REVIEW ARTICLE

Comparison of the efficacy of different protocols of repetitive transcranial magnetic stimulation and transcranial direct current stimulation on motor function, activities of daily living, and neurological function in patients with early stroke: a systematic review and network meta-analysis

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Abstract

Background The application of transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS) in patients with early stroke has recently received considerable attention, but the optimal protocol remains inconclusive. This study intends to evaluate and compare the effects of different protocols of tDCS and rTMS on improving motor function, activities of daily living (ADL), and neurological function in patients with early stroke, and to comprehensively assess their efficacy and safety.

Methods MEDLINE, Embase, Cochrane Library, and Web of Science were searched. Risk of bias (RoB) was assessed using the Cochrane Risk of Bias 2.0 tool, and Bayesian NMA was conducted using R4.3.1 and Stata16.

Results The results of NMA showed that after early intervention, bilateral application of high- and low-frequency rTMS (BL-rTMS) performed best in improving the upper extremity motor function at the end of intervention (SUCRA: 92.8%) and 3 months (SUCRA: 95.4%). Besides, low-frequency rTMS (LF-rTMS) performed best in improving the lower extremity motor function (SUCRA: 67.7%). BL-rTMS was the most effective in ameliorating the ADL at the end of intervention (SUCRA: 100%) and 3 months (SUCRA: 85.6%). In terms of the NIHSS scores, BL-rTMS had the highest probability of being the most effective measure at the end of intervention (SUCRA: 99.7%) and 3 months (SUCRA: 97.05%). Besides, LF-rTMS (0%), 5 Hz-rTMS (0%), and intermittent theta-burst stimulation (iTBS) (0%) all exhibited a good safety profile.

Conclusion BL-rTMS is the optimal stimulation protocol for improving upper extremity motor function, ADL, and neurological function in early stroke, with long-term efficacy.

Keywords rTMS · tDCS · Early stroke · Motor function · ADL · Network meta-analysis

Abbreviations

ADL	Activities of daily living
AEs	Adverse events
BL-rTMS	Bilateral application of high- and low-frequency repetitive transcranial magnetic stimulation
cTBS	Continuous theta-burst stimulation
FMA	Fugl-Meyer assessment scale
FMA-LE	Fugl-Meyer assessment scale for lower extremity
FMA-UE	Fugl-Meyer assessment scale for upper extremity
HF-rTMS	High-frequency repetitive transcranial magnetic stimulation
iTBS	Intermittent theta-burst stimulation
LF-rTMS	Low-frequency repetitive transcranial magnetic stimulation
mBI	modified Barthel index
NIBS	Non-invasive brain stimulation
NIHSS	National Institutes of Health Stroke Scale
NMA	Network meta-analysis
RCTs	Randomized controlled trials
RoB	Risk of bias

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rTMS	Repetitive transcranial magnetic stimulation
tDCS	Transcranial direct current stimulation
TIA	Transient ischemia attack

Introduction

Globally, stroke is the leading cause of death and disability, with approximately 795,000 new or recurrent cases of stroke annually [1]. Stroke can lead to a variety of functional impairments, such as dysphagia, cognitive impairment, dyskinesia, post-stroke pain, and depression, further affecting the activities of daily living (ADL), and resulting in a great economic cost for post-stroke care [2]. The burden of stroke is projected to rise further with an aging population and an increase in non-communicable diseases [3]. Therefore, post-stroke early rehabilitation interventions are crucial.

Early post-stroke period (acute and early subacute) is a critical period for neuroplasticity, in which the body undergoes a series of endogenous molecular, cellular, and electrophysiologic processes, thereby enhancing neurological recovery [4]. Research suggests that this process is completed almost within 30 days [5, 6]. How to intervene effectively in an early stage, a critical period with optimal brain plasticity, to enhance neuroplasticity or even prolong the remodeling duration has been one of the most important concerns of scholars [4, 7–9] Prompt and effective post-stroke rehabilitation interventions can help patients restore function and improve activity and participation abilities, which is an effective way to reduce the burden of stroke. In recent years, substantial evidence suggests that non-invasive brain stimulation (NIBS), especially transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS), is suitable for early stroke patients [10–14]. Several studies have explored NIBS as a complement to routine physiotherapy for early stroke, achieving beneficial effects [11, 15, 16]. A meta-analysis has shown that early NIBS is effective in ameliorating extremity motor function and ADL in acute stroke [17, 18]. The difference in the efficacy of different protocols of early tDCS has been compared in a study [19], and it is found that dual-tDCS is more effective in improving motor function in early stroke patients. Other studies [15, 20] compared the efficacy of high-frequency rTMS (HF-rTMS) and low-frequency rTMS (LF-rTMS), and showed that the two protocols had no significant difference in motor function improvement, but their effects were significantly better than sham.

Due to methodological limitations, the possible differences in treatment outcomes of rTMS and tDCS fail to be fully clarified. The optimal stimulation mode, long-term efficacy, and safety of early NIBS remain unclear. Network meta-analysis (NMA) can provide a more complete review of the efficacy of early tDCS and rTMS on stroke and should

be considered the highest level of evidence in the treatment guidelines [21]. NMA enables simultaneous comparisons of the effects of multiple interventions, as direct comparisons among these stimulations are lacking. In addition, NMA allows for the ranking of interventions, thereby helping health professionals and clinicians to make evidence-based decisions. This study, by an NMA, intends to compare the short- and long-term effects of different protocols of tDCS and rTMS on improving motor function, ADL, and neurological function in patients with early stroke and the safety of early intervention. The findings will offer a rationale for the use of NIBS in early stroke patients and help clinical practitioners develop evidence-based treatment protocols, thereby enhancing the rehabilitation outcomes of stroke patients and reducing the social and economic burdens of stroke.

Materials and methods

Study protocol

This systematic review and NMA followed the PRISMA 2020 Statement [22] and PRISMA extension for network meta-analyses [23], and was registered with PROSPERO (http://www.crd.york.ac.uk/prospero/) (CRD42023492164).

Search strategy

We searched MEDLINE, Embase, Cochrane Library, and Web of Science for randomized controlled trials (RCTs) from inception to October 7, 2023. Medical subject headings with free words were used, including "Stroke*", "Cerebrovascular Accident*", "Brain Vascular Accident*", "Transcranial Direct Current Stimulation", "Transcranial Magnetic Stimulation", "Non-invasive Brain Stimulation*", "Acute", "Early Stage", and "Randomized Controlled Trial". The search strategy is detailed in the Supplementary File 1.

Eligibility criteria

For this review, "early intervention" was defined as the initiation of NIBS, including different protocols of TMS and tDCS, within one month after acute stroke onset. The National Institutes of Health Stroke Scale (NIHSS) was applied to assess neurological function, Fugl-Meyer assessment scale (FMA) to assess motor function, including FMA for upper extremity (FMA-UE) and FMA for lower extremity (FMA-LE), modified Barthel index (mBI) to assess ADL, and adverse events (AEs) to assess the safety of early intervention.

We included studies that met the following criteria: (1) Population: adults ≥ 18 years; patients diagnosed with a stroke by computed tomography or magnetic resonance;

stoke onset ≤ 1 month. (2) Intervention: The intervention of the experiment group included tDCS and/or rTMS. (3) Comparison: Control measures included conventional treatment and the sham or blank of rTMS/tDCS; or other types of rTMS/tDCS. (4) Outcome: At least one of the following outcomes was reported: (a) Motor function measured by FMA (FMA-UE, and FMA-LE); (b) ADL assessed by mBI; (c) safety assessed by AEs; (d) Stroke severity measured by NIHSS. (5) Study type: RCTs. (6) Language: English.

The exclusion criteria were as follows: (1) Transient ischemia attack (TIA). (2) Duration of disease > 30 days. (3) Non-RCTs such as case reports, literature reviews, conference abstracts, animal experiments, and retrospective studies. (4) Studies with incomplete data and original data unavailable after emailing the author. (5) Duplicate publications.

Data extraction

All studies retrieved were checked for eligibility independently by two reviewers (XYN and ZNY) based on the above criteria. After duplicate publications were excluded using EndNote 21 (Clarivate Analytics, Philadelphia, PA, USA), potentially eligible studies were identified by reading titles and abstracts. Then the full text was further read to finally include eligible studies. Disagreement could be resolved by discussion with a third reviewer (YP). The following information was extracted from the included studies: first author, year of publication, sample size, age, sex, type of stroke, duration of disease, interventions, comparisons, and outcomes mentioned above.

Quality assessment

Risk of bias (RoB) was assessed independently by two reviewers (XYN and ZNY) using the Cochrane Risk of Bias 2.0 tool [24] from the deviations from intended interventions, randomization process, measurement of the outcome, missing outcome data, selection of the reported result, and overall bias. The studies were classified as "low risk", "high risk", and "some concerns". Disagreement could be resolved by discussion with a third reviewer (YP).

Synthesis methods

R4.3.1 and Stata16 were used for calculation and plotting. Continuous outcomes (including FMA, mBI, and NIHSS) were described by mean difference (MD) and 95% confidence interval (CI). The Markov Chain Monte Carlo method was utilized, with four chains running and 2,0000 iterations of pre-simulation for annealing. The surface under the cumulative ranking curve (SUCRA, 0–100%) was calculated to estimate the probability of being the optimal intervention.

Local inconsistency between direct and indirect evidence was checked by the node-splitting method. Using the Bayesian information criterion, consistency and inconsistency models were fit. The I^2 values of 25%, 50%, and 75% corresponded to low, moderate, and high degrees of heterogeneity, respectively. Network diagrams were plotted using Stata. The publication bias in primary outcome measures was detected by funnel plots.
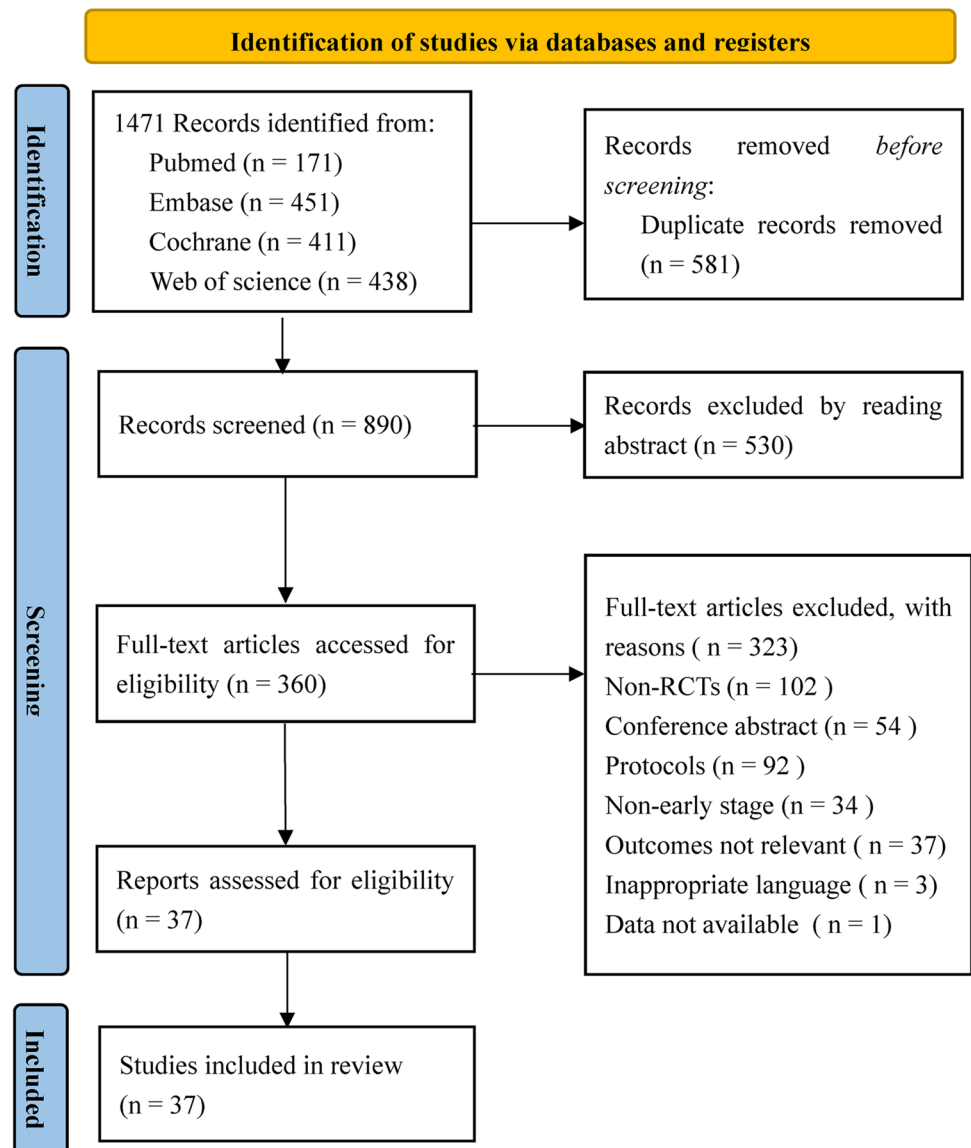
Results

Study selection

A total of 1471 studies were initially retrieved. After 581 duplicate publications were excluded, another 530 non-relevant studies were excluded by reading titles and abstracts. Among the remaining 360 studies, 102 non-RCTs, 54 conference abstracts, 92 study protocols, and 75 RCTs that did not satisfy the above eligibility criteria were excluded. Finally, 37 studies were included [11, 15, 16, 19, 20, 25–56]. The study screening process is described in Fig. 1.

