egger's test $p = 0.273$; Supplementary Figure 10A), FMA-LE (post-stroke time > 1 month; Egger's test $p = 0.807$; Supplementary Figure 10B), FMA-LE (post-stroke time \leq 1 month; Egger's test $p = 0.601$; Supplementary Figure 10C), BBS (Egger's test $p = 0.843$; Supplementary Figure 10D), TUGT (Egger's test $p = 0.123$; Supplementary Figure 10E), MEP amplitude (Egger's test $p = 0.089$; Supplementary Figure 10F), and speed (Egger's test $p = 0.556$; Supplementary Figure 10G), indicating that there was no publication bias in this study.

3.7 Adverse events

Among the 38 included studies, 16 had no adverse events during the course of the experiment, 7 reported adverse events in detail, and the remaining studies did not describe adverse events

Intervention	FMA-LE MD (95%CI)	LFrTMS-M1	0.09 (-1.23, 1.42)	HFrTMS-M1	1.23 (-1.17, 3.63)	dTMS-M1	1.26 (-0.85, 3.37)	iTBS-Cerebellum	2.73 (-0.50, 5.95)	iTBS-M1	2.83 (1.96, 3.70)	Placebo
		1.13 (-1.37, 3.64)	1.16 (-1.07, 3.40)	0.03 (-2.92, 2.98)	1.47 (-2.18, 5.12)	0.10 (-3.00, 3.21)						
		2.63 (-0.67, 5.94)	1.50 (-2.33, 5.33)	1.57 (-0.35, 3.50)								
		2.74 (1.60, 3.87)	1.60 (-0.63, 3.84)	1.57 (-0.35, 3.50)								
Intervention	FMA-LE (post-stroke time >1 month) MD (95%CI)	HFrTMS-M1	1.02 (-0.75, 2.79)	LFrTMS-M1	2.34 (-0.26, 4.93)	dTMS-M1	2.36 (0.00, 4.73)	iTBS-Cerebellum	3.84 (0.52, 7.16)	iTBS-M1	3.94 (2.50, 5.38)	Placebo
		1.32 (-1.11, 3.74)	1.34 (-0.83, 3.52)	0.03 (-2.83, 2.88)	1.47 (-2.06, 5.01)	0.10 (-2.89, 3.10)						
		2.82 (-0.37, 6.01)	1.50 (-2.19, 5.19)	1.58 (-0.30, 3.45)								
		2.92 (1.82, 4.02)	1.60 (-0.56, 3.76)	1.58 (-0.30, 3.45)								
Intervention	FMA-LE (post-stroke time ≤1 month) MD (95%CI)	LFrTMS-M1	1.49 (0.05, 2.93)	HFrTMS-M1	2.47 (1.41, 3.53)	Placebo						
			0.98 (-0.32, 2.28)									
Intervention	BBS MD (95%CI)	HFrTMS-M1	2.60 (-0.74, 5.95)	LFrTMS-M1	3.68 (-0.33, 7.68)	iTBS-Cerebellum	6.36 (0.65, 12.07)	iTBS-M1	6.97 (3.95, 9.98)	Placebo		
		1.07 (-2.50, 4.64)	3.76 (-1.64, 9.15)	2.69 (-2.85, 8.22)	0.60 (-4.25, 5.45)							
		4.36 (2.00, 6.72)	3.29 (0.63, 5.95)									
Intervention	TUGT MD (95%CI)	HFrTMS-M1	-0.53 (-2.83, 1.77)	LFrTMS-M1	-2.87 (-15.34, 9.61)	iTBS-Cerebellum	-2.55 (-6.93, 1.84)	iTBS-M1	-3.25 (-5.19, -1.30)	Placebo		
		-2.34 (-14.72, 10.04)	-2.02 (-6.14, 2.10)	0.32 (-12.61, 13.25)	-0.70 (-4.63, 3.23)							
Intervention	MEP amplitude SMD (95%CI)	HFrTMS-M1	0.66 (-0.22, 1.54)	LFrTMS-M1	1.09 (-0.63, 2.81)	iTBS-Cerebellum	0.99 (0.17, 1.82)	Placebo				
		0.43 (-1.24, 2.09)	0.33 (-0.37, 1.03)	-0.10 (-1.61, 1.41)								
Intervention	Speed SMD (95%CI)	LFrTMS-M1	0.19 (-0.31, 0.69)	HFrTMS-M1	1.01 (0.64, 1.38)	Placebo						
			0.82 (0.49, 1.15)									

FIGURE 4 Network meta-analysis of head-to-head comparisons. Red and bold numbers are statistically significant. HFrTMS, high-frequency repetitive transcranial magnetic stimulation; LFrTMS, low-frequency repetitive transcranial magnetic stimulation; iTBS, intermittent theta-burst stimulation; dTMS, deep transcranial magnetic stimulation; M1, primary motor cortex.

(Supplementary Table 7). The adverse events reported were mild, such as headache, dizziness, nausea, and vomiting.

4 Discussion

Stroke is a common disease worldwide and causes severe disabilities for patients. More than two-thirds of stroke survivors have post-stroke sequelae, including impairment in motor function, balance, gait, and ADL (Paul et al., 2007). Improving lower extremity motor function and balance ability can significantly impact gait function, ADL, and quality of life in stroke patients (Smith et al.,

2017). Although the use of rTMS for stroke has attracted considerable attention, there is still a lack of consensus on the optimal protocol for rTMS to improve lower extremity motor function in stroke patients. To the best of our knowledge, this is the first NMA to compare the effects of different rTMS protocols on lower extremity motor function in stroke patients by taking stimulation frequency, stimulation target, and stimulation mode of rTMS and post-stroke time into account simultaneously.

