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Examining the effectiveness of motor imagery combined with non-invasive brain stimulation for upper limb recovery in stroke patients: a systematic review and meta-analysis of randomized clinical trials

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Abstract

Background Transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS) are common non-invasive brain stimulation (NIBS) methods for functional recovery after stroke. Motor imagery (MI) can be used in the rehabilitation of limb motor function after stroke, but its effectiveness remains to be rigorously established. Furthermore, there is a growing interest in the combined application of NIBS with MI, yet the evidence regarding its impact on the recovery of upper limb function after stroke is inconclusive. This meta-analysis aimed to demonstrate whether combining the two is superior to NIBS alone or MI alone to provide a reference for clinical decision-making.

Methods PubMed, EMBASE, Cochrane Library, Web of Science, Science Direct, CNKI, WANFANG, and VIP databases were searched for randomized controlled trials on the effects of MI combined NIBS in motor function recovery after stroke until February 2024. The outcomes of interest were associated with body functions or structure (impairment) and activity (functional). The primary outcome was assessed with the Fugl-Meyer assessment of the upper extremity (FMA-UE) for motor function of the upper limbs and the modified Barthel Index (MBI) for the ability to perform daily living activities. For secondary outcomes, functional activity level was measured using wolf motor function test (WMFT) and action research arm test (ARAT), and cortical excitability was assessed using cortical latency of motor evoked potential (MEP-CL) and central motor conduction time (CMCT). The methodological quality of the selected studies was evaluated using the evidence-based Cochrane Collaboration's tool. A meta-analysis was performed to calculate the mean differences (MD) or the standard mean differences (SMD) and 95% confidence intervals (CI) with random-effect models.

Results A total of 14 articles, including 886 patients, were reviewed in the meta-analysis. In comparison with MI or NIBS alone, the combined therapy significantly improved the motor function of the upper limbs (MD = 5.43; 95% CI 4.34–6.53; $P < 0.00001$) and the ability to perform activities of daily living (MD = 11.07; 95% CI 6.33–15.80; $P < 0.00001$). Subgroup analyses showed an interaction between the stage of stroke, the type of MI, and the type of NIBS with the effect of the combination therapy.

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Conclusion The combination of MI and NIBS may be a promising therapeutic approach to enhance upper limb motor function, functional activity, and activities of daily living after stroke.

Systematic registration PROSPERO registration CRD42023493073.

Keywords Motor imagery, Non-invasive brain stimulation, Stroke, Repetitive transcranial magnetic stimulation, Transcranial direct current stimulation, Meta-analysis

Background

Stroke is the leading cause of disability worldwide, affecting 80 million people worldwide [1]. It has been estimated that the global incidence of stroke will increase by > 13.7 million new cases each year [2]. Up to approximately 80% of stroke survivors have varying degrees of upper limb motor dysfunction, seriously affecting the patient's independence in daily living activities and bringing a substantial economic burden to families and society [3, 4]. In addition, American Stroke Association (ASA) recommends early rehabilitation treatment to patients hospitalized for stroke as this can improve the rehabilitation effect and reduce other complications [6]. Since the motor and sensory function areas of the upper limb and hand occupy the most significant proportion in the brain function area, it is the most difficult to restore the function of the upper limb after brain injury. In recent years, many rehabilitation measures have been developed to maximize the restoration of upper limb function in stroke patients because most tasks in daily life involve the use of both upper limbs and hands [5]. However, this is a complex and long-term rehabilitation process.

Motor imagery (MI) involves as the mental presentation of an action without voluntary body movement [6]. During MI, mental imagery of the action or task to be learned is systematically repeated. This type of training shows potential in the rehabilitation of motor function in stroke patients, particularly considering the analogous pre-processing steps and structural overlap between MI and movement execution [7]. Tong et al. [8] have shown that motor imagery activates sensorimotor regions of the brain, including the primary motor cortex (M1), supplementary motor area (SMA), and parietal cortex, which are closely related to motor control and planning. Therefore, MI may promote motor network remodeling in patients after stroke by increasing neural activity in specific brain areas and changing functional connections, thereby improving motor function [9, 10]. Similar studies have also revealed consistent findings; e.g., Kim et al. [11] found that motor imagery training can improve functional flexibility during stroke rehabilitation and positively impact upper limb motor function. However, motor imagery training alone is not superior to other traditional means of rehabilitation, and its effectiveness may require optimization through complementary therapy [7, 12]. In addition, conventional post-stroke rehabilitation relying on physical movement may be ineffective during the early stage of post-stroke motor recovery as stroke patients are often severely paralyzed and unable to initiate any movement, making them unable to actively participate in physical rehabilitation. Consequently, motor imagery provides an opportunity for early rehabilitation of stroke patients [13]; yet, due to a lack of evidence-based research, motor imagery training is not widely used in clinical practice.

Transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS) are two of the most commonly used non-invasive brain stimulation (NIBS) methods and promising neurorehabilitation interventions [1, 14]. NIBS regulates the excitability of the cerebral cortex primarily through electric or magnetic fields and regulates network recombination by inducing neuroplasticity for more favorable functional recovery [15, 16]. In rTMS, time-varying magnetic fields act on the cerebral cortex to generate induced currents that affect brain metabolism in specific brain networks to induce changes in the stimulated neurons and remotely interconnected brain regions. High frequencies (> 1 Hz) induce predominantly excitatory effects, while low frequencies (≤ 1 Hz) induce predominantly inhibitive effects [17]. In order to improve brain function in patients with various diseases, the optimal therapeutic effect can be attained by adjusting the intensity, frequency, location, and direction of the coil [14, 18]. tDCS regulates the excitability of the cortex by transmitting a weak (about 0.5–2.0 mA) current to the cortex through two polarized electrodes (anode, cathode), with anodal tDCS increasing cortical excitability and cathodal decreasing cortical excitability [19, 20]. Hummel et al. [21] found that unilateral anodal transcranial direct current stimulation (a-tDCS) can excite the sensorimotor cortex in stroke, improving a variety of motor outcomes in stroke patients and thus being the most widely used method in research. However, Fregni et al. [22] study reported that unilateral cathodal transcranial direct current stimulation (c-tDCS) can effectively modulate the imbalance between cerebral hemispheres by inhibiting the overactive contralateral cortex. Muffel et al. [23] showed that tDCS could effectively promote motor and sensory function recovery in patients with chronic stroke. At the

same time, bilateral-transcranial direct current stimulation (bi-tDCS) combines the promotion of the contralateral cortex (anode component) and the inhibition of the contralateral cortex (cathodic component), resulting in higher efficacy of bi-tDCS over a-tDCS. However, there is no consistent standard for tDCS parameter selection in stroke treatment [24].

Several recent studies have combined motor imagery with tDCS or rTMS for the treatment of upper limb dysfunction after stroke [25–38]. However, no systematic reviews and meta-analyses confirm the effectiveness of MI combined with NIBS in upper limb rehabilitation in stroke patients. Therefore, this systematic review and meta-analysis aimed to determine whether the combined use of MI and NIBS enhances the function of the upper limbs in people with stroke compared to MI alone or NIBS alone.

Methods

This study was prospectively registered on PROSPERO (ID: CRD42023493073) and conducted with PRISMA Protocol [39] for systematic reviews of randomized controlled trials.

Date sources and search strategy

Two independent researchers independently searched the following Databases for relevant literature: PubMed, Cochrane Library, Science Direct, Web of Science, EMBASE, CNKI, WANFANG, and VIP. Moreover, the reference lists of all relevant articles were manually searched to identify studies that may have not been identified by the database search. The databases were searched from their inception until February 1, 2024. There were no restrictions on publishing articles in any country or language. Combinations of the following keywords were used to search the abovementioned databases: "transcranial direct current stimulation", "repetitive transcranial magnetic stimulation", "tDCS", "rTMS", "non-invasive brain stimulation", "motor imagery", "MI", and "stroke".

Eligibility criteria and study selection

The studies were selected based on the PRISMA checklist and PICOS method, as follows: P-population: stroke patients with upper limb dysfunction; I-intervention: tDCS or rTMS combined MI; C-control: tDCS alone or rTMS alone or MI alone; O-outcome: reference to the International Classification of Functioning, Disability and Health (ICF) were included (a) body structure/function [e.g., Fugl Meyer assessment of upper extremity (FMA-UE)]; (b) activity levels [e.g., modified Barthel Index (MBI)]; (c) functional activity levels [e.g., wolf motor function test (WMFT), action research arm test (ARAT)]; (d) Neurophysiological indicators [e.g., cortical latency of motor evoked potential (MEP-CL), central motor conduction time(CMCT)]. S-study design: randomized controlled trials.