Study characteristics

A total of 1766 patients were included in the 37 studies [11, 15, 16, 19, 20, 25–56] involving 10 types of rTMS and tDCS. There were 271 cases in the HF-rTMS (≥ 10 Hz) group [15, 16, 20, 26, 30, 33, 43, 47, 51, 53, 54], 27 cases in the 5 Hz-rTMS group [39, 42], 77 cases in the 3 Hz-rTMS group [44, 53, 55, 56], 301 cases in the LF-rTMS (≤ 1 Hz) group [11, 15, 16, 20, 26, 32, 37, 38, 44, 45, 48, 51, 55], 99 cases in the bilateral application of high- and low-frequency repetitive transcranial magnetic stimulation (BL-rTMS) group [16, 31, 38, 47], 28 cases in the continuous theta-burst stimulation (cTBS) group [27], 28 cases in the intermittent theta-burst stimulation (iTBS) group [35, 37], 57 cases in the cathodal-tDCS group [11, 19, 40, 49], 83 cases in the anodal-tDCS group [19, 36, 46, 52], and 137 cases in the dual-tDCS group [19, 25, 28, 29, 34, 41, 50] The study characteristics are detailed in Table 1.

RoB assessment

In terms of the randomization process, 21 studies [15, 16, 19, 20, 25, 31, 34–36, 38–42, 44, 46, 48, 50, 53, 54, 56] were rated as low risk, 13 studies [11, 26–29, 32, 37, 43, 45, 49, 51, 52, 55] as some concerns, and three studies [30, 33, 47] as high risk. In terms of deviations from intended interventions, 26 studies [11, 15, 16, 19, 20, 25, 28, 31, 32, 34–36, 38–42, 44, 45, 48–50, 53–56] were rated as low risk, and 11 studies [26, 27, 29, 30, 33, 37, 43, 46, 47, 51, 52] as some concerns. For missing outcome data, 32

Fig. 1 Flowchart of the study selection process

Identification of studies via databases and registers

Identification

1471 Records identified from:
  Pubmed (n = 171)
  Embase (n = 451)
  Cochrane (n = 411)
  Web of science (n = 438)

Records removed *before screening*:
  Duplicate records removed (n = 581)

Screening

Records screened (n = 890)

Records excluded by reading abstract (n = 530)

Full-text articles accessed for eligibility (n = 360)

Full-text articles excluded, with reasons (n = 323)
Non-RCTs (n = 102)
Conference abstract (n = 54)
Protocols (n = 92)
Non-early stage (n = 34)
Outcomes not relevant (n = 37)
Inappropriate language (n = 3)
Data not available (n = 1)

Reports assessed for eligibility (n = 37)

Included

Studies included in review (n = 37)

[11, 19, 25–27, 29–47, 49–56] studies and 5 studies [15, 16, 20, 28, 48]were rated as low risk and some concerns, respectively. For measurement of the outcome, 31 studies [11, 15, 16, 19, 20, 25, 26, 28, 31–36, 38–42, 44–51, 53–56], five studies [27, 29, 30, 43, 52], and one study [37] were rated as low risk, some concerns, and high risk, respectively. For selection of the reported result, 36 studies [11, 15, 16, 19, 20, 25–27, 29–56] were rated as low risk, and one study [28] as some concerns. The RoB assessment results are displayed in Fig. 2. To sum up, low risk, some concerns, and high risk were identified in 16 studies [19, 25, 31, 34–36, 38–42, 44, 50, 53, 54, 56], 20 studies [11, 15, 16, 20, 26–30, 32, 33, 37, 43, 45, 46, 48, 49, 51, 52, 55], and one study [47], respectively.

FMA

FMA-UE

FMA-UE of post-early intervention was reported in 14 studies [11, 15, 16, 20, 26–28, 31, 32, 35, 38, 41, 42, 49], with 896 patients treated with LF-rTMS, 5 Hz-rTMS, HF-rTMS, BL-rTMS, cTBS, iTBS, cathodal-tDCS, and dual-tDCS. In the network diagram (Fig. 3A), the dots represented the interventions, their size represented the sample size, and the thickness of connecting lines represented the number of studies. It was found that direct comparisons were present between LF-rTMS and HF-rTMS, BL-rTMS, HF-rTMS, and cathodal-tDCS, while indirect comparisons

Table 1 Characteristics of included studies

Study	Sample size (E/C)	Age (E/C)	Gender (M/F)	Stroke type (infarction/ hemorrhage)	Onset time (d)	Intervention (E/C)	Outcome
Yagüe [25]	9/9	56 ± 14.2 / 59.4 ± 12.6	11/7	9/9	(5–17)	dual-tDCS / Sham	①
Wang [26]	80/80/80	63.85 ± 9.54 / 63.92 ± 10.28 / 64.10 ± 9.96	157/83	240/0	21.33 ± 3.06	HF-rTMS / LF-rTMS / Sham	① ③ ④ ⑥
Vink [27]	28/31	56.8 ± 12 / 63.4 ± 12	40/19	50/9	16 ± 4	cTBS / Sham	① ② ④ ⑤ ⑧
Garrido [28]	35/35	65 ± 12 / 65 ± 14	37/33	68/2	6 ± 4	dual-tDCS / Sham	① ②
Zhao [29]	30/30	59.57 ± 10.41 / 62.87 ± 8.40	39/21	60/0	7.62 ± 2.67	dual-tDCS / Control	⑧
Komatsu [30]	22/22	52(47,62) / 57(49,63)	30/14	0/44	9(6–12)	HF-rTMS / Control	⑧
Klomjai [19]	18/21/20/20	61.11 ± 9.70 / 59.94 ± 9.80 / 57.20 ± 12.54 / 60.18 ± 10.20	49/30	79/0	3.88 ± 1.34	cathodal-tDCS / anodal-tDCS / dual-tDCS / Sham	⑧
Juan [15]	15/17/14	51 ± 10 / 56 ± 10 / 52 ± 11	38/8	46/0	4.61 ± 3.45	HF-rTMS / LF-rTMS / Sham	① ②
Chen [31]	22/22	56.0(39.3,64.0) / 60.5(54.3,65.5)	33/11	44/0	6.25 ± 3.95	BL-rTMS / Sham	① ② ⑤ ⑧
Chen [16]	25/25/25/25	58.0(44.5,65.5) / 62.0(49.0,67.0) / 63.0(43.0,67.0) / 65.0(52.0,73.0)	70/30	100/0	(4–14)	BL-rTMS / HF-rTMS / LF-rTMS / Sham	① ② ④ ⑤ ⑥ ⑦ ⑧
Miu [11]	25/26	63.2 ± 12.8 / 66.5 ± 10.1	25/26	37/14	within 1 month	LF-rTMS / cathodal-tDCS	① ④
Kim [22]	8/12	67.00 ± 12.92 / 62.17 ± 16.25	12/8	20/0	within 1 month	LF-rTMS / Control	① ③ ④ ⑧
Ke [33]	32/16	55.6 ± 8.86 / 58.3 ± 8.3	20/20	48/0	11.6 ± 2.85	HF-rTMS / Sham	⑧
Bolognini [34]	16/16	68 ± 13 / 69 ± 8.5	21/11	25/7	(2–3)	dual-tDCS / Sham	④ ⑥ ⑧
Khan [35]	20/20	63.55 ± 12.67 / 64.60 ± 12.99	25/15	40/0	16.78 ± 5.12	iTBS / Control	① ② ④ ⑤ ⑥ ⑦
Du [20]	20/20/20	54 ± 12 / 56 ± 9 / 56 ± 11	48/12	60/0	5 ± 3.73	HF-rTMS / LF-rTMS / Sham	① ② ⑥ ⑧
Bornheim [36]	25/25	62.48 ± 11.86 / 63.48 ± 12.94	33/17	50/0	within 1 month	anodal-tDCS / Sham	⑧
Watanabe [37]	8/7/6	72.5 ± 6.5 / 67.6 ± 6.4 / 75.2 ± 5.5	14/7	21/0	within 7 days	iTBS / LF-rTMS / Sham	⑧
Long [38]	21/21/20	57.00 ± 11.78 / 55.90 ± 8.89 / 56.85 ± 5.48	47/15	32/30	19.49 ± 2.67	LF-rTMS / BL-rTMS / Sham	① ② ⑧
Li [39]	6/6	56.9(30–76)	1/11	12/0	within 1 week	5 Hz-rTMS / Sham	⑧
Rabadi [40]	8/8	62 ± 11 / 63 ± 6	0/16	16/0	6.4 ± 3.2	cathodal-tDCS / Sham	⑧
Oveisgharan [41]	10/10	52.1 ± 12.8 / 65.3 ± 16.5	10/10	20/0	3.0 ± 4.1	dual-tDCS / Sham	① ⑧

Table 1 (continued)

Study	Sample size (E/C)	Age (E/C)	Gender (M/F)	Stroke type (infarction/ hemorrhage)	Onset time (d)	Intervention (E/C)	Outcome
Guan [42]	21/21	59.7±6.8 / 57.4±14.0	30/12	42/0	4.6±3.7	5 Hz-rTMS / Sham	① ② ③ ④ ⑤ ⑥ ⑦ ⑧
Guo [43]	7/8	67.71±7.4 / 66.63±9.24	7/8	15/0	4.80±1.26	HF-rTMS / Sham	④ ⑥ ⑧
Du [44]	23/23/23	56.78±8.47 / 56.78±12.4 / 53.61±13.55	45/24	69/0	(3–24)	3 Hz-rTMS / LF-rTMS / Sham	⑥ ⑤ ⑧
Matsuura [45]	10/10	72.2±6.0 / 74.7±12.7	11/9	20/0	9.6±4.13	LF-rTMS / Sham	⑧
Chang [46]	12/12	59.9±10.2 / 65.8±10.6	15/9	24/0	16.3±5.6	anodal-tDCS / Sham	③
Sasaki [47]	27/31	66.6±9.5 / 62.7±10.9	41/17	36/22	9.72±3.29	HF-rTMS / BL-rTMS	⑧
Kim [48]	42/16	67.07±7.67 / 65.51±11.24	30/28	58/0	15.86±11.06	LF-rTMS / Sham	⑧
Fusco [49]	5/6	58.36±14.35	5/6	11/0	19.09±8.04	cathodal-tDCS / Sham	① ④
Di [50]	17/17	63.12±6.01/ 70.00±4.49	22/12	34/0	3.25±1.58	dual-tDCS / Sham	⑥ ⑦
Sasaki [51]	9/11/9	65.7±9.1 / 68.6±8.7 / 63.0±9.3	20/9	13/16	17.4±5.4	HF-rTMS / LF-rTMS / Sham	⑧
Rossi [52]	25/25	66.1±14.3 / 70.3±13.5	26/24	50/0	9.65±2.59	anodal-tDCS / Sham	⑥ ⑧
Khedr [53]	16/16/16	58.25±15.07 / 58.37±13.96 / 58±11.64	24/24	48/0	6.5±3.63	3 Hz-rTMS / HF-rTMS / Sham	⑥ ⑧ ⑦
Chang [54]	18/10	56.4±11.2 / 57.0±14.5	17/11	28/0	13.4±5.4	HF-rTMS / Sham	⑧
Khedr [55]	12/12/12	54.7±9.7 / 59.0±13.5 / 60.0±9.5	19/17	36/0	17.1±3.6	LF-rTMS / 3 Hz-rTMS / Sham	④ ⑤ ⑥ ⑦ ⑧
Khedr [56]	26/26	53.5±9.5 / 52.2±8.4	36/16	52/0	7.2±1.44	3 Hz-rTMS / Sham	④ ⑥ ⑧

Data are expressed as the mean ± SD or Mean (range) for age and onset time; ①Fugl-Meyer assessment scale for upper extremity (FMA-UE); ②FMA-UE (3 month follw-up); ③Fugl-Meyer assessment scale for lower extremity (FMA-LE); ④modified Barthel Index (mBI); ⑤mBI (3 month follw-up); ⑥National Institute of Health Stroke Scale (NIHSS); ⑦NIHSS (3 month follw-up); ⑧adverse events (AE)

E; experimental group, *C;* control group, *F;* female, *M;* male, *d;* day, *HF-rTMS;* high-frequency repetitive transcranial magnetic stimulation, *LF-rTMS;* low-frequency repetitive transcranial magnetic stimulation, *BL-rTMS;* bilateral application of HF- rTMS and LF-rTMS, *iTBS;* intermittent theta-burst stimulation, *cTBS;* continuous theta-burst stimulation, *tDCS;* transcranial direct current stimulation

were present between dual-tDCS, iTBS, cTBS, and 5 Hz-rTMS and other interventions. The analysis results converged satisfactorily (Supplementary File 2), and good consistency was exposed by the node-splitting method. As shown in the league table (Table 2), the efficacy of BL-rTMS was superior to cathodal-tDCS (SMD = 12.77, 95% CI: 0.02–25.41), HF-rTMS (SMD = 10.95, 95% CI: 1.43–20.11), LF-rTMS (SMD = 10.69, 95% CI: 2.45–18.97), and sham (SMD = 14.96, 95% CI: 7.18–22.84). The forest plot revealed that only BL-rTMS (SMD = 14.96, 95% CI: 7.18–22.84) was more efficacious than sham in improving

FMA-UE scores (Fig. 3B). In addition, BL-rTMS had the highest probability of being effective (SUCRA: 92.8%), and acted as the optimal stimulation protocol for improving FMA-UE scores, followed by iTBS (SUCRA: 79.9%) and LF-rTMS (SUCRA: 57.0%) (Fig. 3C). The funnel plot was largely symmetric, with a few studies located outside of the funnel plot, suggesting low risk of publication bias (Fig. 3D).

The long-term effect (3-month follow-up) on FMA-UE was reported in nine studies [15, 16, 20, 27, 28, 31, 35, 38, 42], with 458 patients treated with LF-rTMS, 5 Hz-rTMS,

Fig. 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

HF-rTMS, BL-rTMS, cTBS, iTBS, and dual-tDCS. The network diagram showed that direct comparisons were present between LF-rTMS and HF-rTMS, BL-rTMS, and HF-rTMS, while indirect comparisons were present between dual-tDCS, iTBS, cTBS, and 5 Hz-rTMS and other interventions (Fig. 4A). The 3-month follow-up results converged satisfactorily (Supplementary File 2), and good consistency was exposed by the node-splitting method. As shown in the league table (Table 3), the efficacy of BL-rTMS was superior to LF-rTMS (SMD = 12.42, 95% CI: 0.76–23.89) and sham (SMD = 20.24, 95% CI: 9.8–31.11). The forest plot revealed that only BL-rTMS (SMD = 20.24, 95% CI: 9.8–31.11) was more effective than sham in improving FMA-UE scores (Fig. 4B). In addition, BL-rTMS had the highest probability of being effective (SUCRA: 95.4%), and acted as the optimal stimulation protocol for improving FMA-UE scores,

followed by iTBS (SUCRA: 66.5%) and cTBS (SUCRA: 55.1%) (Fig. 4C). The funnel plot was largely symmetric, with some studies deviating considerably from the funnel plot, especially on the left side, suggesting that the efficacy might be underestimated in some studies (Fig. 4D).