The FMA-LE can predict lower extremity motor recovery in individuals with stroke (Balasubramanian et al., 2016). This assessment exhibits good internal consistency and reliability, discriminative validity, and responsiveness to interventions

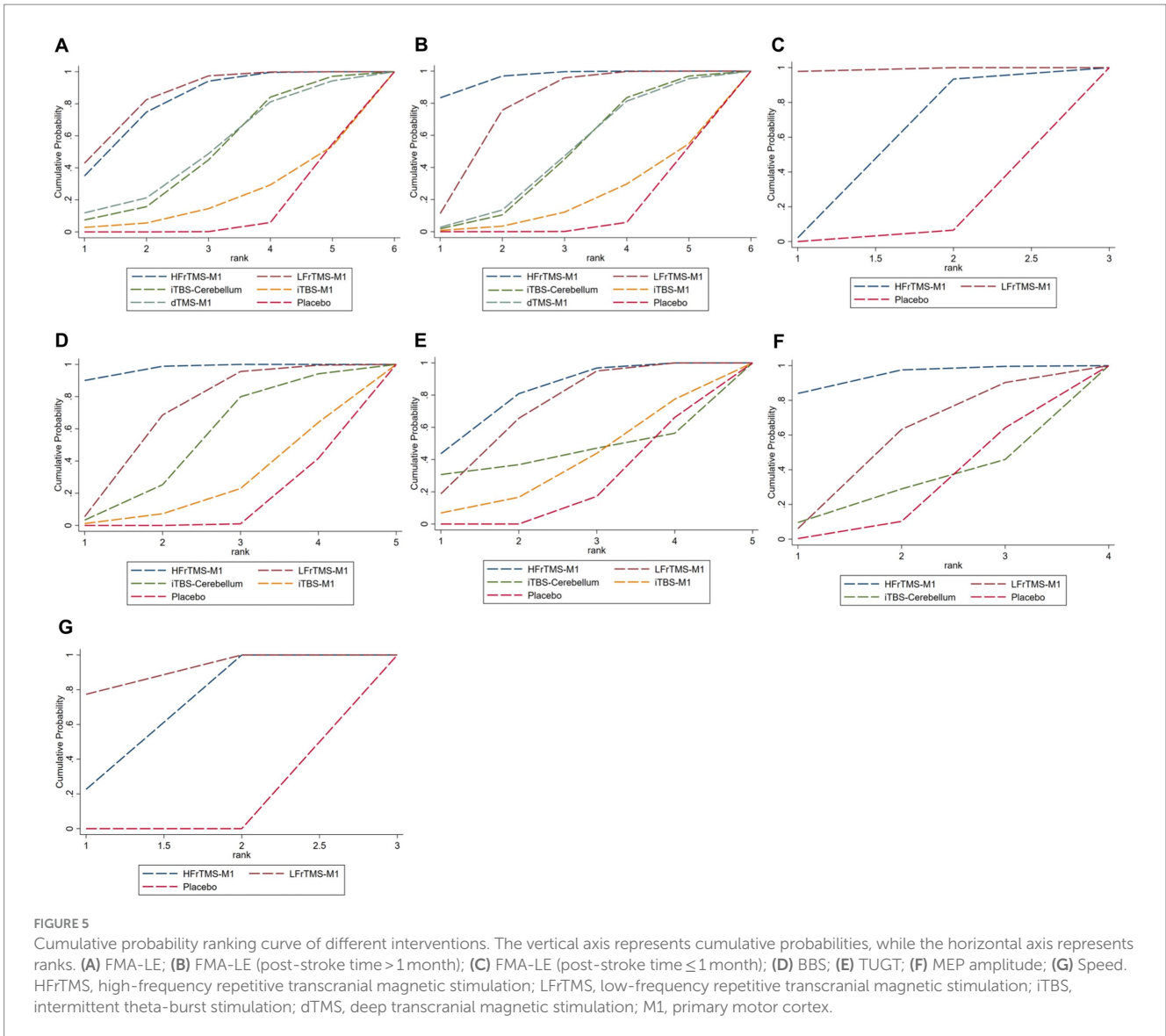


TABLE 3 SUCRA values of different interventions for outcomes.

Outcomes	HFrtTMS-M1	LFrtTMS-M1	iTBS-cerebellum	iTBS-M1	dTMS-M1	Placebo
FMA-LE	80.7% ^b	84.6% ^a	49.9%	21.2%	51.5%	12.2%
FMA-LE (post-stroke time > 1 month)	95.8% ^a	76.8% ^b	47.4%	20.0%	28.0%	11.9%
FMA-LE (post-stroke time ≤ 1 month)	47.8% ^b	98.9% ^a	NR	NR	NR	3.3%
BBS	96.8% ^a	67.7% ^b	51.8%	22.7%	NR	11.0%
TUGT	80.3% ^a	69.8% ^b	42.8%	36.2%	NR	20.8%
MEP amplitude	93.7% ^a	53.2% ^b	28.2%	NR	NR	24.9%
Speed	63.1% ^b	88.7% ^a	NR	NR	NR	0.0%

^aPresents the first-ranking. ^bPresents the second-ranking.

HFrtTMS, high-frequency repetitive transcranial magnetic stimulation; LFrTMS, low-frequency repetitive transcranial magnetic stimulation; iTBS, intermittent theta-burst stimulation; dTMS, deep transcranial magnetic stimulation; M1, primary motor cortex; NR, not reported.

(Hsieh et al., 2009). This study found that compared with Placebo, LFrTMS-M1 and HFrtTMS-M1 significantly improved FMA-LE in stroke patients, and LFrTMS in the contralateral hemisphere was more effective than HFrtTMS in the ipsilateral hemisphere. Xie et al. (2021a) suggested that LFrTMS in the contralateral hemisphere was more

effective than HFrtTMS in the ipsilateral hemisphere, which was consistent with our findings. However, a novel finding from this NMA is that the subgroup analyses of FMA-LE showed that at ≤1 month after stroke, HFrtTMS-M1 was the optimal stimulation protocol for improving stroke patients' lower extremity motor function. At