Exclusion criteria encompassed the book chapters, study protocol, and abstracts. Also, studies with a sample size of < 10 people were excluded. Two independent researchers screened studies for inclusion and exclusion criteria. During the screening process, the title and abstract were read first, and articles that were not eligible were excluded, after which the full text was read through to determine the final literature to be included. Disagreements were resolved by consensus with a third researcher.

Data extraction

Two independent researchers extracted the data using a chart designed for this purpose. A third researcher assisted the team in comparing both charts and presenting the final results collected. The following information was extracted: study information (authors, year and country), study design, characteristics of the sample (age, type of stroke, affected limb, duration of disease), NIBS parameters (the type of stimulus, the pattern, the specific frequency, and the timing), MI parameters (mode and application time), stimulation timing for MI and NIBS, type of control group, duration of intervention, outcomes, follow-up, and occurrence of adverse events. Corresponding authors were contacted for additional information. Tables were used to describe the characteristics of the studies and the extracted data. In addition, if there were multiple outcomes at the functional activity level, they were selected in the following order: WMFT > ARAT.

Quality assessment

The potential risk of bias was assessed based on Cochrane Collaboration's guidelines [40], including the terms of random sequence generation, the rules for assignment hiding, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. A third investigator resolved the staging generated during the above process. Review Manager (Rev Man) software (computer program, version 5.4, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used to perform the analysis. There were three associated risk levels, i.e., High Risk—Red, Low Risk—Green, and Unclear—Yellow. Those not registered or without protocol were noted as inconclusive for selective reporting items. Full-text and study quality were synthesized to consider other sources of bias. The results of the bias assessment were presented in the form of graphs.

Statistical analysis

Quantitative synthesis was performed using Rev Man 5.4. A random effects model was used to assess whether the pooled effects combined from individual studies were significant ($P \leq 0.05$). The primary outcomes were motor function of the upper limb and ability to perform activities of daily living. Secondary outcomes were functional activity level and neurophysiological indicators for each study. The mean difference (MD) was used for the upper limb motor function, ability to perform activities of daily living results, and neurophysiological indicators, which were expressed on the same scale in the included studies. The standardized mean difference (SMD) was used to express the results for upper limb functional activities since these variables are sometimes [e.g., WMFT, ARAT] reported with different scales or units. The 95% confidence interval (95% CI) was calculated for all outcomes. Statistical heterogeneity was evaluated using the chi-squared test (with statistical significance set at $P \leq 0.05$) and was measured by calculating the I^2, with values of 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respectively [41]. We also performed sensitivity analyses for cases with moderate to high heterogeneity by iteratively deleting studies to determine whether our results were due to a single study. Regardless of heterogeneity, a random-effects model was used for our analysis. Forest plot graphics were generated to illustrate the pooled effect, and funnel plot analyses were used to assess the likelihood of publication bias in meta-analyses. Usually, tests for funnel plot asymmetry are performed only when at least 10 studies are included in a meta-analysis [16].

In all included studies, the intervention was MI combined with NIBS in the experimental group and either MI alone or NIBS alone in the control group. For studies featuring two control groups (e.g., NIBS alone and MI alone), each group was considered as a separate entity in the analysis. The two subgroup analyses were set up based primarily on the type of control group, comparing MI with NIBS alone. Furthermore, subgroup analyses were performed according to the stage of stroke onset before intervention (acute phase [≦1 month], subacute phase [1–6 months], or chronic phase [>6 months]), the type of NIBS (the frequency of rTMS (low frequency rTMS [LF-rTMS] at ≤1 Hz, high frequency rTMS [HF-rTMS] at >1 Hz), as well as the following forms of transcranial direct stimulation: a-tDCS, c-tDCS, or bi-tDCS, the stimulation time of NIBS (≤20 min or >20 min), parameters of MI, the time of MI (≤30 min or >30 min), stimulation timing for MI and NIBS (NIBS first then MI or simultaneously). Subgroup analyses were performed to elucidate potential factors that might affect the combined effects of MI with NIBS on overall outcomes.

Results

Among 685 identified articles that met the study characteristics, 74 were duplicates, 496 were deleted after reading the title and abstract, and 101 were deleted after reading the full text. Moreover, the authors of 3 studies were asked to provide additional information, and only 1 author responded. Finally, 14 studies involving 886 people with stroke were included in the review (Fig. 1).