FMA-LE

FMA-LE of post-early intervention was reported in four studies [26, 32, 42, 46], with 333 patients treated with LF-rTMS, 5 Hz-rTMS, HF-rTMS, and anodal-tDCS. The network diagram showed that LF-rTMS and HF-rTMS had direct comparisons, while anodal-tDCS and 5 Hz-rTMS had indirect comparisons with other interventions (Fig. 5A). The analysis results converged satisfactorily (Supplementary File 2). No statistically significant
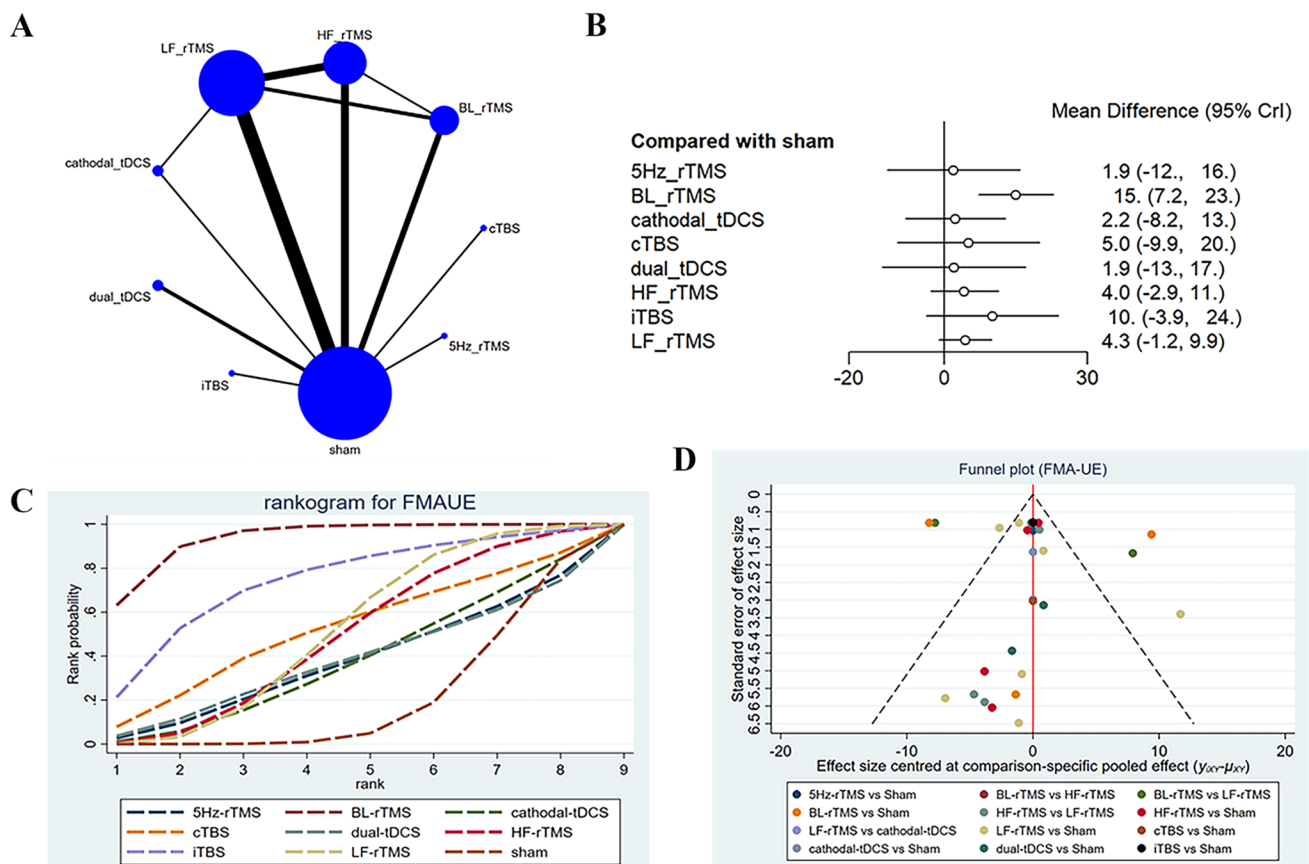
Fig. 3 Network meta-analysis results for FMA-UE (end of treatment). **A**: Network plot; **B**: Forest plot; **C**: Cumulative probability ranking curve of different interventions; **D**: Funnel plot. HF-rTMS, high-frequency repetitive transcranial magnetic stimulation; LF-rTMS, low-frequency repetitive transcranial magnetic stimulation; BL-rTMS, bilateral application of HF- rTMS and LF-rTMS; cTBS, continuous theta-burst stimulation; iTBS, intermittent theta-burst stimulation; tDCS, transcranial direct current stimulation

Table 2 The result of network meta-analysis comparing the effect of all interventions on Fugl-Meyer assessment-upper limb (end of treatment) including SMD and 95% CI

	5Hz-rTMS							
BL-rTMS	-13.1 (-29.12, 2.87)	**BL-rTMS**						
Cathodal-tDCS	-0.33 (-17.79, 17.11)	12.77 (0.02, 25.41)	**Cathodal-tDCS**					
cTBS	-3.14 (-23.56, 17.23)	9.96 (-6.85, 26.81)	-2.82 (-20.94, 15.37)	**cTBS**				
Dual-tDCS	-0.02 (-20.44, 20.4)	13.06 (-3.94, 30.02)	0.29 (-18.03, 18.8)	3.1 (-18.12, 24.4)	**Dual-tDCS**			
HF-rTMS	-2.15 (-17.99, 13.25)	10.95 (1.43, 20.11)	-1.82 (-14.11, 10.17)	1 (-15.67, 17.36)	-2.06 (-18.95, 14.38)	**HF-rTMS**		
iTBS	-8.11 (-27.77, 11.56)	4.97 (-10.94, 20.9)	-7.8 (-25.14, 9.65)	-4.95 (-25.38, 15.37)	-8.07 (-28.63, 12.45)	-5.99 (-21.32, 9.71)	**iTBS**	
LF-rTMS	-2.4 (-17.43, 12.54)	10.69 (2.45, 18.97)	-2.05 (-12.7, 8.53)	0.76 (-15.19, 16.61)	-2.36 (-18.41, 13.64)	-0.27 (-7.26, 7.06)	5.73 (-9.2, 20.66)	**LF-rTMS**
sham	1.88 (-12.03, 15.79)	14.96 (7.18, 22.84)	2.19 (-8.24, 12.78)	5.02 (-9.91, 19.92)	1.91 (-13.11, 17.05)	4.01 (-2.87, 11.33)	10 (-3.87, 23.93)	4.28 (-1.23, 9.85)	sham

Red and bold numbers are statistically significant. *HF-rTMS;* high-frequency repetitive transcranial magnetic stimulation, *LF-rTMS;* low-frequency repetitive transcranial magnetic stimulation, *BL-rTMS;* bilateral application of HF- rTMS and LF-rTMS, *iTBS;* intermittent theta-burst stimulation, *cTBS;* continuous theta-burst stimulation, *tDCS;* transcranial direct current stimulation

difference was found in the improvement of FMA-LE scores among interventions (Table 4). LF-rTMS had the highest probability of being effective (SUCRA: 67.7%), followed by 5 Hz-rTMS (SUCRA: 46.9%) and sham (SUCRA: 46.7%) (Fig. 5C). The funnel plot was globally symmetric, suggesting no significant publication bias (Fig. 5D).

mBI

A total of 14 studies [11, 16, 26, 27, 31, 32, 34, 35, 42–44, 49, 55, 56] reported mBI, with 849 patients treated with LF-rTMS, 3 Hz-rTMS, 5 Hz-rTMS, HF-rTMS, BL-rTMS, cTBS, iTBS, cathodal-tDCS, and dual-tDCS. The network diagram showed direct comparisons of LF-rTMS with
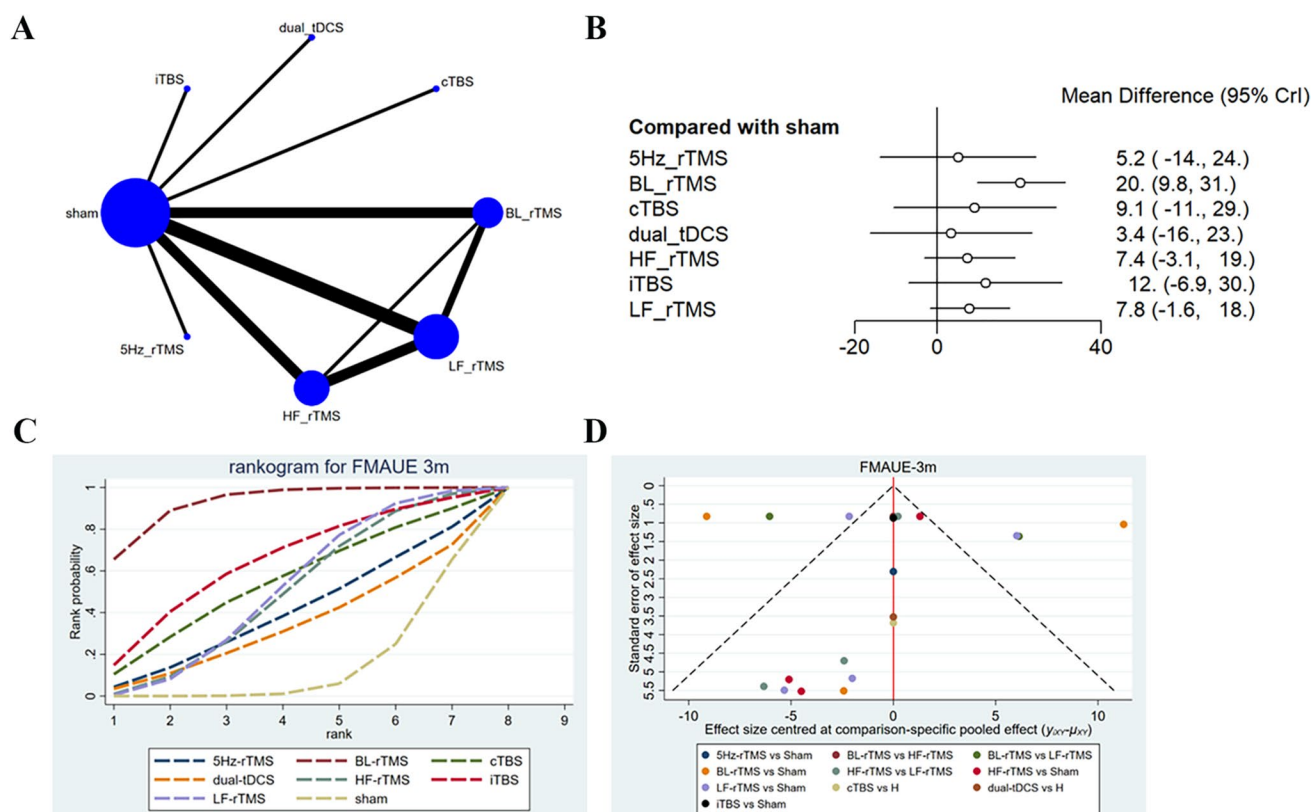
Fig. 4 Network meta-analysis results for FMA-UE (3 month follwup). **A**: Network plot; **B**: Forest plot; **C**: Cumulative probability ranking curve of different interventions; **D**: Funnel plot. HF-rTMS, high-frequency repetitive transcranial magnetic stimulation; LF-rTMS, low-frequency repetitive transcranial magnetic stimulation; BL-rTMS, bilateral application of HF- rTMS and LF-rTMS; cTBS, continuous theta-burst stimulation; iTBS, intermittent theta-burst stimulation; tDCS, transcranial direct current stimulation

Table 3 The result of network meta-analysis comparing the effect of all interventions on Fugl-Meyer assessment-upper limb (3 month follwup) including SMD and 95% CI

	5Hz-rTMS							
BL-rTMS	-15.03 (-37.01, 6.56)	**BL-rTMS**						
cTBS	-3.94 (-31.3, 23.32)	11.1 (-11.26, 33.75)	**cTBS**					
dual-tDCS	1.82 (-25.46, 29.2)	16.87 (-5.3, 39.43)	5.76 (-22.07, 33.79)	**dual-tDCS**				
HF-rTMS	-2.25 (-24.77, 19.22)	12.82 (-0.58, 25.52)	1.69 (-21.33, 23.95)	-4.03 (-27.03, 17.93)	**HF-rTMS**			
iTBS	-6.63 (-33.31, 20)	8.42 (-12.86, 30.14)	-2.67 (-29.95, 24.46)	-8.4 (-35.66, 18.69)	-4.37 (-25.44, 17.88)	**iTBS**		
LF-rTMS	-2.6 (-24.27, 18.42)	12.42 (0.76, 23.89)	1.3 (-20.94, 23.22)	-4.43 (-26.6, 17.25)	-0.39 (-11.18, 10.88)	3.98 (-17.44, 24.83)	**LF-rTMS**	
sham	5.21 (-13.88, 24.13)	20.24 (9.8, 31.11)	9.14 (-10.63, 29.01)	3.4 (-16.22, 23.07)	7.44 (-3.07, 18.91)	11.81 (-6.91, 30.45)	7.83 (-1.6, 17.71)	**sham**