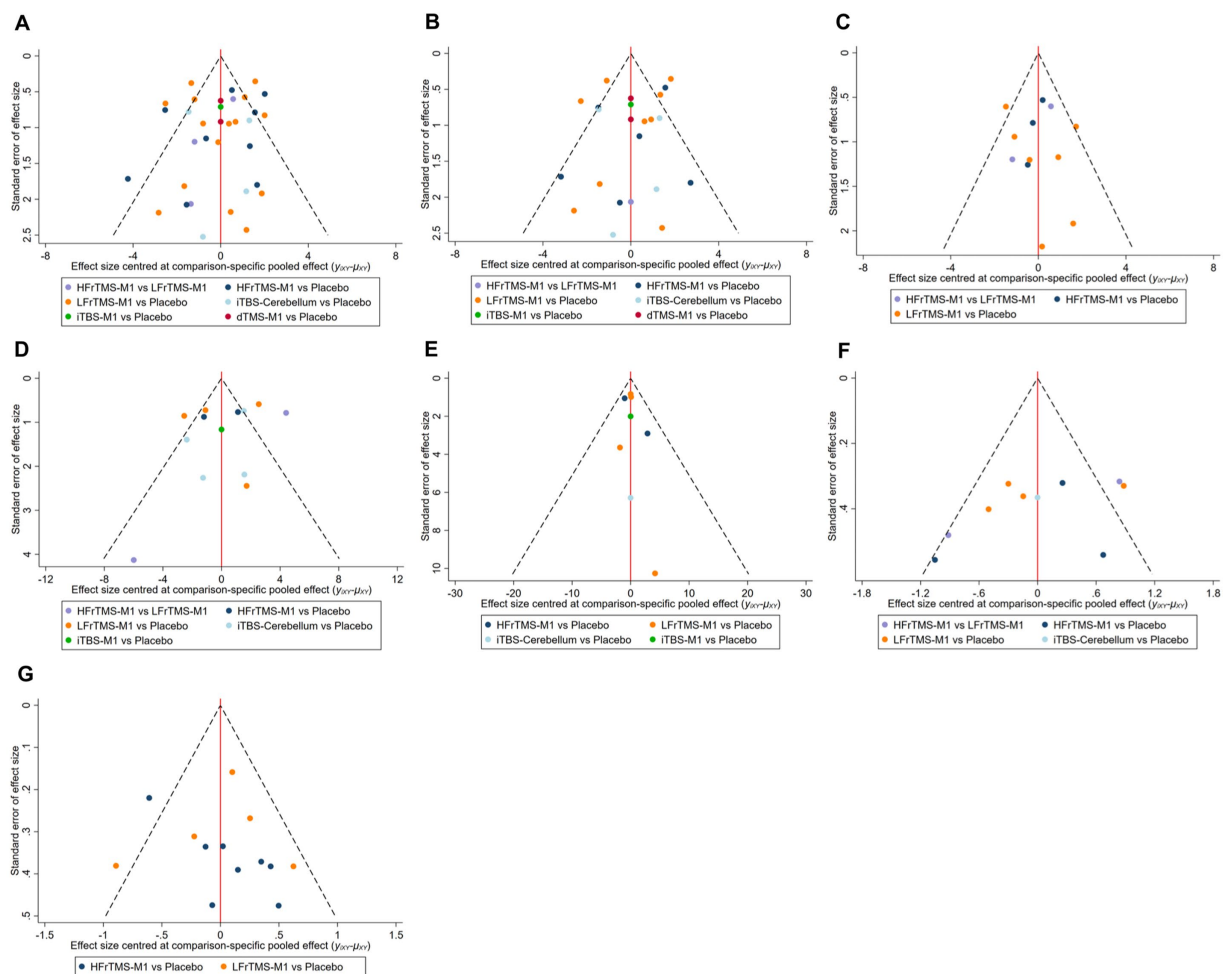


FIGURE 6

Funnel plot of publication bias. (A) FMA-LE; (B) FMA-LE (post-stroke time > 1 month); (C) FMA-LE (post-stroke time ≤ 1 month); (D) BBS; (E) TUGT; (F) MEP amplitude; (G) Speed. HF rTMS, high-frequency repetitive transcranial magnetic stimulation; LFrTMS, low-frequency repetitive transcranial magnetic stimulation; iTBS, intermittent theta-burst stimulation; dTMS, deep transcranial magnetic stimulation; M1, primary motor cortex.

≤ 1 month after stroke, LFrTMS-M1 was the best protocol, which was superior to HF rTMS-M1. The difference between these two studies was that when grouping rTMS protocols, we considered that the same rTMS mode applied to different stimulation targets would produce different therapeutic effects. Therefore, we divided stimulation targets into M1 and Cerebellum rather than simply grouping very different stimulation targets together, which allowed the intervention protocol to be more refined. Second, we included more articles that met our research objectives to expand the sample size. Finally, we also carried out a subgroup analysis of the patients on the efficacy of rTMS at different protocols to improve the accuracy of the outcome evidence. In addition, we also found that 10 Hz and 1 Hz were the most commonly used stimulation frequencies for HF rTMS and LFrTMS, respectively, regarding rTMS prescription settings, which was the same conclusion as Fan et al. (2021). Meanwhile, rTMS sessions of 15 or 20 min each and lasting 3 or 4 weeks were the most common. In clinical practice, clinicians or rehabilitation therapists can flexibly formulate the best stimulation prescription according to the specific situation of patients and the recommended protocols mentioned above.

In fact, early hyperexcitability and increased interhemispheric inhibition of the contralesional motor cortex have been demonstrated using TMS after unilateral stroke. Therefore, LFrTMS can effectively

improve the motor function of stroke patients by reducing the excitability of the motor cortex of the contralateral hemisphere to restore the balance of competitive inhibition between the two hemispheres in the acute phase of stroke. However, in the post-stroke convalescent phase, the interhemispheric competition is less pronounced than in the acute phase, as it is commonly observed that the transcallosal asymmetry decreases with time (Swayne et al., 2008). LFrTMS may reduce the compensatory effect of the contralateral hemisphere by inhibiting its excitability, thereby hindering functional recovery after stroke. Therefore, HF rTMS-M1 may be more effective than LFrTMS-M1 in the convalescent phase of stroke. Xia et al. (2022) also recommended the application of HF rTMS in patients with stroke patients during the convalescent phase.

The BBS is the most widely used clinical scale for assessing balance performance in individuals with neurological conditions, including static and dynamic balance (Neuls et al., 2011). The sum of the scores for the 14 items (each item was rated from 0 to 4) yielded a balance score ranging from 0 to 56 (Neuls et al., 2011). TUGT is a rapid and quantitative assessment of dynamic balance and functional walking ability and is closely related to other measures of gait and balance in stroke patients (Flansbjerg et al., 2005). TUGT assesses the time taken to complete a series of actions, including standing up from a chair,

walking forward three meters, turning, and returning to the chair. According to the ranking probability of our NMA, HFrTMS-M1 was more advantageous in improving BBS and TUGT. Therefore, we recommend HFrTMS-M1 as a complementary rehabilitation therapy to improve balance function in stroke patients in clinical practice.

Walking speed can reflect the recovery of lower extremity function and walking quality in stroke patients (Patterson et al., 2008). Our NMA results showed that compared with Placebo, LFrTMS-M1 and HFrTMS-M1 significantly improved the speed in stroke patients. LFrTMS-M1 had more advantages in improving the speed of stroke patients. However, Tung et al. (2019) found that HFrTMS was superior to LFrTMS in improving speed in stroke patients. Further understanding of the relationship between different rTMS protocols and walking speed is needed in the future. Transcranial magnetic stimulation (TMS) is a non-invasive neuromodulation technique that produces pulsed magnetic fields that form induced currents in the motor cortex of the brain. After the induced current stimulates one side of the motor cortex, the conduction nerve impulses are transmitted downward, which will cause the target muscle on the opposite side of the subject to produce action potentials, called motor-evoked potentials (MEPs). MEPs is a quantitative evaluation index of central motor conduction function, which can objectively reflect the excitability of the motor cortex. In this study, we used MEP amplitude to assess the functional status of motor conduction pathways, and the results showed that HFrTMS-M1 was the most effective in improving MEP amplitude. However, MEP amplitude included only a few studies, meaning this ranking result should be treated critically. In addition, to ensure the objectivity of the study results, more high-quality RCTs with large sample sizes are needed for further verification.