Characteristics of the trials

The characteristics of participants in the trials selected for this systematic review and meta-analysis are shown in Table 1 [25–38]. The detailed interventions for the included trials are shown in Table 2. There were 886 stroke patients, with an average age of 57.86 ± 9.99 years. Except for one study that did not report the type of stroke, the remaining studies involved a total of 585 patients with cerebral infarction and 282 patients with cerebral hemorrhage. Three of the included studies did not report on the hemiplegic side; 290 of the remaining patients had the left limb, and 378 had the right limb affected. Two of the studies involved two control groups [31, 35], so they were split into four studies [Ren et al. -A (MI alone), Ren et al. -B (tDCS alone), Jia et al.-A (rTMS alone), Jia et al.-B (MI alone)]. Therefore, a total of 16 studies were included in the meta-analysis. Of the types of control groups, MI was used in 10 studies, and NIBS was used in 6 studies. Regarding types of MI, 10 studies used video and audio-assisted MI training, 4 used brain-computer interface (BCI) to achieve MI, and 2 used graded MI training. Eleven studies reported pre- and post-intervention outcomes, and the remaining 5 also included follow-up measures after intervention. In 8 studies, NIBS and MI were used simultaneously; 5 studies first performed NIBS followed by MI, and 3 studies did not specify the order of precedence. Only one study had an intervention duration of eight weeks, while the rest had an intervention duration of two or four weeks. The mean and standard deviations of the FMA-UE scores change for the MI + NIBS group and control groups in each included study were presented in Table 3.

Risk of bias in the included studies

The risk of bias for the 16 studies/14 articles is shown in Fig. 2. All studies mentioned the method of randomization, six used computer-generated random sequences and eight used random number tables. Two studies mentioned randomization but did not specify the method of randomization. Thirteen studies indicated allocation concealment. In 5 studies, participants or interveners were unaware of the specified protocol, and in 3 studies, they were aware of the trial protocol; this was unspecified