Red and bold numbers are statistically significant. *HF-rTMS;* high-frequency repetitive transcranial magnetic stimulation, *LF-rTMS;* low-frequency repetitive transcranial magnetic stimulation, *BL-rTMS;* bilateral application of HF- rTMS and LF-rTMS, *iTBS;* intermittent theta-burst stimulation, *cTBS;* continuous theta-burst stimulation, *tDCS;* transcranial direct current stimulation

HF-rTMS, BL-rTMS, cathodal-tDCS, and 3 Hz-rTMS, and indirect comparisons of dual-tDCS, cTBS, iTBS, and 5 Hz-rTMS with other interventions (Fig. 6A). The analysis results converged satisfactorily (Supplementary File 2), and good consistency was exposed by the node-splitting method. The efficacy of LF-rTMS (SMD = 11.76, 95% CI: 7.08–15.3), 3 Hz-rTMS (SMD = 11.99, 95% CI: 4.16–18.98),

HF-rTMS (SMD = 6.34, 95% CI: 0.44–10.66), BL-rTMS (SMD = 25.7, 95% CI: 17.81–30.59), iTBS (SMD = 10.44, 95% CI: 0.75–20.27), and cathodal-tDCS (SMD = 11.74, 95% CI: 3.7–18.62) was better than sham (Fig. 6B). As shown in the league table (Table 5), different interventions had significant differences in improving FMA-UE scores. The efficacy of BL-rTMS was better than cathodal-tDCS
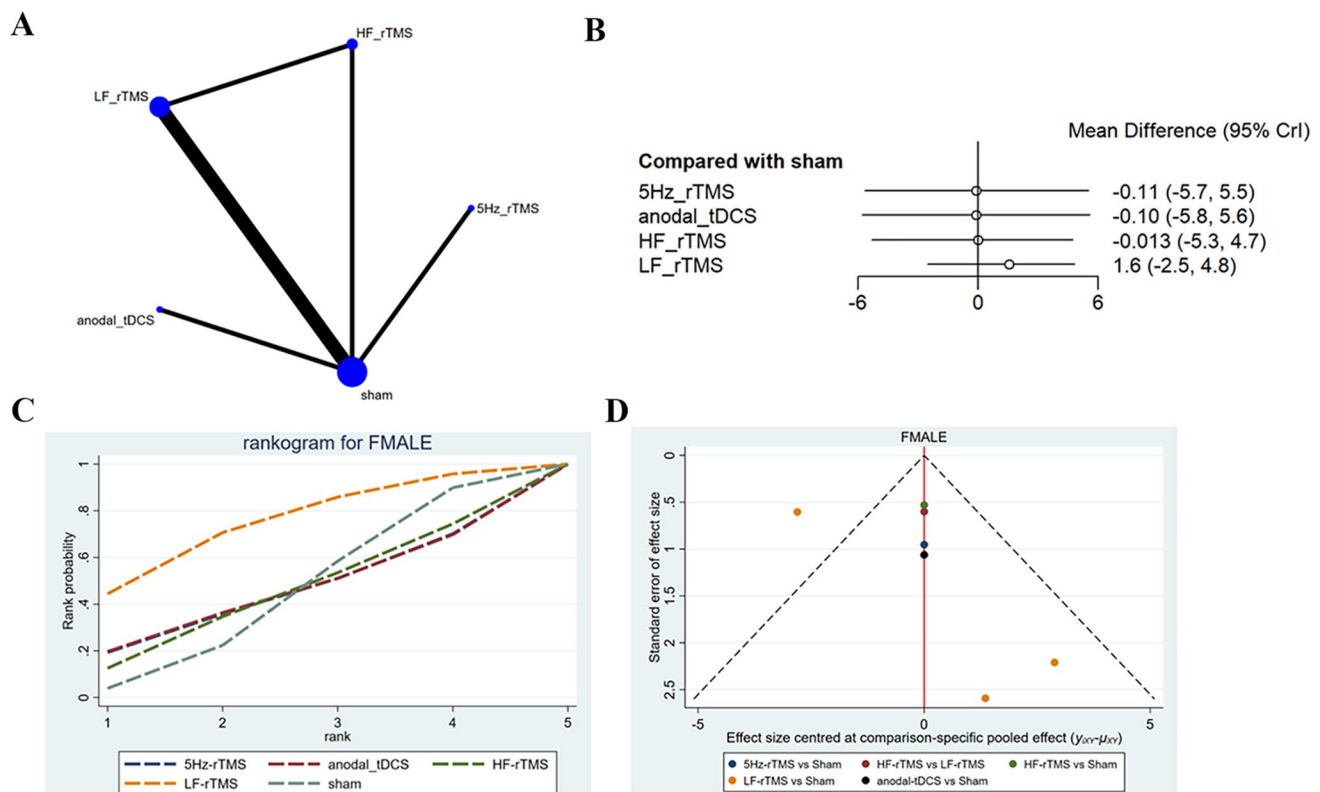
Fig. 5 Network meta-analysis results for FMA-LE (end of treatment). **A**: Network plot; **B**: Forest plot; **C**: Cumulative probability ranking curve of different interventions; **D**: Funnel plot. HF-rTMS, high-fre-quency repetitive transcranial magnetic stimulation; LF-rTMS, low-frequency repetitive transcranial magnetic stimulation; tDCS, tran-scranial direct current stimulation

Table 4 The result of network meta-analysis comparing the effect of all interventions on Fugl-Meyer assessment-lower limb (end of treatment) including SMD and 95% CI

	5 Hz-rTMS				
anodal-tDCS	0 (−7.97, 8.07)	anodal-tDCS			
HF-rTMS	−0.09 (−7.31, 7.78)	−0.08 (−7.37, 7.81)	HF-rTMS		
LF-rTMS	−1.74 (−7.9, 5.53)	−1.73 (−7.98, 5.57)	−1.7 (−6.49, 3.67)	LF-rTMS	
sham	−0.11 (−5.68, 5.52)	−0.1 (−5.8, 5.6)	−0.01 (−5.35, 4.72)	1.57 (−2.54, 4.82)	sham

HF-rTMS, high-frequency repetitive transcranial magnetic stimulation; LF-rTMS, low-frequency repetitive transcranial magnetic stimulation; tDCS, transcranial direct current stimulation

(SMD = 13.81, 95% CI: 4.01–22.46), cTBS (SMD = 24.09, 95% CI: 12.35–32.41), dual-tDCS (SMD = 25.4, 95% CI: 8.02–41.88), HF-rTMS (SMD = 19.37, 95% CI: 11.72–25.45), iTBS (SMD = 15.41, 95% CI: 2.11–25.61), and LF-rTMS (SMD = 13.92, 95% CI: 6.53–19.55), and LF-rTMS was also superior to cTBS (SMD=−10.16, 95% CI: −18.18 to −0.95). BL-rTMS had the highest probability of being effective (SUCRA: 100%), and acted as the opti-mal stimulation protocol for ameliorating FMA-UE scores, followed by 3 Hz-rTMS (SUCRA: 72.4%) and LF-rTMS (SUCRA: 72.0%) (Fig. 6C). The funnel plot was glob-ally symmetric, suggesting no significant publication bias (Fig. 6D).

Seven studies [16, 27, 31, 35, 42, 44, 55] reported the long-term effects on mBI (3-month follow-up), with 361 patients treated with LF-rTMS, 3 Hz-rTMS, 5 Hz-rTMS, HF-rTMS, BL-rTMS, cTBS, and iTBS. The net-work diagram showed direct comparisons of LF-rTMS with HF-rTMS, BL-rTMS, and 3 Hz-rTMS, and indi-rect comparisons of cTBS, iTBS, and 5 Hz-rTMS with other interventions (Fig. 7A). The 3-month follow-up results converged satisfactorily (Supplementary File 2), and good consistency was exposed by the node-splitting method. The forest plot revealed that only LF-rTMS (SMD = 15.25, 95% CI: 0–27.11) and BL-rTMS (SMD = 31.15, 95% CI: 12.41–44.26) were superior to
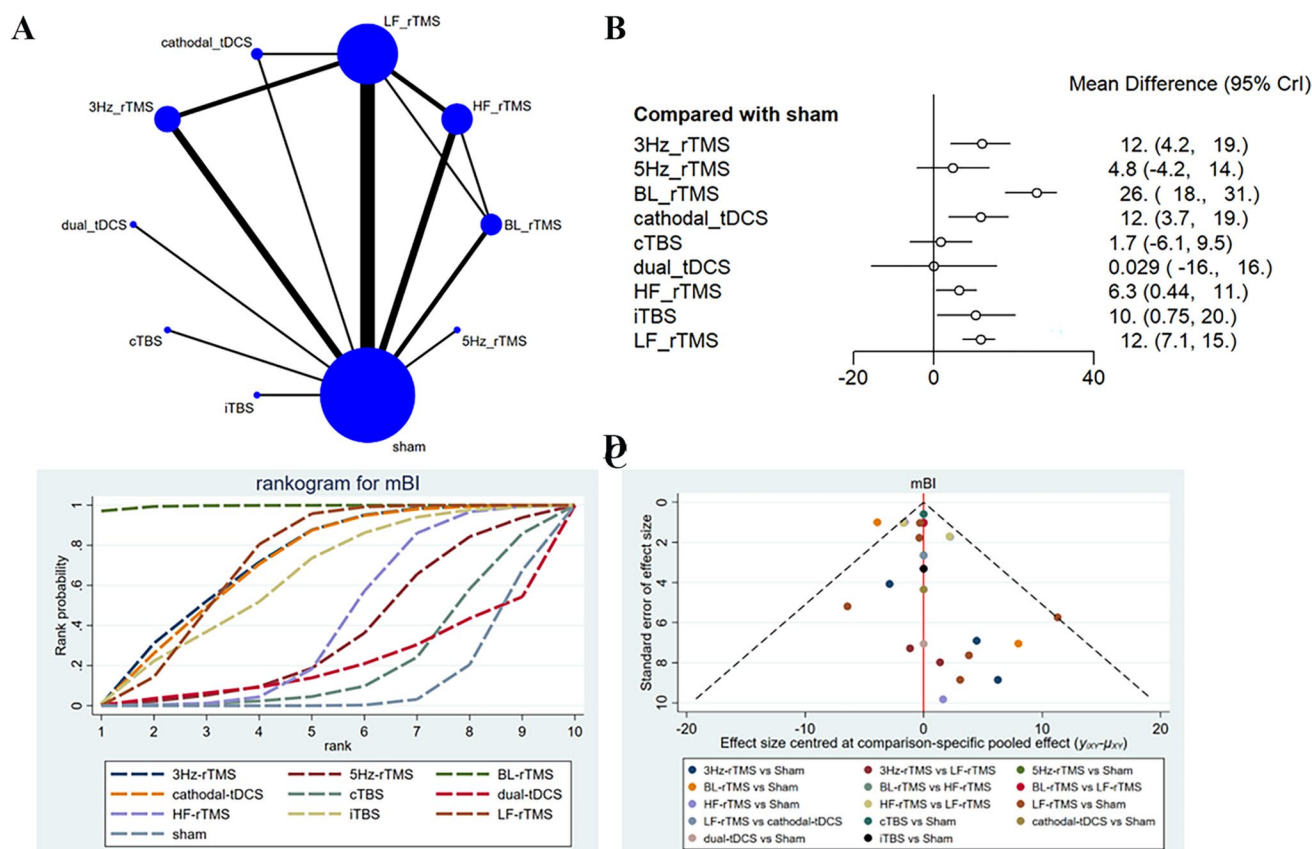
Fig. 6 Network meta-analysis results for mBI (end of treatment). **A**: Network plot; **B**: Forest plot; **C**: Cumulative probability ranking curve of different interventions; **D**: Funnel plot. HF-rTMS, high-frequency repetitive transcranial magnetic stimulation; LF-rTMS, low-frequency repetitive transcranial magnetic stimulation; BL-rTMS, bilateral application of HF- rTMS and LF-rTMS; cTBS, continuous theta-burst stimulation; iTBS, intermittent theta-burst stimulation; tDCS, transcranial direct current stimulation

Table 5 The result of network meta-analysis comparing the effect of all interventions on Modified Barthel Index (end of treatment) including SMD and 95% CI

	3Hz-rTMS	5Hz-rTMS	BL-rTMS	cathodal-tDCS	cTBS	dual-tDCS	HF-rTMS	iTBS	LF-rTMS	sham
3Hz-rTMS	3Hz-rTMS									
5Hz-rTMS	7.2 (-4.92, 18.33)	5Hz-rTMS								
BL-rTMS	**-13.47 (-22.42, -3.7)**	**-20.8 (-30.57, -8.39)**	BL-rTMS							
cathodal-tDCS	0.27 (-9.86, 10.45)	-6.94 (-18.05, 5.32)	**13.81 (4.01, 22.46)**	cathodal-tDCS						
cTBS	10.37 (-0.9, 20.28)	3.14 (-8.76, 14.98)	**24.09 (12.35, 32.41)**	10.13 (-1.41, 20.1)	cTBS					
dual-tDCS	11.91 (-5.54, 29.08)	4.79 (-13.03, 22.85)	**25.4 (8.02, 41.88)**	11.67 (-5.9, 28.75)	1.67 (-15.58, 19.11)	dual-tDCS				
HF-rTMS	5.79 (-2.89, 14.39)	-1.46 (-11.14, 9.55)	**19.37 (11.72, 25.45)**	5.51 (-2.97, 13.95)	-4.72 (-13.12, 5.47)	-6.14 (-22.46, 10.45)	HF-rTMS			
iTBS	1.57 (-11.29, 13.25)	-5.61 (-19, 7.52)	**15.14 (2.11, 25.61)**	1.3 (-11.68, 13.01)	-8.73 (-21.29, 3.56)	-10.44 (-29.05, 8.01)	-4.16 (-15.95, 6.18)	iTBS		
LF-rTMS	0.32 (-7.62, 8.01)	-6.9 (-16.27, 3.5)	**13.92 (6.53, 19.55)**	0.03 (-7.27, 7.1)	**-10.16 (-18.18, -0.59)**	-11.61 (-27.78, 4.69)	-5.44 (-10.83, -0.33)	-1.29 (-11.34, 9.91)	LF-rTMS	
sham	**11.99 (4.16, 18.98)**	4.83 (-4.24, 13.78)	**25.7 (17.81, 30.59)**	**11.74 (3.7, 18.62)**	1.69 (-6.1, 9.49)	0.03 (-15.77, 15.7)	**6.34 (0.44, 10.66)**	**10.44 (0.75, 20.27)**	**11.76 (7.08, 15.3)**	sham

Red and bold numbers are statistically significant. *HF-rTMS;* high-frequency repetitive transcranial magnetic stimulation, *LF-rTMS;* low-frequency repetitive transcranial magnetic stimulation, *BL-rTMS,* bilateral application of HF- rTMS and LF-rTMS, *iTBS;* intermittent theta-burst stimulation, *cTBS;* continuous theta-burst stimulation, *tDCS;* transcranial direct current stimulation

sham in the efficacy (Fig. 7B). No statistically significant difference was observed in the long-term effects of other interventions on mBI (Table 6.). BL-rTMS had the highest probability of being effective (SUCRA: 85.6%), and acted as the optimal stimulation protocol for ameliorating FMA-UE scores, followed by LF-rTMS (SUCRA: 62.2%) and 3 Hz-rTMS (SUCRA: 52.7%) (Fig. 7C). The funnel plot was globally symmetric, with a few studies deviating

from the funnel plot, suggesting low publication bias and reliable results (Fig. 7D).