Like TMS, functional magnetic resonance imaging (fMRI), electroencephalography (EEG), and other neuroimaging techniques are also of great significance in the assessment of motor function in stroke. fMRI can evaluate the neurovascular response induced by rTMS, and the activity changes of brain nerves can be observed through intuitive and visual images (Bergmann et al., 2016). In addition, fMRI can also be used to study the excitability and functional connectivity of the cerebral cortex and subcortex in stroke patients under rTMS intervention. Guo et al. (2021) used fMRI to find that both LFrTMS stimulation in the unaffected hemisphere and HFrTMS stimulation in the affected hemisphere could promote the reorganization of the motor network, and the changes in functional connectivity between the contralateral PMA and the ipsilateral M1, and between the bilateral M1 induced by rTMS were related to motor recovery. Transcranial magnetic stimulation combined with electroencephalography (TMS-EEG) is a new evaluation method in recent years. TMS-EEG can reflect the direct relationship between brain regions and motor function in stroke patients and predict the recovery of motor function after stroke. Koch et al. (2019) performed motor assessment on 34 stroke subjects who received iTBS-Cerebellum or sham iTBS treatment by Fugl-Meyer scale, gait analysis, and so on, and recorded cerebral cortical activity through TMS-EEG to achieve the combination of treatment and assessment feedback. At present, there are relatively few studies using fMRI and EEG to explore the treatment of rTMS to promote the recovery of dysfunction after stroke, and most of the trials are small in sample size and scale. In the future, large-sample, multi-center, and high-quality RCTs should be carried out, and the results of imaging and electrophysiology of

stroke patients should be comprehensively analyzed to improve the accuracy and scientificity of rehabilitation efficacy evaluation.

The M1 is the most essential part of the motor cortex in the human cerebral cortex, located in the precentral gyrus. M1 is the most frequently stimulated target in noninvasive brain stimulation studies for post-stroke gait and balance recovery (Parikh et al., 2023). Among the 38 studies included in this article, 33 studies selected M1 as the stimulation target. Recent electrophysiological and imaging evidence underlined that a large motor network includes other key brain areas during the process of post-stroke functional recovery (Koch and Hummel, 2017). The cerebellum is a crucial structure involved in balance and motor control, and it is essential in motor adaptation and learning processes. Therefore, the cerebellum has been proposed as one of the alternative targets of M1. A total of 5 studies in our NMA used the cerebellum as the stimulation target and selected the iTBS mode for intervention. iTBS is a new rTMS mode that lasts only about 5 min, with the characteristics of short time-consuming, low intensity, and strong effect. iTBS can induce long-term potentiation, which helps promote neural plasticity and produce a safer and lasting intervention effect for stroke patients. Our findings showed that iTBS-Cerebellum can significantly improve balance function in stroke patients. Liao et al. (2024) compared the efficacy and safety of iTBS to the cerebellum or M1 on balance and motor recovery in stroke patients. They found that both iTBS-M1 and iTBS-Cerebellum could improve balance function and that iTBS-Cerebellum, but not iTBS-M1, had a more significant effect on motor recovery. Like our findings, Manto et al. (2012) suggested that iTBS-Cerebellum could be a potential therapeutic approach to improve balance and gait function in stroke patients. Thus, iTBS-Cerebellum may be a valuable new therapeutic option in stroke rehabilitation programs. At the same time, our NMA also included a study on the iTBS-M1 protocol, but the limited number of studies and participants may have led to inaccurate results.

It is worth noting that among the included studies, Chieffo et al. (2014) and Chieffo et al. (2021) used H-coil. The H-coil differs from conventional figure-of-8 coil and circular coil in that it can stimulate deeper cortical areas and neural networks (Roth et al., 2014). Roth et al. (2007) found that H-coil, figure-of-8 coil, and double-cone coil could generate the maximum induced electric field in the surface region of the saline head model at 0.9% concentration. With the increased distance from the simulated skull to the brain tissue, the induced electric field generated by the figure-of-8 coil and the double-cone coil decreased to less than 10% of the maximum induced electric field at 6 cm. In comparison, the electric field intensity of the H-coil was more than 63% of the maximum induced electric field. H-coil can theoretically stimulate deeper leg-related cortical motor areas within the intercerebral fissure approximately 3 to 4 cm below the skull. However, the results of Chieffo et al. (2014) and Chieffo et al. (2021) did not show a favorable advantage of dTMS. We suspect this may be due to the small number of current studies. In the future, more RCTs are needed to confirm the applicability and safety of dTMS in stroke patients.

5 Limitations

The study also has some limitations, including: (1) Coil type, stimulation intensity, total number of pulses, and duration of intervention were not exactly the same among the included studies, resulting in potential heterogeneity. (2) Despite including the full stimulation protocol in this analysis, the iTBS-M1 and dTMS-M1

groups accounted for 2.6 and 5.3% of the total data, respectively. This affects, to some extent, the quality of the conclusions of this study. (3) The age and disease severity of the included patients were slightly different, and some data indicators will be affected. Further subgroup analysis according to age and disease severity is needed in the future. (4) Adverse events may not be strictly reported in the included studies, so the safety of each intervention protocol needs to be further studied.

6 Conclusion

In this NMA, we found differences in the therapeutic effects between different rTMS protocols. Considering the impact of the stroke phase on the lower extremity motor function, the current research evidence shows that HFrTMS-M1 may be the preferred stimulation protocol to improve the lower extremity motor function of patients for post-stroke time > 1 month, and LFrTMS-M1 for post-stroke time ≤ 1 month. In the future, high-quality, large-sample, multi-center, and long-term follow-up RCTs are needed to verify the conclusions of this study.

Data availability statement

The original contributions presented in the study are included in the article/[Supplementary material](#), further inquiries can be directed to the corresponding authors.