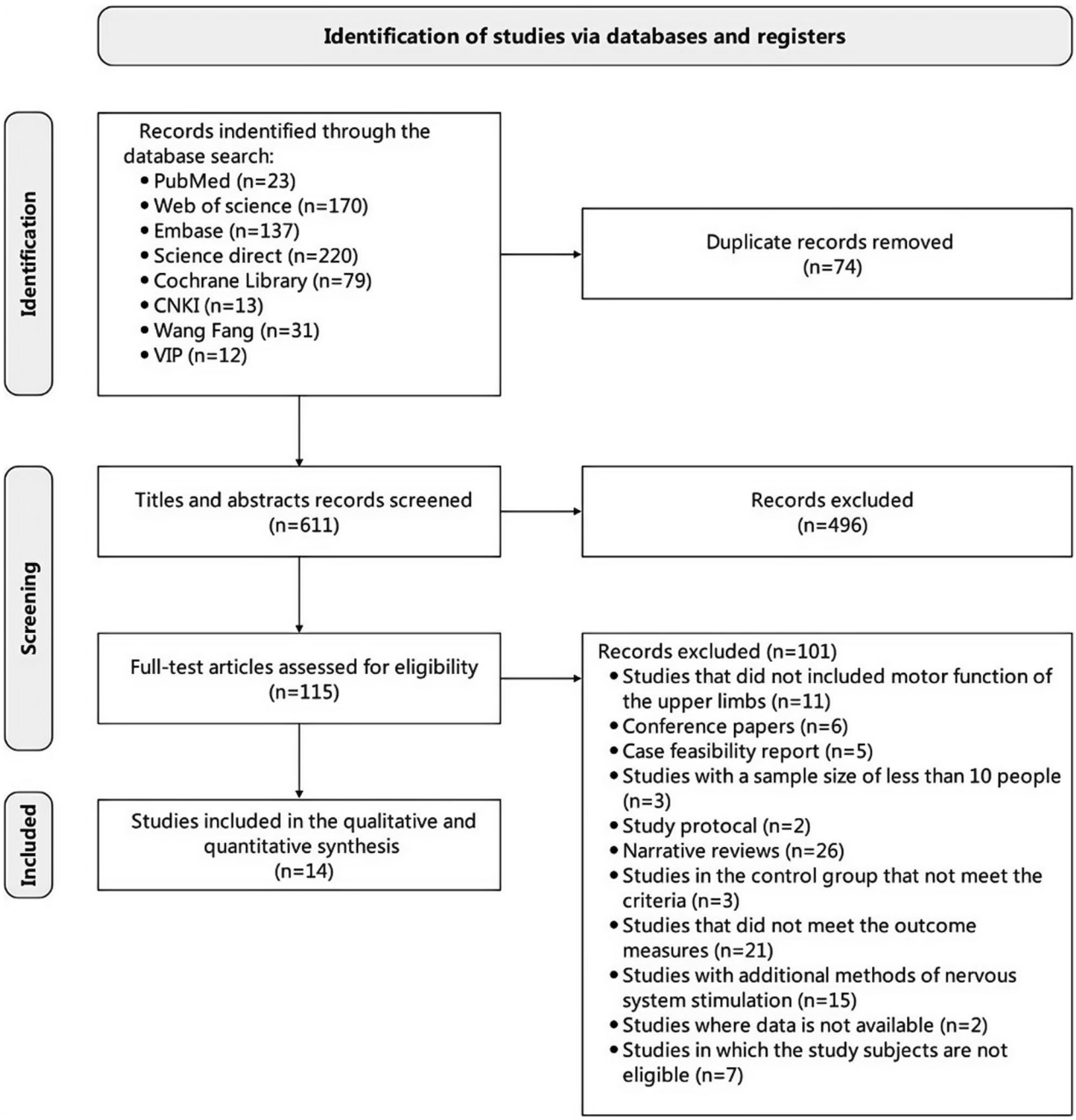


Fig. 1 Study flow chart

in the remaining studies. Twelve studies specified that the evaluator was blinded, i.e., did not know which group the participant was assigned to at the assessment time. One study did not blind the evaluators, and the rest did not specify the specific blinding situation. All studies reported full results. Three studies presented an unclear selection bias since the protocols had not been previously registered. Other potential sources of bias could not be identified in all studies. A sensitivity analysis showed that pooled effect size was not over-affected by the specific study, indicating the relative robustness of the results. Funnel charts were made for each observation. There was no substantial evidence of publication risk, and the risk of publication bias was considered low since the distribution of the main variable in the funnel plots was not asymmetrical.

Table 1 Sample characteristic, study design, intervention, and outcome measure used in the systematic review