NIHSS

NIHSS scores of post-early intervention were described in 12 studies [16, 20, 26, 34, 35, 42, 43, 50, 52, 53, 55, 56], with 727 patients treated with LF-rTMS, 3 Hz-rTMS, 5 Hz-rTMS,
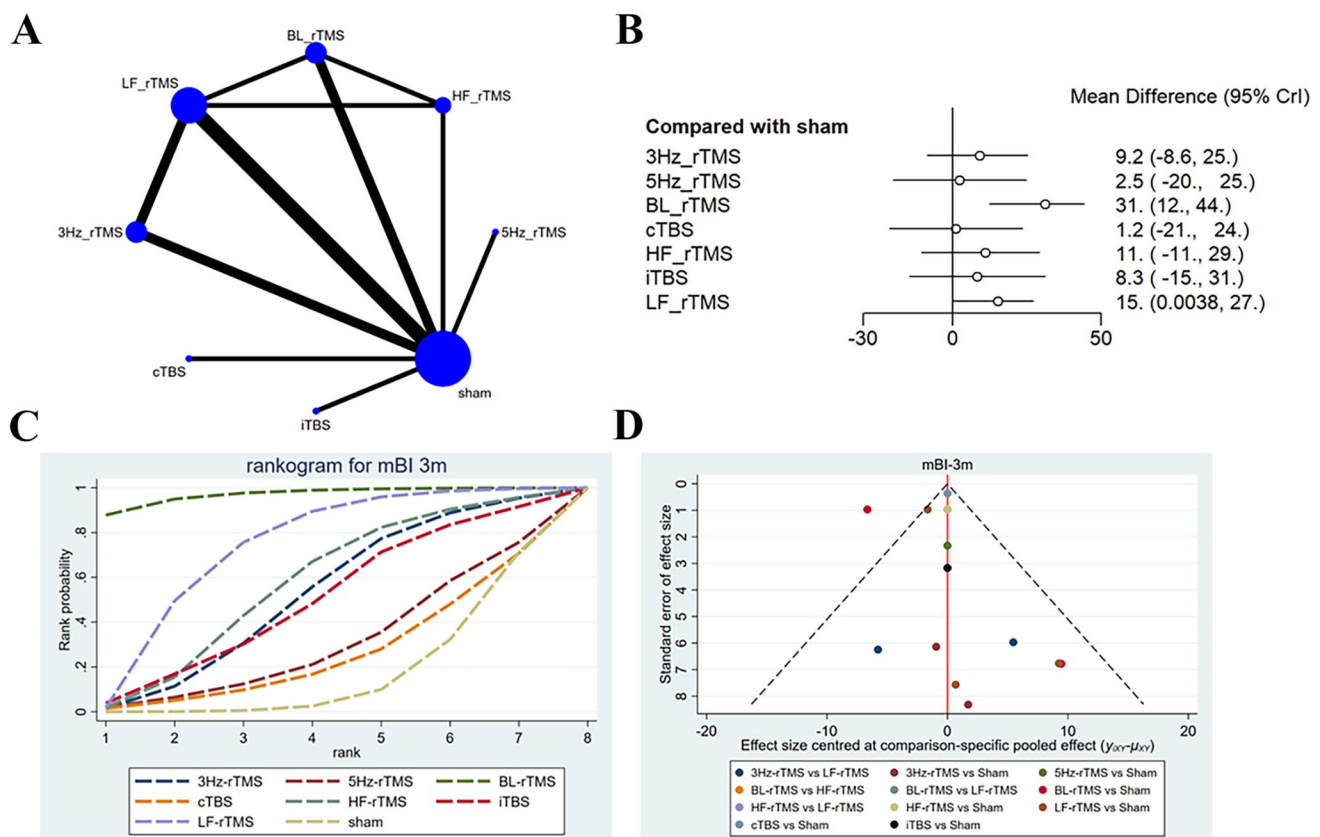
Fig. 7 Network meta-analysis results for mBI (3 month follw-up) (**A**): Network plot; **B**: Forest plot; **C**: Cumulative probability ranking curve of different interventions; **D**: Funnel plot. HF-rTMS, high-frequency repetitive transcranial magnetic stimulation; LF-rTMS, low-frequency repetitive transcranial magnetic stimulation; BL-rTMS, bilateral application of HF- rTMS and LF-rTMS; cTBS, continuous theta-burst stimulation; iTBS, intermittent theta-burst stimulation; tDCS, transcranial direct current stimulation

Table 6. The result of network meta-analysis comparing the effect of all interventions on Modified Barthel Index limb (3 month follw-up) including SMD and 95% CI

	3Hz-rTMS							
5Hz-rTMS	6.75 (-22.24, 33.8)	**5Hz-rTMS**						
BL-rTMS	-21.83 (-41.87, 1.83)	-28.85 (-53.5, 1.72)	**BL-rTMS**					
cTBS	8.08 (-20.79, 35)	1.3 (-30.36, 32.76)	30.29 (-0.3, 54.41)	**cTBS**				
HF-rTMS	-1.55 (-25.45, 23.41)	-8.46 (-36.78, 23.05)	20.61 (-2, 39.89)	-10 (-37.8, 21.79)	**HF-rTMS**			
iTBS	0.99 (-28.63, 28.57)	-5.79 (-37.84, 26.21)	22.97 (-7.88, 48.05)	-7.05 (-39.03, 25.05)	2.64 (-29.14, 31.39)	**iTBS**		
LF-rTMS	-5.89 (-21.73, 11.33)	-12.83 (-37.28, 15.27)	16.12 (-3.11, 32.77)	-14.32 (-38.49, 13.66)	-4.5 (-24.57, 16.25)	-6.98 (-31.93, 21.29)	**LF-rTMS**	
sham	9.15 (-8.57, 25.29)	2.48 (-19.97, 24.83)	**31.15 (12.41, 44.26)**	1.21 (-21.23, 23.63)	11.05 (-10.54, 29.24)	8.28 (-14.63, 31.25)	**15.25 (0, 27.11)**	**sham**

Red and bold numbers are statistically significant. *HF-rTMS*, high-frequency repetitive transcranial magnetic stimulation, *LF-rTMS;* low-frequency repetitive transcranial magnetic stimulation, *BL-rTMS;* bilateral application of HF- rTMS and LF-rTMS, *iTBS;* intermittent theta-burst stimulation, *cTBS;* continuous theta-burst stimulation

HF-rTMS, BL-rTMS, iTBS, anodal-tDCS, and dual-tDCS. The network diagram revealed direct comparisons of LF-rTMS with HF-rTMS, BL-rTMS, and 3 Hz-rTMS, and indirect comparisons of dual-tDCS, iTBS, 5 Hz-rTMS, and anodal-tDCS with other interventions (Fig. 8A). The analysis results converged satisfactorily (Supplementary File 2), and good consistency was exposed by the node-splitting method. The forest plot revealed that LF-rTMS (SMD = 2.36, 95% CI: 1.4–3.19), 3 Hz-rTMS (SMD = 2.54, 95% CI: 1.13–3.91), HF-rTMS

(SMD = 1.39, 95% CI: 0.56–3.58), BL-rTMS (SMD = 4.44, 95% CI: 2.98–5.91), and iTBS (SMD = 1.96, 95% CI: 0.32–20.27) outperformed sham in the efficacy (Fig. 8B). Different interventions had significant differences in the effect on NIHSS scores (Table 7). The efficacy of BL-rTMS was superior to 5 Hz-rTMS (SMD = 3.56, 95% CI: 1.54–5.56), anodal-tDCS (SMD = 4.15, 95% CI: 1.06–7.23), dual-tDCS (SMD = 3.42, 95% CI: 1.39–5.52), HF-rTMS (SMD = 3.05, 95% CI: 1.64–4.48), iTBS (SMD = 2.49, 95% CI: 0.32–4.68),
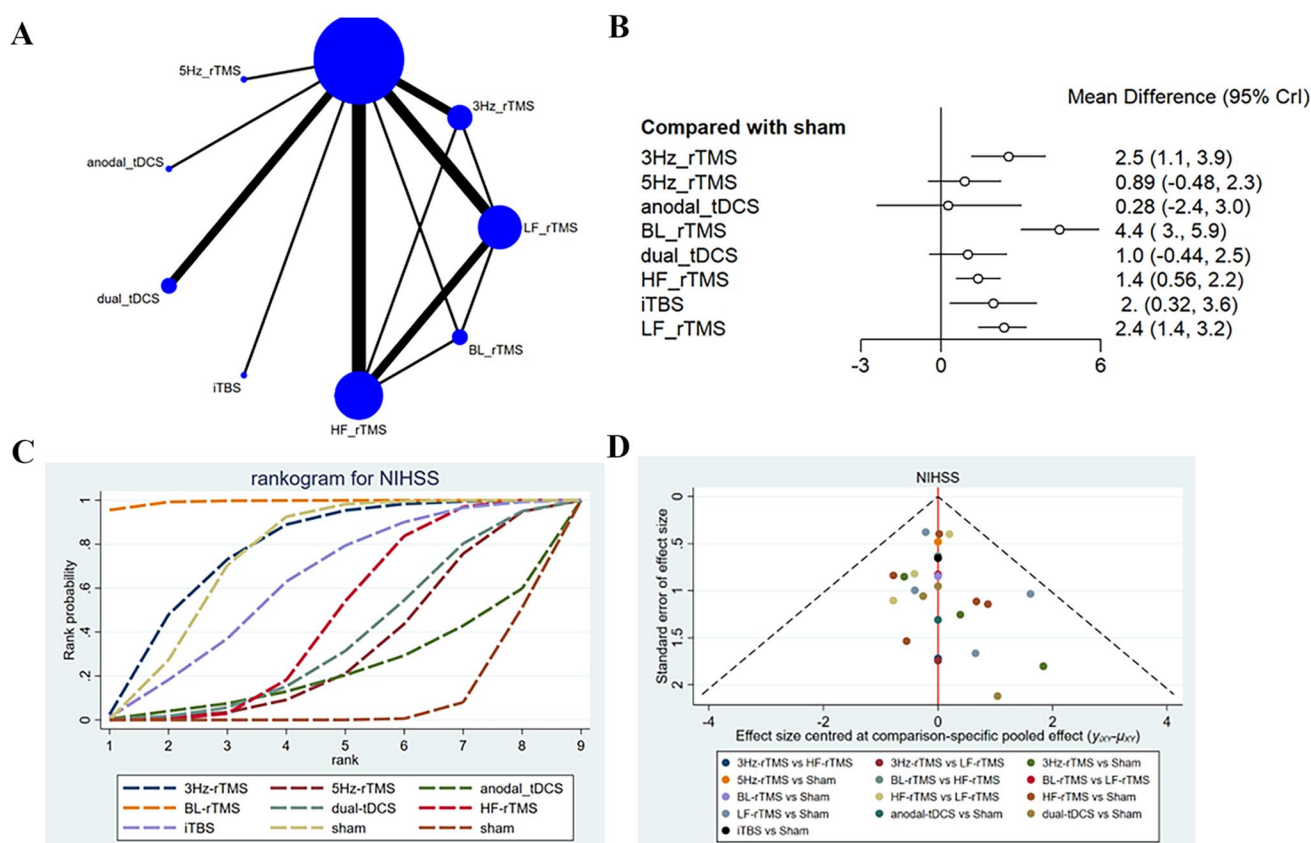
Fig. 8 Network meta-analysis results for NIHSS (end of treatment). **A**: Network plot; **B**: Forest plot; **C**: Cumulative probability ranking curve of different interventions; **D**: Funnel plot. HF-rTMS, high-frequency repetitive transcranial magnetic stimulation; LF-rTMS, low-frequency repetitive transcranial magnetic stimulation; BL-rTMS, bilateral application of HF- rTMS and LF-rTMS; iTBS, intermittent theta-burst stimulation; tDCS, transcranial direct current stimulation

Table 7 The result of network meta-analysis comparing the effect of all interventions on National Institutes of Health Stroke Scale (end of treatment) including SMD and 95% CI