Author contributions

CW: Software, Writing – original draft. QZ: Software, Writing – original draft. LZ: Data curation, Methodology, Supervision, Writing – review & editing. DZ: Data curation, Methodology, Supervision, Writing – review & editing. YX: Data curation, Methodology, Supervision, Writing – review & editing. ZL: Data curation, Methodology, Supervision,

References

- Balasubramanian, C. K., Li, C.-Y., Bowden, M. G., Duncan, P. W., Kautz, S. A., and Velozo, C. A. (2016). Dimensionality and item-difficulty hierarchy of the lower extremity Fugl-Meyer assessment in individuals with subacute and chronic stroke. *Arch. Phys. Med. Rehabil.* 97, 582–589.e2. doi: 10.1016/j.apmr.2015.12.012
- Bergmann, T. O., Karabanov, A., Hartwigsen, G., Thielscher, A., and Siebner, H. R. (2016). Combining non-invasive transcranial brain stimulation with neuroimaging and electrophysiology: current approaches and future perspectives. *Neuroimage* 140, 4–19. doi: 10.1016/j.neuroimage.2016.02.012
- Brunelli, S., Iosa, M., Fusco, F. R., Pirri, C., Di Giunta, C., Foti, C., et al. (2019). Early body weight-supported overground walking training in patients with stroke in subacute phase compared to conventional physiotherapy: a randomized controlled pilot study. *Int. J. Rehabil. Res.* 42, 309–315. doi: 10.1097/MRR.0000000000000363
- Cárdenas-Morales, L., Nowak, D. A., Kammer, T., Wolf, R. C., and Schönfeldt-Lecuona, C. (2010). Mechanisms and applications of theta-burst rTMS on the human motor cortex. *Brain Topogr.* 22, 294–306. doi: 10.1007/s10548-009-0084-7
- Ceng, B., Fan, S., Li, Y., and Wang, P. (2022). Transcranial magnetic stimulation combined with the dual task training on stroke patients with hemiplegia lower limb motor function. *Chin J Integr Med Cardio Cerebrovasc Dis* 20, 4585–4588. doi: 10.12102/j.issn.1672-1349.2022.24.034
- Cha, H. G., and Kim, M. K. (2017). Effects of strengthening exercise integrated repetitive transcranial magnetic stimulation on motor function recovery in subacute stroke patients: a randomized controlled trial. *Technol. Health Care* 25, 521–529. doi: 10.3233/THC-171294

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Conflict of interest

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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Supplementary material

The Supplementary material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fnins.2024.1352212/full#supplementary-material>

- Cha, H. G., Kim, M. K., Nam, H. C., and Ji, S. G. (2014). Effects of high frequency repetitive transcranial magnetic stimulation on function in subacute stroke patients. *J Magn* 19, 192–196. doi: 10.4283/JMAG.2014.19.2.192
- Chen, Y. (2018). Effects of repetitive transcranial magnetic stimulation on spasm and motor function of lower limbs in patients with stroke. *Chongqing Med J* 47, 3292–3295+3298. doi: 10.3969/j.issn.1671-8348.2018.25.012
- Chen, J., Shi, M., Chen, J., Zhang, J., Chen, R., Tu, J., et al. (2023). The effects of supplementing theta burst stimulation of the cerebellum with physical therapy on balance and gait recovery after a stroke: a randomized clinical trial. *Chin J Phys Med Rehabil* 45, 402–407. doi: 10.3760/cma.j.issn.0254-1424.2023.05.004
- Chieffo, R., De Prezzo, S., Houdayer, E., Nuara, A., Di Maggio, G., Coppi, E., et al. (2021). Deep repetitive transcranial magnetic stimulation with H-coil on lower limb motor function in chronic stroke: a pilot study. *Arch. Phys. Med. Rehabil.* 95, 1141–1147. doi: 10.1016/j.apmr.2014.02.019
- Chieffo, R., Giatsidis, F., Santangelo, R., Alyagon, U., Comola, M., Zangen, A., et al. (2021). Repetitive transcranial magnetic stimulation with H-coil coupled with cycling for improving lower limb motor function after stroke: An exploratory study. *Neuromodulation* 24, 916–922. doi: 10.1111/ner.13228
- Chung, S. W., Hoy, K. E., and Fitzgerald, P. B. (2015). Theta-burst stimulation: a new form of TMS treatment for depression? *Depress. Anxiety* 32, 182–192. doi: 10.1002/da.22335
- Dias, S., Welton, N. J., Caldwell, D. M., and Ades, A. E. (2010). Checking consistency in mixed treatment comparison meta-analysis. *Stat. Med.* 29, 932–944. doi: 10.1002/sim.3767