	3Hz-rTMS							
5Hz-rTMS	1.65 (-0.34, 3.53)	**5Hz-rTMS**						
anodal-tDCS	2.27 (-0.82, 5.29)	0.62 (-2.44, 3.64)	**anodal-tDCS**					
BL-rTMS	-1.91 (-3.9, 0.05)	-3.56 (-5.56, -1.54)	-4.15 (-7.23, -1.06)	**BL-rTMS**				
dual-tDCS	1.53 (-0.49, 3.48)	-0.13 (-2.1, 1.9)	-0.73 (-3.81, 2.31)	3.42 (1.39, 5.52)	**dual-tDCS**			
HF-rTMS	1.15 (-0.43, 2.68)	-0.51 (-2.11, 1.11)	-1.13 (-3.96, 1.75)	3.05 (1.64, 4.48)	-0.37 (-2.06, 1.27)	**HF-rTMS**		
iTBS	0.6 (-1.58, 2.66)	-1.07 (-3.17, 1.07)	-1.7 (-4.82, 1.56)	2.49 (0.32, 4.68)	-0.96 (-3.1, 1.25)	-0.57 (-2.39, 1.3)	**iTBS**	
LF-rTMS	0.19 (-1.37, 1.77)	-1.47 (-3.04, 0.24)	-2.07 (-4.91, 0.83)	2.09 (0.63, 3.64)	-1.34 (-3.02, 0.38)	-0.96 (-1.83, -0.01)	-0.39 (-2.22, 1.49)	**LF-rTMS**
sham	2.54 (1.13, 3.91)	0.89 (-0.48, 2.26)	0.28 (-2.42, 3.02)	4.44 (2.98, 5.91)	1.01 (-0.44, 2.45)	1.39 (0.56, 2.22)	1.96 (0.32, 3.58)	2.36 (1.4, 3.19)	sham

Red and bold numbers are statistically significant. HF-rTMS, high-frequency repetitive transcranial magnetic stimulation; LF-rTMS, low-frequency repetitive transcranial magnetic stimulation; BL-rTMS, bilateral application of HF- rTMS and LF-rTMS; iTBS, intermittent theta-burst stimulation; tDCS, transcranial direct current stimulation

and LF-rTMS (SMD = 2.09, 95% CI: 0.63–3.64). BL-rTMS had the highest probability of being effective (SUCRA: 99.7%) and acted as the optimal stimulation protocol for ameliorating FMA-UE scores, followed by 3 Hz-rTMS (SUCRA: 77.9%) and LF-rTMS (SUCRA: 75.7%) (Fig. 8C). The funnel plot was roughly symmetric, suggesting almost no publication bias, and reliable and consistent results (Fig. 8D).

The long-term effects (3-month follow-up) on NIHSS scores were described in six studies [16, 35, 42, 50, 53, 55],

with 271 patients treated with LF-rTMS, 3 Hz-rTMS, 5 Hz-rTMS, HF-rTMS, BL-rTMS, iTBS, and dual-tDCS. The network diagram revealed direct comparisons of LF-rTMS with HF-rTMS, BL-rTMS, and 3 Hz-rTMS, and indirect comparisons of dual-tDCS, iTBS, and 5 Hz-rTMS with other interventions (Fig. 9A). The 3-month follow-up results converged satisfactorily (Supplementary File 2), and good consistency was exposed by the node-splitting method. The forest plot revealed that only BL-rTMS (SMD = 6.36, 95% CI:
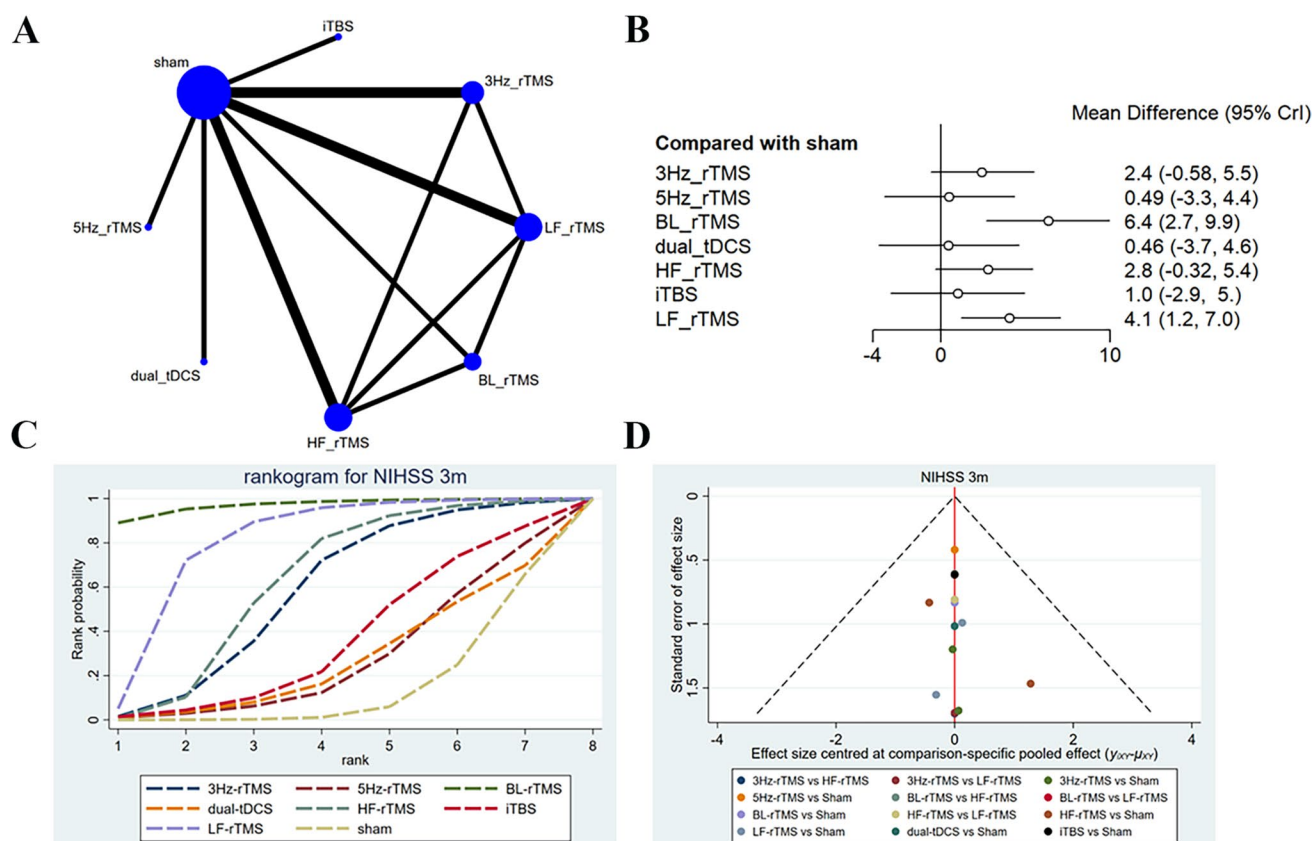
Fig. 9 Network meta-analysis results for NIHSS (3 month follw-up). **A**: Network plot; **B**: Forest plot; **C**: Cumulative probability ranking curve of different interventions; **D**: Funnel plot. HF-rTMS, high-frequency repetitive transcranial magnetic stimulation; LF-rTMS, low-frequency repetitive transcranial magnetic stimulation; BL-rTMS, bilateral application of HF- rTMS and LF-rTMS; iTBS, intermittent theta-burst stimulation; tDCS, transcranial direct current stimulation

2.68–9.93) and LF-rTMS (SMD = 4.07, 95% CI: 1.21–7.04) were superior to sham in the efficacy (Fig. 9B). Different interventions had significant differences in the effect on NIHSS scores (Table 8). The efficacy of BL-rTMS was better than 5 Hz-rTMS (SMD = 5.86, 95% CI: 0.54–11.08), dual-tDCS (SMD = 4.07, 95% CI: 1.21–7.04), and HF-rTMS (SMD = 4.07, 95% CI: 1.21–7.04). BL-rTMS had the highest probability of being effective (SUCRA: 97.05%) and acted as the optimal stimulation protocol for ameliorating

FMA-UE scores, followed by LF-rTMS (SUCRA: 80.0%) and HF-rTMS (SUCRA: 62.0%) (Fig. 9C). The funnel plot was largely symmetric, suggesting almost no publication bias (Fig. 9D).

AEs

AEs were reported in 29 studies (Table 9), including mild AEs (tingling, itching, burning, headache, fatigue,

Table 8 The result of network meta-analysis comparing the effect of all interventions on National Institutes of Health Stroke Scale (3 month follow-up) including SMD and 95% CI

	3Hz-rTMS	5Hz-rTMS	BL-rTMS	dual-tDCS	HF-rTMS	iTBS	LF-rTMS	sham
5Hz-rTMS	1.93 (-2.88, 6.82)	**5Hz-rTMS**						
BL-rTMS	-3.94 (-8.2, 0.48)	**-5.86 (-11.08, -0.54)**	**BL-rTMS**					
dual-tDCS	1.97 (-3.13, 7.12)	0.04 (-5.62, 5.71)	**5.88 (0.33, 11.37)**	**dual-tDCS**				
HF-rTMS	-0.35 (-3.68, 3.42)	-2.31 (-6.85, 2.71)	**3.55 (0.07, 7.4)**	-2.33 (-7.13, 2.94)	**HF-rTMS**			
iTBS	1.42 (-3.5, 6.42)	-0.52 (-5.95, 5)	5.35 (-0.04, 10.61)	-0.55 (-6.2, 5.23)	1.8 (-3.32, 6.43)	**iTBS**		
LF-rTMS	-1.63 (-5.19, 1.9)	-3.56 (-8.41, 1.18)	2.31 (-1.56, 5.92)	-3.59 (-8.7, 1.41)	-1.26 (-4.86, 1.7)	-3.06 (-8.02, 1.78)	**LF-rTMS**	
sham	2.43 (-0.58, 5.49)	0.49 (-3.33, 4.36)	**6.36 (2.68, 9.93)**	0.46 (-3.66, 4.6)	2.79 (-0.32, 5.44)	1 (-2.94, 4.96)	**4.07 (1.21, 7.04)**	**sham**

Red and bold numbers are statistically significant. *HF-rTMS;* high-frequency repetitive transcranial magnetic stimulation, *LF-rTMS;* low-frequency repetitive transcranial magnetic stimulation, *BL-rTMS;* bilateral application of HF- rTMS and LF-rTMS, *iTBS,* intermittent theta-burst stimulation, *tDCS;* transcranial direct current stimulation

Table 9 Summary of adverse events

Study	Sessions	E/C	n	AE
Vink [27]	10	cTBS	28	headache(10 cases); Muscle pain(2 cases)
		sham	31	Nausea(1 case); headache(3 cases); Sensory impairment(1 case); Slowed thinking(2 cases)
Garrido [28]	7	dual-tDCS	29	itching(18) cases; tingling(10 cases); headache(3 cases); burning(3 cases); fatigued(2 cases)
		Sham	27	itching(14 cases); tingling(7 cases); headache(2 cases); burning(2 cases); fatigued(1 case)
Zhao [29]	12	dual-tDCS	30	slight tingling pain(1 case)
		Control	30	None
Komatsu [30]	10	HF-rTMS	22	None
		Control	22	None
Klomjai [19]	5	anodal-tDCS	20	tingling(50%); dizziness (20%); itching(10%); burning(10%); sleepiness(10%)
		cathodal-tDCS	18	
		dual-tDCS	20	
		Sham	20	None
Chen [16]	20	BL-rTMS	22	headache(1 case); tingling(1 case)
		Sham	22	None
Chen [31]	20	BL-rTMS	25	headache(3 cases); tingling(2 cases)
		HF-rTMS	25	
		LF-rTMS	25	
		Sham	25	None
Kim [32]	15	LF-rTMS	8	None
		Control	12	None
Ke [33]	10	HF-rTMS	32	None
		Sham	16	None
Bolognini [34]	10	dual-tDCS	16	No severe AEs
		Sham	16	No severe AEs
Du [20]	5	HF-rTMS	18	headache(2 cases)
		LF-rTMS	19	None
		Sham	16	None
Bornheim [36]	20	anodal-tDCS	23	tingling(22 cases); itching(15 cases); burning(9 cases); headache(2 cases)
		Sham	23	tingling(18 cases); itching(12 cases); burning(11 cases)
Watanabe [37]	10	iTBS	8	None
		LF-rTMS	7	None
		Sham	6	None
Long [38]	15	LF-rTMS	21	None
		BL-rTMS	21	None
		Sham	20	None
Li [39]	10	5 Hz rTMS	6	None
		Sham	6	None
Rabadi [40]	10	cathodal-tDCS	8	Tingling(NR)
		Sham	8	tingling(NR)
Oveisgharan [41]	10	dual-tDCS	10	None
		Sham	10	None
Guan [42]	10	5 Hz rTMS	13	None
		Sham	14	None
Guo [43]	10	HF-rTMS	7	None
		Sham	8	None
Du [44]	5	3 Hz rTMS	20	headache(3 cases); tingling(1 case)
		LF-rTMS	16	
		Sham	19	None
Matsuura [45]	5	LF-rTMS	10	None
		Sham	10	None

Table 9 (continued)

Study	Sessions	E/C	n	AE
Sasaki [47]	5	HF-rTMS	31	None
		BL-rTMS	27	None
Kim [48]	5	LF-rTMS	22	None
		Sham	10	None
Sasaki [51]	5	LF-rTMS	11	None
		HF-rTMS	9	None
		Sham	9	None
Rossi [52]	5	anodal-tDCS	25	None
		Sham	25	None
Khedr [53]	5	3 Hz rTMS	16	None
		HF-rTMS	16	None
		Sham	16	None
Chang [54]	10	HF-rTMS	18	None
		Sham	10	None
Khedr [55]	5	LF-rTMS	12	None
		3 Hz rTMS	12	None
		Sham	12	None
Khedr [56]	10	3 Hz rTMS	26	headache(NR)
		Sham	26	None

drowsiness, and dizziness), and severe AEs (stroke recurrence, worsened nerve injury indicated by changes in NIHSS or mRS scores, and epileptic seizure). Overall, no severe AEs were caused by stimulations in the included studies, and all mild AEs resolved spontaneously after treatment. The incidence rate of AEs for each protocol is shown in Table 10.

Discussion

This NMA included 37 studies involving 1731 patients, and the differences in the efficacy between tDCS and rTMS protocols were compared, thereby providing a rationale for the recovery of motor function, ADL, and neurological function in early stroke patients following TMS and tDCS, as well

Table 10 Incidence of adverse events

Treatment	LF-rTMS	HF-rTMS	BL-rTMS	cTBS	iTBS	dual-tDCS	anodal-tDCS	5 Hz-rTMS	3 Hz-rTMS	sham
No. of studies	8	8	3	1	1	3	2	2	2	19
Sample siza	110	153	70	28	8	69	48	19	28	317
treatment sessions	875	1160	890	280	80	663	585	190	140	2889
headache	0	2	1	10	0	3	2	0	0	5
Muscle pain	0	0	0	2	0	0	0	0	0	0
Nausea	0	0	0	0	0	0	0	0	0	1
Sensory impairment	0	0	0	0	0	0	0	0	0	1
Slowed thinking	0	0	0	0	0	0	0	0	0	2
itching	0	0	0	0	0	18	15	0	0	26
tingling	0	0	1	0	0	11	22	0	0	25
burning	0	0	0	0	0	3	9	0	0	13
fatigued	0	0	0	0	0	2	0	0	0	1
dizziness	0	0	0	0	0	0	0	0	0	0
sleepiness	0	0	0	0	0	0	0	0	0	0
Total probability	0.00%	0.17%	0.22%	4.29%	0.00%	5.58%	8.21%	0.00%	0.00%	2.56%

as for the safety of early interventions. In terms of motor function, early BL-rTMS improved FMA-UE scores and achieved a long-term effect compared with other protocols; for the lower extremity motor function, none of the stimulation protocols included had a statistically significant difference in FMA-LE improvement from the control group. In terms of ADL, early BL-rTMS, LF-rTMS, HF-rTMS, 3 Hz-rTMS, iTBS, and cathodal-tDCS were all more effective than sham or conventional treatment alone, with LF-rTMS and BL-rTMS exerting long-term effects of improving mBI. Moreover, LF-rTMS, 3Hzr-TMS, HF-rTMS, BL-rTMS, and iTBS were more effective than sham in improving NIHSS scores, with BL-rTMS and LF-rTMS exerting long-term effects. To sum up, BL-rTMS is the optimal early stimulation protocol for ameliorating upper extremity motor function, ADL, and neurological function, achieving long-term effects. Besides, neither early rTMS nor tDCS led to severe AEs within 30 days after the onset of the disease.

Patients often experience multiple dysfunctions, primarily motor dysfunction, following a stroke, which can severely impact their quality of life [3]. FMA-UE and FMA-LE scales are designed to assess upper and lower extremity motor function, with good reliability and validity [57] In this NMA, early BL-rTMS was the most effective in improving upper extremity motor function in stroke patients. Stroke usually induces an imbalance of interhemispheric inhibition [58, 59], and BL-rTMS may contribute to motor functional improvement by restoring the balance of interhemispheric cortical excitability [60]. The effects of LF-rTMS, HF-rTMS, and BL-rTMS on cortical excitability in early stroke patients have been studied [16], and the results showed that both the amplitude of motor evoked potentials and resting motor thresholds are improved more significantly in the BL-rTMS group than other groups. Such improvement in motor function displays a significant correlation with the change in motor cortex excitability in the affected hemisphere [61]. BL-rTMS produces a synergistic effect by combining inhibitory and facilitatory stimulations [16, 62], enhancing the coordination of interhemispheric competition [20], which may account for the superiority of BL-rTMS.

In this NMA, LF-rTMS had the highest probability of being effective in improving the lower extremity motor function based on SUCRA, similar to previous findings [63]. An NMA on the effect of different types of rTMS on lower extremity motor function [63] has manifested that LF-rTMS ranks first in efficacy and only LF-rTMS outperforms sham in improving lower extremity motor function. In this NMA, however, the stimulations showed no statistically significant difference in the improvement of FMA-LE as compared to sham. The inconsistent findings may be attributed to the small number of studies involving FMA-LE and samples, and high heterogeneity. Therefore, it is recommended that more studies on the

effect of early NIBS on FMA-LE should be included to further verify the efficacy of different stimulations on early stroke.

Post-stroke dysfunction seriously affects patients' ADL. mBI is a widely-used tool for assessing ADL in stroke patients, with good reliability, validity, and sensitivity [64]. In this NMA, BL-rTMS was the best protocol for improving mBI after intervention and at 3-month follow-up, consistent with the findings of Chen et al. [65], who reported that BL-rTMS was the most effective in improving FMA, mBI, and NIHSS scores in acute stroke patients. Improvement in upper extremity motor function contributes to better ADL, the latter of which is not solely based on improvement in arm function on the hemiplegic side [66] but on a generalized treatment effect. Sasaki et al. [47] found that BL-rTMS is far better than HF-rTMS as assessed by the Brunnstrom Recovery Stage, possibly indicating the benefits of BL-rTMS in ameliorating the overall function in hemiplegic patients.

NIHSS scores are a good indicator of the severity of post-stroke nerve injury [67, 68]. In this NMA, BL-rTMS performed best in improving the NIHSS scores after early intervention and at 3-month follow-up. The reason is that with a synergistic effect of low- and high-frequency stimulation, BL-rTMS can excite/inhibit the corresponding cerebral cortex, thereby ameliorating the neurological function [16, 62].

In the acute stage (within one week after stroke onset), restorative therapy is initiated in relatively few studies [4, 7] NIBS is a promising therapy in the acute stage, but the safety of its early use, especially the risk of post-injury epileptic seizure [69], is one of the major concerns [70]. In this NMA, 21 out of the 37 included studies involved acute-phase interventions within one week in stroke (infarction and hemorrhage) by LF-rTMS, 3 Hz-rTMS, 5 Hz-rTMS, HF-rTMS, BL-rTMS, iTBS, cathodal-tDCS, anodal-tDCS, and dual-tDCS. No severe AEs were reported, while only mild AEs such as dizziness, tingling, fatigue, and itching occurred, which were relieved after resting, proving to a certain extent the safety of early intervention. Specifically, LF-rTMS, iTBS, and 5 Hz-rTMS showed a rate of AEs of 0%, exhibiting a better safety profile. Previous study [71] has concluded that LF-rTMS has higher safety; in particular, low-frequency stimulation helps to reduce cortical hyperexcitability in early stroke patients, thereby reducing the potential risk. However, not all of the included studies reported AEs in a strict and standardized manner, and thus further statistical analyses of the incidence of AEs following different interventions had to be abandoned. Therefore, it is recommended that AEs should be reported rigorously and in detail in future studies to provide guidance on the safety of early NIBS.

This study still had some limitations. First, the duration of intervention, site of stimulation, and severity of stroke varied across the included studies, leading to potential heterogeneity. Second, despite complete protocols of stimulation, the sample sizes were small in the iTBS and cTBS groups, each accounting for 2.53% of the total, which

affected to some extent the quality of the findings. In addition, not all of the included studies reported AEs rigorously. Therefore, the safety of each intervention protocol remains to be further investigated. Finally, as non-English-language studies were not included in this NMA, relevant studies of other languages may be missed.

Conclusion

BL-rTMS is the optimal stimulation protocol for improving upper extremity motor function, ADL, and neurological function in early stroke, with its positive effects persisting for at least three months. However, the conclusions need to be further verified. It is recommended that BL-rTMS should be used as an adjuvant therapy in early stroke rehabilitation in clinical practice. In the future, high-quality, large-sample, multicenter, long-term follow-up randomized controlled trials are required to validate these findings.

Declarations

Ethical statement As this was a systematic review and meta-analysis, ethical approval was not necessary.

Consent to participate Not applicable.

Competing interests The authors have no competing interests to declare that are relevant to the content of this article.

References

1. Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP et al (2019) Heart Disease and Stroke Statistics—2019 update: a Report from the American Heart Association. Circulation 139(10). https://doi.org/10.1161/cir.0000000000000659

2. Rajsic S, Gothe H, Borba HH, Sroczynski G, Vujicic J, Toell T et al (2018) Economic burden of stroke: a systematic review on post-stroke care. Eur J Health Econ 20(1):107–134. https://doi.org/10.1007/s10198-018-0984-0

3. Johnson CO, Nguyen M, Roth GA, Nichols E, Alam T, Abate D et al (2019) Global, regional, and national burden of stroke, 1990–2016: a systematic analysis for the global burden of Disease Study 2016. Lancet Neurol 18(5):439–458. https://doi.org/10.1016/s1474-4422(19)30034-1

4. Bernhardt J, Hayward KS, Kwakkel G, Ward NS, Wolf SL, Borschmann K et al (2017) Agreed definitions and a shared vision for new standards in stroke recovery research: the Stroke Recovery and Rehabilitation Roundtable taskforce. Int J Stroke 12(5):444–450. https://doi.org/10.1177/1747493017711816

5. Clarkson AN, Huang BS, Macisaac SE, Mody I, Carmichael ST (2010) Reducing excessive GABA-mediated tonic inhibition promotes functional recovery after stroke. Nature 468(7321):305–309. https://doi.org/10.1038/nature09511

6. Krakauer JW, Carmichael ST, Corbett D, Wittenberg GF (2012) Getting neurorehabilitation right: what can be learned from animal models? Neurorehabil Neural Repair 26(8):923–931. https://doi.org/10.1177/1545968312440745

7. Coleman ER, Moudgal R, Lang K, Hyacinth HI, Awosika OO, Kissela BM et al (2017) Early Rehabilitation after Stroke: a Narrative Review. Curr Atheroscler Rep 19(12):59. https://doi.org/10.1007/s11883-017-0686-6

8. group ATC (2015) Efficacy and safety of very early mobilisation within 24 h of stroke onset (AVERT): a randomised controlled trial. Lancet 386(9988):46–55. https://doi.org/10.1016/s0140-6736(15)60690-0

9. Carey JR, Chappuis DM, Finkelstein MJ, Frost KL, Leuty LK, McNulty AL et al (2017) Importance and difficulties of pursuing rTMS Research in Acute Stroke. Phys Ther 97(3):310–319. https://doi.org/10.1093/ptj/pzx005

10. Tomeh A, Khan A, Sulaiman WAW (2022) Repetitive transcranial magnetic stimulation of the primary motor cortex in stroke survivors-more than motor rehabilitation: a mini-review. Front Aging Neurosci 14:7. https://doi.org/10.3389/fnagi.2022.897837

11. Miu KYD, Kok C, Leung SS, Chan EYL, Wong E (2020) Comparison of Repetitive Transcranial Magnetic Stimulation and Transcranial Direct Current Stimulation on Upper Limb Recovery among patients with recent stroke. Annals Rehabilitation Medicine-Arm 44(6):428–437. https://doi.org/10.5535/arm.20093

12. Badoiu A, Mitran SI, Catalin B, Balseanu TA, Popa-Wagner A, Gherghina FL et al (2023) From Molecule to Patient Rehabilitation: The Impact of Transcranial Direct Current Stimulation and Magnetic Stimulation on Stroke-A Narrative Review. Neural Plast 2023:5044065. https://doi.org/10.1155/2023/5044065

13. Cai M, Zhang JL, Wang XJ, Cai KR, Li SY, Du XL et al (2024) Clinical application of repetitive transcranial magnetic stimulation in improving functional impairments post-stroke: review of the current evidence and potential challenges. Neurol Sci 45(4):1419–1428. https://doi.org/10.1007/s10072-023-07217-6

14. Jiang TT, Wei XP, Wang MZ, Xu J, Xia N, Lu M (2024) Theta burst stimulation: what role does it play in stroke rehabilitation? A

systematic review of the existing evidence. BMC Neurol 24(1):23. https://doi.org/10.1186/s12883-023-03492-0

15. Juan D, Yao W, Li J, Yang F, Hu J, Xu Q et al (2022) Motor Network Reorganization After Repetitive Transcranial Magnetic Stimulation in Early Stroke Patients: a Resting State fMRI Study. Neurorehabilitation and neural repair 36(1):61-68. https://doi.org/10.1177/15459683211054184

16. Chen QM, Shen D, Sun HW, Ke J, Wang HX, Pan SJ et al (2021) Effects of coupling inhibitory and facilitatory repetitive transcranial magnetic stimulation on motor recovery in patients following acute cerebral infarction. NeuroRehabilitation 48(1):83–96. https://doi.org/10.3233/nre-201606

17. Zhang L, Xing G, Fan Y, Guo Z, Chen H, Mu Q (2017) Short- and long-term effects of Repetitive Transcranial Magnetic Stimulation on Upper Limb Motor function after stroke: a systematic review and Meta-analysis. Clin Rehabil 31(9):1137–1153. https://doi.org/10.1177/0269215517692386

18. Hara Y (2015) Brain plasticity and rehabilitation in stroke patients. J Nippon Med Sch 82(1):4–13. https://doi.org/10.1272/jnms.82.4

19. Klomjai W, Aneksan B, Chotik-Anuchit S, Jitkaew P, Chaichanudomsuk K, Piriyaprasarth P et al (2022) Effects of different montages of Transcranial Direct current stimulation on haemodynamic responses and motor performance in Acute Stroke: a Randomized Controlled Trial. J Rehabil Med 54:jrm00331. https://doi.org/10.2340/jrm.v54.3208

20. 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. https://doi.org/10.1016/j.nicl.2018.101620

21. Leucht S, Chaimani A, Cipriani AS, Davis JM, Furukawa TA, Salanti G (2016) Network meta-analyses should be the highest level of evidence in treatment guidelines. Eur Arch Psychiatry Clin Neurosci 266(6):477–480. https://doi.org/10.1007/s00406-016-0715-4

22. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD et al (2021) The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. PLoS Med 18(3):e1003583. https://doi.org/10.1371/journal.pmed.1003583

23. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, 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(11):777–784. https://doi.org/10.7326/m14-2385

24. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I et al (2019) RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 366:l4898. https://doi.org/10.1136/bmj.l4898