- Di Pino, G., Pellegrino, G., Assenza, G., Capone, F., Ferreri, F., Formica, D., et al. (2014). Modulation of brain plasticity in stroke: a novel model for neurorehabilitation. *Nat Rev Neurol* 10, 597–608. doi: 10.1038/nrneurol.2014.162
- Du, J., Yang, F., Hu, J., Hu, J., Xu, Q., Cong, N., et al. (2019). 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 Clin* 21:101620. doi: 10.1016/j.nicl.2018.101620
- Elkholy, S. H., Atteya, A. A., Hassan, W. A., Sharaf, M., and Gohary, A. M. E. (2014). Low rate repetitive transcranial magnetic stimulation (rTMS) and gait rehabilitation after stroke. *Int J Neurorehabil* 1:109. doi: 10.4172/2376-0281.1000109
- Eng, J. J., and Tang, P.-F. (2007). Gait training strategies to optimize walking ability in people with stroke: a synthesis of the evidence. *Expert Rev Neurother* 7, 1417–1436. doi: 10.1586/14737175.7.10.1417
- Fan, H., Song, Y., Cen, X., Yu, P., Biró, I., and Gu, Y. (2021). The effect of repetitive transcranial magnetic stimulation on lower-limb motor ability in stroke patients: a systematic review. *Front. Hum. Neurosci.* 15:620573. doi: 10.3389/fnhum.2021.620573
- Flansbjerg, U.-B., Holmbäck, A. M., Downham, D., Patten, C., and Lexell, J. (2005). Reliability of gait performance tests in men and women with hemiparesis after stroke. *J Rehabil. Med.* 37, 75–82. doi: 10.1080/16501970410017215
- Fleiss, J. L. (1993). The statistical basis of meta-analysis. *Stat. Methods Med. Res.* 2, 121–145. doi: 10.1177/096228029300200202
- George, M. S., and Aston-Jones, G. (2010). Noninvasive techniques for probing neurocircuitry and treating illness: vagus nerve stimulation (VNS), transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). *Neuropsychopharmacology* 35, 301–316. doi: 10.1038/npp.2009.87
- Gong, Y., Long, X.-M., Xu, Y., Cai, X.-Y., and Ye, M. (2021). Effects of repetitive transcranial magnetic stimulation combined with transcranial direct current stimulation on motor function and cortex excitability in subacute stroke patients: a randomized controlled trial. *Clin. Rehabil.* 35, 718–727. doi: 10.1177/0269215520972940
- Guan, Y.-Z., Li, J., Zhang, X.-W., Wu, S., Du, H., Cui, L.-Y., et al. (2017). Effectiveness of repetitive transcranial magnetic stimulation (rTMS) after acute stroke: a one-year longitudinal randomized trial. *CNS Neurosci. Ther.* 23, 940–946. doi: 10.1111/cns.12762
- Guo, Z., Jin, Y., Bai, X., Jiang, B., He, L., McClure, M. A., et al. (2021). Distinction of high- and low-frequency repetitive transcranial magnetic stimulation on the functional reorganization of the motor network in stroke patients. *Neural Plast.* 2021, 8873221–8873221. doi: 10.1155/2021/8873221
- Higgins, J. P. T., Thompson, S. G., Deeks, J. J., and Altman, D. G. (2003). Measuring inconsistency in meta-analyses. *BMJ* 327, 557–560. doi: 10.1136/bmj.327.7414.557
- Hsieh, Y., Wu, C., Lin, K., Chang, Y., Chen, C., and Liu, J. (2009). Responsiveness and validity of three outcome measures of motor function after stroke rehabilitation. *Stroke* 40, 1386–1391. doi: 10.1161/STROKEAHA.108.530584
- Hua, Y., Li, B., Wang, K., Guo, H., and Gou, L. (2019). Different frequency repetitive transcranial magnetic stimulation treatment of ischemic cerebral apoplexy patients curative effect observation. *Chin J Phys Med Rehabil* 41, 745–748. doi: 10.3760/cma.j.isn.0254-1424.2019.10.006
- Huang, Y.-Z., Edwards, M. J., Rounis, E., Bhatia, K. P., and Rothwell, J. C. (2005). Theta burst stimulation of the human motor cortex. *Neuron* 45, 201–206. doi: 10.1016/j.neuron.2004.12.033
- Huang, Y.-Z., Lin, L.-F., Chang, K.-H., Hu, C.-J., Liou, T.-H., and Lin, Y.-N. (2018). Priming with 1-Hz repetitive transcranial magnetic stimulation over Contralateral leg motor cortex does not increase the rate of regaining ambulation within 3 months of stroke: a randomized controlled trial. *Am. J. Phys. Med. Rehabil.* 97, 339–345. doi: 10.1097/PHM.0000000000000850
- Huang, Y.-Z., Rothwell, J. C., Chen, R.-S., Lu, C.-S., and Chuang, W.-L. (2011). The theoretical model of theta burst form of repetitive transcranial magnetic stimulation. *Clin. Neurophysiol.* 122, 1011–1018. doi: 10.1016/j.clinph.2010.08.016
- Hutton, B., Salanti, G., Caldwell, D. M., Chaimani, A., Schmid, C. H., Cameron, C., et al. (2015). The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann. Intern. Med.* 162, 777–784. doi: 10.7326/M14-2385
- Ji, S.-G., Cha, H.-G., Kim, K.-J., and Kim, M.-K. (2014). Effects of motor imagery practice in conjunction with repetitive transcranial magnetic stimulation on stroke patients. *J Magn* 19, 181–184. doi: 10.4283/JMAG.2014.19.2.181
- Ji, S. G., and Kim, M. K. (2015). The effects of repetitive transcranial magnetic stimulation on the gait of acute stroke patients. *J Magn* 20, 129–132. doi: 10.4283/JMAG.2015.20.2.129
- Kakuda, W., Abo, M., Nakayama, Y., Kiyama, A., and Yoshida, H. (2013). High-frequency rTMS using a double cone coil for gait disturbance. *Acta Neurol. Scand.* 128, 100–106. doi: 10.1111/ane.12085
- Kesikburun, S. (2022). Non-invasive brain stimulation in rehabilitation. *Turk J Phys Med Rehabil* 68, 1–8. doi: 10.5606/tftrd.2022.10608
- Koch, G., Bonni, S., Casula, E. P., Iosa, M., Paolucci, S., Pellicciari, M. C., et al. (2019). Effect of cerebellar stimulation on gait and balance recovery in patients with hemiparetic stroke: a randomized clinical trial. *JAMA Neurol.* 76, 170–178. doi: 10.1001/jamaneurol.2018.3639