25. Yagüe S, Veciana M, Martínez-Yélamos A, Pedro J, Cardona P, Quesada H et al (2023) Effects of Bihemispheric Transcranial Direct current stimulation combined with repetitive peripheral nerve stimulation in Acute Stroke patients. J Clin Neurophysiol 40(1):63–70. https://doi.org/10.1097/WNP.0000000000000840

26. Wang C, Zeng Q, Yuan Z, Wang W, 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(1):11–18. https://doi.org/10.1097/nrl.0000000000000435

27. Vink JJT, Van Lieshout ECC, Otte WM, Van Eijk RPA, Kouwenhoven M, Neggers SFW et al (2023) Continuous Theta-Burst Stimulation of the Contralesional Primary Motor Cortex for Promotion of Upper Limb Recovery after Stroke: a Randomized Controlled Trial. Stroke 54(8):1962–1971. https://doi.org/10.1161/STROKEAHA.123.042924

28. Garrido M, Alvarez EE, Acevedo PF, Moyano VA, Castillo NN, Ch GC (2023) Early transcranial direct current stimulation with modified constraint-induced movement therapy for motor and functional upper limb recovery in hospitalized patients with stroke: a randomized, multicentre, double-blind, clinical trial. Brain Stimul 16(1):40–47. https://doi.org/10.1016/j.brs.2022.12.008

29. Zhao L, Liu Z, Sun Q, Li H (2022) Effect of transcranial direct current stimulation combined with a smart hand joint training device on hand dysfunction in patients with early stroke. Folia Neuropathol 60(2):177–184. https://doi.org/10.5114/fn.2022.117534

30. Komatsu T, Hada T, Sasaki N, Kida H, Takahashi J, Maku T et al (2022) Effects and safety of high-frequency rTMS in acute intracerebral hemorrhage patients: a pilot study. J Neurol Sci 443. https://doi.org/10.1016/j.jns.2022.120473

31. Chen QM, Yao FR, Sun HW, Chen ZG, Ke J, Liao J et al (2021) Combining inhibitory and facilitatory repetitive transcranial magnetic stimulation (rTMS) treatment improves motor function by modulating GABA in acute ischemic stroke patients. Restor Neurol Neurosci 39(6):419–434. https://doi.org/10.3233/RNN-211195

32. Kim JH, Han JY, Song MK, Park GC, Lee JS (2020) Synergistic effects of Scalp acupuncture and Repetitive Transcranial Magnetic Stimulation on cerebral infarction: a Randomized Controlled Pilot Trial. Brain Sci 10(2). https://doi.org/10.3390/brainsci10020087

33. Ke J, Zou X, Huang M, Huang Q, Li H, Zhou X (2020) High-frequency rTMS with two different inter-train intervals improves upper limb motor function at the early stage of stroke. J Int Med Res 48(6). https://doi.org/10.1177/0300060520928737

34. Bolognini N, Russo C, Souza MIC, Nicotra A, Olgiati E, Spandri V et al (2020) Bi-hemispheric transcranial direct current stimulation for upper-limb hemiparesis in acute stroke: a randomized, double-blind, sham-controlled trial. Eur J Neurol 27(12):2473–2482. https://doi.org/10.1111/ene.14451

35. Khan F, Rathore C, Kate M, Joy J, Zachariah G, Vincent PC et al (2019) The comparative efficacy of theta burst stimulation or functional electrical stimulation when combined with physical therapy after stroke: a randomized controlled trial. Clin Rehabil 33(4):693–703. https://doi.org/10.1177/0269215518820896

36. Bornheim S, Croisier JL, Maquet P, Kaux JF (2019) Transcranial direct current stimulation associated with physical-therapy in acute stroke patients - a randomized, triple blind, sham-controlled study. Brain Stimul 13(2):329–336. https://doi.org/10.1016/j.brs.2019.10.019

37. Watanabe K, Kudo Y, Sugawara E, Nakamizo T, Amari K, Takahashi K et al (2018) Comparative study of ipsilesional and contralesional repetitive transcranial magnetic stimulations for acute infarction. J Neurol Sci 384:10–14. https://doi.org/10.1016/j.jns.2017.11.001

38. Long H, Wang H, Zhao C, Duan Q, Feng F, Hui N et al (2018) Effects of combining high- and low-frequency repetitive transcranial magnetic stimulation on upper limb hemiparesis in the early phase of stroke. Restor Neurol Neurosci 36(1):21–30. https://doi.org/10.3233/RNN-170733

39. Li J, Zuo Z, Zhang X, Shao X, Lu J, Xue R et al (2018) Excitatory repetitive transcranial magnetic stimulation induces contralesional cortico-cerebellar pathways after acute ischemic stroke: a preliminary DTI study. Front Behav Neurosci 12. https://doi.org/10.3389/fnbeh.2018.00160

40. Rabadi MH, Aston CE (2017) Effect of Transcranial Direct Current Stimulation on severely affected arm-hand motor function in patients after an Acute ischemic stroke: a pilot randomized Control Trial. Am J Phys Med Rehabil 96(10 Suppl 1):S178–S184. https://doi.org/10.1097/PHM.0000000000000823

41. Oveisgharan S, Organji H, Ghorbani A (2017) Enhancement of Motor Recovery through Left Dorsolateral Prefrontal Cortex Stimulation after Acute ischemic stroke. J Stroke Cerebrovasc Dis 27(1):185–191. https://doi.org/10.1016/j.jstrokecerebrovasdis.2017.08.026

42. Guan YZ, Li J, Zhang XW, Wu S, Du H, Cui LY et al (2017) Effectiveness of repetitive transcranial magnetic stimulation (rTMS) after acute stroke: a one-year longitudinal randomized

trial. CNS Neurosci Ther 23(12):940–946. https://doi.org/10.1111/cns.12762

43. Guo ZW, Jin Y, Peng HT, Xing GQ, Liao X, Wang YF et al (2016) Ipsilesional high frequency repetitive transcranial magnetic stimulation Add-On Therapy Improved Diffusion parameters of Stroke patients with Motor Dysfunction: a preliminary DTI Study. https://doi.org/10.1155/2016/6238575. Neural Plasticity 2016

44. Du J, Tian L, Liu W, Hu J, Xu G, Ma M et al (2016) Effects of repetitive transcranial magnetic stimulation on motor recovery and motor cortex excitability in patients with stroke: a randomized controlled trial. Eur J Neurol 23(11):1666–1672. https://doi.org/10.1111/ene.13105

45. Matsuura A, Onoda K, Oguro H, Yamaguchi S (2015) Magnetic stimulation and movement-related cortical activity for acute stroke with hemiparesis. Eur J Neurol 22(12):1526–1532. https://doi.org/10.1111/ene.12776

46. Chang MC, Kim DY, Park DH (2015) Enhancement of cortical excitability and lower Limb Motor function in patients with stroke by Transcranial Direct Current Stimulation. Brain Stimul 8(3):561–566. https://doi.org/10.1016/j.brs.2015.01.411

47. Sasaki N, Kakuda W, Abo M (2014) Bilateral high- and low-frequency rTMS in acute stroke patients with hemiparesis: a comparative study with unilateral high-frequency rTMS. Brain Injury 28(13–14):1682–1686. https://doi.org/10.3109/02699052.2014.947626

48. Kim WS, Jung SH, Oh MK, Min YS, Lim JY, Paik NJ (2014) Effect of repetitive transcranial magnetic stimulation over the cerebellum on patients with ataxia after posterior circulation stroke: a pilot study. J Rehabil Med 46(5):418–423. https://doi.org/10.2340/16501977-1802

49. Fusco A, Assenza F, Iosa M, Izzo S, Altavilla R, Paolucci S et al (2014) The ineffective role of cathodal tDCS in enhancing the functional motor outcomes in early phase of stroke rehabilitation: an experimental trial. Biomed Res Int 2014:547290. https://doi.org/10.1155/2014/547290

50. Di Lazzaro V, Dileone M, Capone F, Pellegrino G, Ranieri F, Musumeci G et al (2014) Immediate and late modulation of interhemispheric imbalance with bilateral transcranial direct current stimulation in acute stroke. Brain Stimul 7(6):841–848. https://doi.org/10.1016/j.brs.2014.10.001

51. Sasaki N, Mizutani S, Kakuda W, Abo M (2013) Comparison of the effects of high- and low-frequency repetitive transcranial magnetic stimulation on upper limb hemiparesis in the early phase of stroke. J Stroke Cerebrovasc Dis 22(4):413–418. https://doi.org/10.1016/j.jstrokecerebrovasdis.2011.10.004

52. Rossi C, Sallustio F, Di Legge S, Stanzione P, Koch G (2012) Transcranial direct current stimulation of the affected hemisphere does not accelerate recovery of acute stroke patients. Eur J Neurol 20(1):202–204. https://doi.org/10.1111/j.1468-1331.2012.03703.x

53. Khedr EM, Etraby AE, Hemeda M, Nasef AM, Razek AAE (2010) Long-term effect of repetitive transcranial magnetic stimulation on motor function recovery after acute ischemic stroke. Acta Neurol Scand 121(1):30–37. https://doi.org/10.1111/j.1600-0404.2009.01195.x

54. Chang WH, Kim YH, Bang OY, Kim ST, Park YH, Lee PK (2010) Long-term effects of rTMS on motor recovery in patients after subacute stroke. J Rehabil Med 42(8):758–764. https://doi.org/10.2340/16501977-0590

55. Khedr EM, Abdel-Fadeil MR, Farghali A, Qaid M (2009) Role of 1 and 3 hz repetitive transcranial magnetic stimulation on motor function recovery after acute ischaemic stroke. Eur J Neurol 16(12):1323–1330. https://doi.org/10.1111/j.1468-1331.2009.02746.x

56. Khedr EM, Ahmed MA, Fathy N, Rothwell JC (2005) Therapeutic trial of repetitive transcranial magnetic stimulation after acute ischemic stroke. Neurology 65(3):466–468. https://doi.org/10.1212/01.wnl.0000173067.84247.36

57. Sullivan KJ, Tilson JK, Cen SY, Rose DK, Hershberg J, Correa A et al (2011) Fugl-Meyer assessment of sensorimotor function after stroke: standardized training procedure for clinical practice and clinical trials. Stroke 42(2):427–432. https://doi.org/10.1161/strokeaha.110.592766

58. Zappasodi F, Tecchio F, Marzetti L, Pizzella V, Di Lazzaro V, Assenza G (2019) Longitudinal quantitative electroencephalographic study in mono-hemispheric stroke patients. Neural Regen Res 14(7):1237–1246. https://doi.org/10.4103/1673-5374.251331

59. 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(10):597–608. https://doi.org/10.1038/nrneurol.2014.162

60. Boonzaier J, van Tilborg GAF, Neggers SFW, Dijkhuizen RM (2018) Noninvasive brain stimulation to Enhance Functional Recovery after Stroke: studies in animal models. Neurorehabil Neural Repair 32(11):927–940. https://doi.org/10.1177/1545968318804425

61. Rodríguez A, Amaya-Pascasio L, Gutiérrez-Fernández M, García-Pinteño J, Moreno M, Martínez-Sánchez P (2024) Non-invasive brain stimulation for functional recovery in animal models of stroke: a systematic review. Neurosci Biobehav Rev 156:17. https://doi.org/10.1016/j.neubiorev.2023.105485

62. Sung WH, Wang CP, Chou CL, Chen YC, Chang YC, Tsai PY (2013) Efficacy of coupling inhibitory and facilitatory repetitive transcranial magnetic stimulation to enhance motor recovery in hemiplegic stroke patients. Stroke 44(5):1375–1382. https://doi.org/10.1161/strokeaha.111.000522

63. Xie YJ, Chen Y, Tan HX, Guo QF, Lau BWM, Gao Q (2021) Repetitive transcranial magnetic stimulation for lower extremity motor function in patients with stroke: a systematic review and network meta-analysis. Neural Regen Res 16(6):1168–1176. https://doi.org/10.4103/1673-5374.300341

64. Quinn TJ, Langhorne P, Stott DJ (2011) Barthel Index for Stroke Trials Development, Properties, and application. Stroke 42(4):1146–1151. https://doi.org/10.1161/strokeaha.110.598540

65. Chen Y, Yang L, Li X, Tang L, Pi Y, Bai D (2023) Non-invasive brain stimulation for limb motor function and daily living activity improvement in acute stroke: a meta-analysis. J Stroke Cerebrovasc Dis 32(4):106982. https://doi.org/10.1016/j.jstrokecerebrovasdis.2023.106982

66. Ahmed I, Mustafaoglu R, Rossi S, Cavdar FA, Agyenkwa SK, Pang MYC et al (2023) Non-invasive brain stimulation techniques for the improvement of Upper Limb Motor function and performance in activities of Daily Living after Stroke: a systematic review and network Meta-analysis. Arch Phys Med Rehabil 104(10):1683–1697. https://doi.org/10.1016/j.apmr.2023.04.027

67. Goldstein LB, Samsa GP (1997) Reliability of the National Institutes of Health Stroke Scale. Extension to non-neurologists in the context of a clinical trial. Stroke 28(2):307–310. https://doi.org/10.1161/01.str.28.2.307

68. Goldstein LB, Bertels C, Davis JN (1989) Interrater reliability of the NIH stroke scale. Arch Neurol 46(6):660–662. https://doi.org/10.1001/archneur.1989.00520420080026

69. Henrich-Noack P, Sergeeva EG, Sabel BA (2017) Non-invasive electrical brain stimulation: from acute to late-stage treatment of central nervous system damage. Neural Regen Res 12(10):1590–1594. https://doi.org/10.4103/1673-5374.217322

70. Rossi S, Hallett M, Rossini PM, Pascual-Leone A (2009) Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol 120(12):2008–2039. https://doi.org/10.1016/j.clinph.2009.08.016

71. Chino T, Kinoshita S, Abo M (2023) Repetitive Transcranial Magnetic Stimulation and Rehabilitation Therapy for Upper Limb Hemiparesis in Stroke patients: a narrative review. Progress Rehabilitation Med 8. https://doi.org/10.2490/prm.20230005