- Koch, P. J., and Hummel, F. C. (2017). Toward precision medicine: tailoring interventional strategies based on noninvasive brain stimulation for motor recovery after stroke. *Curr. Opin. Neurol.* 30, 388–397. doi: 10.1097/WCO.0000000000000462
- Langhammer, B., and Stanghelle, J. K. (2011). Can physiotherapy after stroke based on the Bobath concept result in improved quality of movement compared to the motor relearning programme. *Physiother Res Int.* 16, 69–80. doi: 10.1002/pri.474
- Larson, J., Wong, D., and Lynch, G. (1986). Patterned stimulation at the theta frequency is optimal for the induction of hippocampal long-term potentiation. *Brain Res.* 368, 347–350. doi: 10.1016/0006-8993(86)90579-2
- Lee, S. A., and Cha, H. G. (2020). The effect of high frequency repetitive transcranial magnetic stimulation combined with treadmill training on the recovery of lower limb function in chronic stroke patients: a randomized controlled trial. *J Magn* 25, 402–408. doi: 10.4283/JMAG.2020.25.3.402
- Li, Y., Fan, J., Yang, J., He, C., and Li, S. (2018). Effects of repetitive transcranial magnetic stimulation on walking and balance function after stroke: a systematic review and meta-analysis. *Am. J. Phys. Med. Rehabil.* 97, 773–781. doi: 10.1097/PHM.0000000000000948
- Li, Y., Huang, L., Zhang, J., Tian, J., and Yu, X. (2016). Effects of repetitive transcranial magnetic stimulation on the lower limb motor function of cerebral infarction patients. *Chin J Phys Med Rehabil* 38, 839–842. doi: 10.3760/cma.j.isn.0254-1424.2016.11.010
- Liao, L.-Y., Xie, Y.-J., Chen, Y., and Gao, Q. (2021). Cerebellar theta-burst stimulation combined with physiotherapy in subacute and chronic stroke patients: a pilot randomized controlled trial. *Neurorehabil. Neural Repair* 35, 23–32. doi: 10.1177/1545968320971735
- Liao, L.-Y., Zhu, Y., Peng, Q.-Y., Gao, Q., Liu, L., Wang, Q.-H., et al. (2024). Intermittent theta-burst stimulation for stroke: primary motor cortex versus cerebellar stimulation: a randomized sham-controlled trial. *Stroke* 55, 156–165. doi: 10.1161/STROKEAHA.123.044892
- Lin, L.-F., Chang, K.-H., Huang, Y.-Z., Lai, C.-H., Liou, T.-H., and Lin, Y.-N. (2019). Simultaneous stimulation in bilateral leg motor areas with intermittent theta burst stimulation to improve functional performance after stroke: a feasibility pilot study. *Eur. J. Phys. Rehabil. Med.* 55, 162–168. doi: 10.23736/S1973-9087.18.05245-0
- Lin, Y.-N., Hu, C.-J., Chi, J., Lin, L.-F., Yen, T.-H., Lin, Y.-K., et al. (2015). Effects of repetitive transcranial magnetic stimulation of the unaffected hemisphere leg motor area in patients with subacute stroke and substantial leg impairment: a pilot study. *J Rehabil. Med.* 47, 305–310. doi: 10.2340/16501977-1943
- Liu, M., Meng, Y., Li, H., and Zhang, G. (2019). Effects of repetitive transcranial magnetic stimulation on motor function and serum levels of MMP-9/hs-CRP of ischemic stroke patients. *Tianjin Med J* 47, 184–188. doi: 10.11958/20181534
- Ma, Q., Li, Z., Fu, W., and Lin, Q. (2023). Effect of repetitive transcranial magnetic stimulation on walking of stroke patients at recovery stage. *Chin J Rehabil Theory Pract* 29, 167–173. doi: 10.3969/j.issn.1006-9771.2023.02.005
- Manto, M., Bower, J. M., Conforto, A. B., Delgado-García, J. M., da Guarda, S. N. F., Gerwig, M., et al. (2012). Consensus paper: roles of the cerebellum in motor control—the diversity of ideas on cerebellar involvement in movement. *Cerebellum* 11, 457–487. doi: 10.1007/s12311-011-0331-9
- Mead, G. E., Hsieh, C.-F., Lee, R., Kutlubayev, M., Claxton, A., Hankey, G. J., et al. (2013). Selective serotonin reuptake inhibitors for stroke recovery: a systematic review and meta-analysis. *Stroke* 44, 844–850. doi: 10.1161/STROKEAHA.112.673947
- Mo, L., and Liu, A. (2020). Effects of transcranial Magnetic Stimulation combined with Rehabilitation training on gait, balance and FMA score in patients with post stroke hemiplegia. *Chin J Integr Med Cardio-Cerebrovasc Dis* 18, 4065–4068. doi: 10.12102/j.issn.1672-1349.2020.23.038
- Mou, G., Liu, Y., Ruan, Z., Dai, Y., Xie, L., Ai, Q., et al. (2021). Effects of low frequency repetitive transcranial magnetic stimulation on motor function of lower extremity in early re-recovery stroke patients. *Chin J Rehabil* 36, 465–468. doi: 10.3870/zgkf.2021.08.004
- Nathou, C., Duprey, E., Simon, G., Razafimandimby, A., Leroux, E., Dollfus, S., et al. (2018). Effects of low- and high-frequency repetitive transcranial magnetic stimulation on long-latency auditory evoked potentials. *Neurosci. Lett.* 686, 198–204. doi: 10.1016/j.neulet.2018.09.002
- Neuls, P. D., Clark, T. L., Van Heuklon, N. C., Proctor, J. E., Kilker, B. J., Bieber, M. E., et al. (2011). Usefulness of the berg balance scale to predict falls in the elderly. *J Geriatr. Phys. Ther.* 34, 3–10. doi: 10.1097/JPT.0b013e3181ff2b0e
- Ng, S. S. M., and Hui-Chan, C. W. Y. (2010). Transcutaneous electrical stimulation on acupoints combined with task-related training to improve motor function and walking performance in an individual 7 years poststroke: a case study. *J. Neurol. Phys. Ther.* 34, 208–213. doi: 10.1097/NPT.0b013e3181fe0ab0
- Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., et al. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 372:n71. doi: 10.1136/bmj.n71
- Parikh, V., Medley, A., Chung, Y.-C., and Goh, H.-T. (2023). Optimal timing and neural loci: a scoping review on the effect of non-invasive brain stimulation on post-stroke gait and balance recovery. *Top. Stroke Rehabil.* 30, 84–100. doi: 10.1080/10749357.2021.1990467

- Park, C. S., and An, S. H. (2016). Reliability and validity of the modified functional ambulation category scale in patients with hemiparesis. *J. Phys. Ther. Sci.* 28, 2264–2267. doi: 10.1589/jpts.28.2264
- Park, H.-J., Oh, D.-W., Kim, S.-Y., and Choi, J.-D. (2011). Effectiveness of community-based ambulation training for walking function of post-stroke hemiparesis: a randomized controlled pilot trial. *Clin. Rehabil.* 25, 451–459. doi: 10.1177/0269215510389200
- Patterson, K. K., Parafianowicz, I., Danells, C. J., Closson, V., Verrier, M. C., Staines, W. R., et al. (2008). Gait asymmetry in community-ambulating stroke survivors. *Arch. Phys. Med. Rehabil.* 89, 304–310. doi: 10.1016/j.apmr.2007.08.142
- Paul, S. L., Srikanth, V. K., and Thrift, A. G. (2007). The large and growing burden of stroke. *Curr. Drug Targets* 8, 786–793. doi: 10.2174/138945007781077418
- Roth, Y., Levkovitz, Y., Pell, G. S., Ankry, M., and Zangen, A. (2014). Safety and characterization of a novel multi-channel TMS stimulator. *Brain Stimul.* 7, 194–205. doi: 10.1016/j.brs.2013.09.004
- Roth, Y., Padberg, F., and Zangen, A. (2007). Transcranial magnetic stimulation of deep brain regions: principles and methods. *Adv Biol Psychiatr.* 23, 204–225. doi: 10.1159/000101039
- Rouse, B., Chaimani, A., and Li, T. (2017). Network meta-analysis: an introduction for clinicians. *Intern. Emerg. Med.* 12, 103–111. doi: 10.1007/s11739-016-1583-7
- Savović, J., Weeks, L., Sterne, J. A. C., Turner, L., Altman, D. G., Moher, D., et al. (2014). Evaluation of the Cochrane Collaboration's tool for assessing the risk of bias in randomized trials: focus groups, online survey, proposed recommendations and their implementation. *Syst. Rev.* 3:37. doi: 10.1186/2046-4053-3-37
- Sharma, H., Vishnu, V. Y., Kumar, N., Sreenivas, V., Rajeswari, M. R., Bhatia, R., et al. (2020). Efficacy of low-frequency repetitive transcranial magnetic stimulation in ischemic stroke: a double-blind randomized controlled trial. *Arch Rehabil Res Clin Transl* 2:100039. doi: 10.1016/j.arrct.2020.100039
- Shim, S., Yoon, B.-H., Shin, I.-S., and Bae, J.-M. (2017). Network meta-analysis: application and practice using Stata. *Epidemiol Health* 39:e2017047. doi: 10.4178/epih.e2017047
- Smith, M.-C., Byblow, W. D., Barber, P. A., and Stinear, C. M. (2017). Proportional recovery from lower limb motor impairment after stroke. *Stroke* 48, 1400–1403. doi: 10.1161/STROKEAHA.116.016478
- Swayne, O. B. C., Rothwell, J. C., Ward, N. S., and Greenwood, R. J. (2008). Stages of motor output reorganization after hemispheric stroke suggested by longitudinal studies of cortical physiology. *Cereb. Cortex* 18, 1909–1922. doi: 10.1093/cercor/bhm218
- Tao, F., Wang, C., Chen, B., Qiu, M., and Jiang, L. (2022). Effects of low frequency repetitive transcranial magnetic stimulation combined with mirror therapy on lower limb motor function and balance in stroke patients with hemiplegia. *Chin. J. Rehabil. Med.* 37, 611–615+622. doi: 10.3969/j.issn.1001-1242.2022.05.007
- Tufanaru, C., Munn, Z., Stephenson, M., and Aromataris, E. (2015). Fixed or random effects meta-analysis? Common methodological issues in systematic reviews of effectiveness. *Int. J. Evid. Based Healthc.* 13, 196–207. doi: 10.1097/XEB.0000000000000065
- Tung, Y.-C., Lai, C.-H., Liao, C.-D., Huang, S.-W., Liou, T.-H., and Chen, H.-C. (2019). Repetitive transcranial magnetic stimulation of lower limb motor function in patients with stroke: a systematic review and meta-analysis of randomized controlled trials. *Clin. Rehabil.* 33, 1102–1112. doi: 10.1177/0269215519835889
- Wang, S., and Li, L. (2022). Effects of cerebellar theta-burst stimulation on lower extremity motor function in stroke patients. *Chin J Rehabil Theory Pract* 28, 1205–1210. doi: 10.3969/j.issn.1006-9771.2022.10.011
- Wang, D., Peng, B., Zhang, H., Wang, Y., Liu, N., Shan, C., et al. (2022). Brief report on stroke prevention and treatment in China, 2020. *Chin J Cerebrovasc Dis* 19, 136–144. doi: 10.3969/j.issn.1672-5921.2022.02.011
- Wang, R.-Y., Tseng, H.-Y., Liao, K.-K., Wang, C.-J., Lai, K.-L., and Yang, Y.-R. (2012). rTMS combined with task-oriented training to improve symmetry of interhemispheric corticomotor excitability and gait performance after stroke: a randomized trial. *Neurorehabil. Neural Repair* 26, 222–230. doi: 10.1177/1545968311423265
- Wang, R.-Y., Wang, F.-Y., Huang, S.-F., and Yang, Y.-R. (2019). High-frequency repetitive transcranial magnetic stimulation enhanced treadmill training effects on gait performance in individuals with chronic stroke: a double-blinded randomized controlled pilot trial. *Gait Posture* 68, 382–387. doi: 10.1016/j.gaitpost.2018.12.023
- Wang, C., Zeng, Q., Yuan, Z., Wang, W., and Shen, M. (2023). Effects of low-frequency (0.5 Hz) and high-frequency (10 Hz) repetitive transcranial magnetic stimulation on neurological function, motor function, and excitability of cortex in ischemic stroke patients. *Neurologist* 28, 11–18. doi: 10.1097/NRL.0000000000000435
- Wessel, M. J., and Hummel, F. C. (2018). Non-invasive cerebellar stimulation: a promising approach for stroke recovery? *Cerebellum* 17, 359–371. doi: 10.1007/s12311-017-0906-1
- White, I. R., Barrett, J. K., Jackson, D., and Higgins, J. P. T. (2012). Consistency and inconsistency in network meta-analysis: model estimation using multivariate meta-regression. *Res. Synth. Methods* 3, 111–125. doi: 10.1002/jrsm.1045
- Woodford, H., and Price, C. (2007). EMG biofeedback for the recovery of motor function after stroke. *Cochrane Database Syst. Rev.* 2010:CD004585. doi: 10.1002/14651858.CD004585.pub2
- Xia, Y., Xu, Y., Li, Y., Lu, Y., and Wang, Z. (2022). Comparative efficacy of different repetitive transcranial magnetic stimulation protocols for stroke: a network meta-analysis. *Front. Neurol.* 13:918786. doi: 10.3389/fneur.2022.918786
- Xie, Y.-J., Chen, Y., Tan, H.-X., Guo, Q.-F., Lau, B. W.-M., and Gao, Q. (2021a). Repetitive transcranial magnetic stimulation for lower extremity motor function in patients with stroke: a systematic review and network meta-analysis. *Neural Regen. Res.* 16, 1168–1176. doi: 10.4103/1673-5374.300341
- Xie, Y.-J., Wei, Q.-C., Chen, Y., Liao, L.-Y., Li, B.-J., Tan, H.-X., et al. (2021b). Cerebellar theta burst stimulation on walking function in stroke patients: a randomized clinical trial. *Front. Neurosci.* 15:688569. doi: 10.3389/fnins.2021.688569
- Yan, Y., Yu, L., and Shao, Y. (2023). Effect of low frequency repetitive transcranial magnetic stimulation on lower limb spasticity and balance gait in patients with hemiplegia after stroke. *China Med Her* 20, 81–85. doi: 10.20047/j.issn1673-7210.2023.14.17
- Yang, L., Sheng, Y., Xie, L., Wei, H., and Peng, T. (2016). The effect of repetitive transcranial magnetic stimulation combined with rehabilitation training on the walking function of stroke patients. *Chin J Phys Med Rehabil* 38, 907–909. doi: 10.3760/cma.j.issn.0254-1424.2016.12.007
- Zhao, X., Liu, T., Zhou, Y., and Zhang, L. (2018). The effect of repetitive transcranial magnetic stimulation on dyskinesia in stroke patients. *Chin J Rehabil Med* 33, 800–805. doi: 10.3969/j.issn.1001-1242.2018.07.009
- Zhou, J., Zhang, L., Li, R., Xu, K., and Wu, C. (2020). Effect of repetitive transcranial magnetic stimulation combined with exercise therapy on the motor function in stroke patients with hemiplegia. *Rehabil Med* 30, 235–239. doi: 10.3724/SP.J.1329.2020.03013
- Zhu, D., Liu, S., Wang, L., Huang, Z., and Ni, J. (2022). Effects of repetitive transcranial magnetic stimulation combined with task-oriented training on lower limb function in stroke patients. *Chin J Rehabil Med* 37, 1046–1050. doi: 10.3969/j.issn.1001-1242.2022.08.006