Author (year)	Country	Study design (blindness)	Type of stroke (I/H)	Age (mean ± SD)	Affect limb (L/R)	Duration of disease (mean ± SD)	Intervention	Intervention duration (number of sessions)	Outcomes
Pan et al. (2019)	China	RCT (SB)	EG:21 (3/18) CG_1:21 (4/17)	EG:63.38 ± 6.45 CG_1:64.14 ± 4.49	NA	EG:4.96 ± 1.07(m) CG_1:5.13 ± 1.09(m)	EG: rTMS + MI[s] CG_1: rTMS	Qd, 5 d/w, 2 weeks (10)	WMFT; MBI; BBT, FMA-UE
Kashoo et al. (2022)	Saudi Arabia	RCT (DB)	EG:32 (28/4) CG_1:32 (30/2)	EG:58.7 ± 5.7 CG_1:59.9 ± 5.6	EG:14/18 CG_1:15/12	EG:7.8 ± 1.3(m) CG_1:7.4 ± 1.2(m)	EG: tDCS + MI[s] CG_1:sham tDCS + MI[s]	Qd, 5 d/w, 2 weeks (10)	FMA-UE; ARAT
Hong et al. (2017)	Singapore	RCT (DB)	NA	EG:52.8 ± 12.3 CG_1:56.4 ± 9.6	EG:4/5 CG_1:6/3	EG:33.9 ± 24.6(m) CG_1:33.3 ± 15.1(m)	EG: tDCS + MI[b] CG_1:sham tDCS + MI[b]	Qd, 5 d/w, 2 weeks (10)	FMA-UE; DTI; CBF
Ang et al. (2015)	Singapore	RCT (DB)	EG:10 (6/4) CG_1:9 (7/2)	EG:52.1 ± 11.7 CG_1:56.3 ± 9.5	EG:5/5 CG_1:3/6	EG:1052 ± 722(d) CG_1:1021 ± 465(d)	EG: tDCS + MI[a] CG_1:sham tDCS + MI[a]	Qd, 5 d/w, 2 weeks (10)	FMA-UE; ERD
Chew et al. (2020)	Singapore	RCT (DB)	EG:10 (6/4) CG_1:9 (7/2)	EG:52.2 ± 11.8 CG_1:56.4 ± 9.6	EG:5/5 CG_1:3/6	EG:31.3 ± 24.5(m) CG_1:33.3 ± 15.1(m)	EG: tDCS + MI[a] CG_1:sham tDCS + MI[a]	Qd, 2 weeks (10)	FMA-UE; MEP RMT; $SICI_{2ms}$
Hu et al. (2021)	Singapore	RCT (DB)	EG:10 (6/4) CG_1:9 (6/2)	EG:52.1 ± 11.7 CG_1:54.6 ± 8.5	EG:1/9 CG_1:1/7	EG:1052 ± 721(d) CG_1:1076 ± 466(d)	EG:tDCS + MI[a] CG_1:sham tDCS + MI[a]	Qd, 2 weeks (10)	ReHo; ALFF; FC; FMA-UE
Jia et al. (2023)	China	RCT	EG:19 (16/3) CG_1:18 (15/3) CG_2:19 (16/3)	EG:58.42 ± 8.82 CG_1:55.56 ± 11.28 CG_2:61.89 ± 9.42	EG:10/9 CG_1:7/11 CG_2:9/10	EG:14.6 ± 3.5(d) CG_1:14.0 ± 3.9(d) CG_2:13.5 ± 2.4(d)	EG: rTMS + MI + CR CG_1: rTMS + CR CG_2:MI + CR	Qd, 5 d/w, 4 weeks (20)	FMA-UE, ARAT, MAL-AOU, MAL-QOM, MEP, MBI
Huang et al. (2023)	China	RCT	EG:48 (I) CG_1:48 (I)	EG:58.62 ± 8.15 CG_1:57.84 ± 7.73	EG:24/24 CG_1:26/22	EG:11.85 ± 2.16(d) CG_1:12.15 ± 2.29(d)	EG: rTMS + MI[c] CG_1: rTMS	Qd, 6 d/w, 4 weeks (24)	MBI; FMA, NIHSS; No, ET-1
Zhou et al. (2018)	China	RCT	EG:32 (17/15) CG_1:31 (18/13) CG_2:31 (19/12)	EG:54.25 ± 8.23 CG_1:52.29 ± 10.72 CG_2:53.87 ± 8.91	EG:16/16 CG_1:14/17 CG_2:13/18	EG:36.16 ± 19.90(d) CG_1:36.47 ± 20.58(d) CG_2:34.83 ± 22.91(d)	EG: tDCS + MI[s] CG_1: sham tDCS + MI[s] CG_2:CR	Qd, 6 d/w, 8 weeks (48)	FMA-UE; FTHUE; MBI
Li et al. (2022)	China	RCT	EG: 34 (26/8) CG_1:33 (25/8) CG_2: 34 (27/7)	EG:53.08 ± 9.30 CG_1:51.98 ± 8.65 CG_2:53.11 ± 10.03	EG:21/13 CG_1:18/15 CG_2:20/14	EG:13.19 ± 4.35(d) CG_1:13.28 ± 3.70(d) CG_2:12.87 ± 3.96(d)	EG:rTMS + MI[s] + CR CG_1: MI + CR CG_2: CR	Qd, 6 d/w, 4 weeks (24)	MEP-CL; FMA; CMCT; TUGT; MBI; BBS; MAS; MFES
Ren et al. (2023)	China	RCT	EG:28 (20/8) CG_1:28 (18/10) CG_2:28 (15/13)	EG:66.18 ± 3.98 CG_1:65.86 ± 3.97 CG_2:66.21 ± 4.06	EG:0/28 CG_1:0/28 CG_2:0/28	EG: 62.86 ± 12.67(d) CG_1:61.21 ± 14.36(d) CG_2:56.43 ± 10.18(d)	EG:tDCS + MI CG_1:MI CG_2:tDCS	Dq, 6 d/w, 4 weeks (24)	FMA-UE, WMFT, MBI, MMSE, MoCA
Che et al. (2017)	China	RCT	EG:39 (27/12) CG_1:41 (30/11)	EG:58.77 ± 14.30 CG_1: 61.49 ± 10.51	NA	Within 2 weeks	EG: tDCS + MI[s] CG_1: tDCS	Dq, 5 d/w, 4 weeks (20)	FMA-UE, MBI
He et al. (2020)	China	RCT	EG:52 (25/27) CG_1:52 (23/29)	EG:63.22 ± 6.41 CG_1:62.75 ± 7.04	EG:28/24 CG_1:27/25	6.31 ± 1.36(w)	EG:tDCS + MI[s] CG_1:tDCS	Dq, 7 d/w, 4 weeks (28)	NIHSS, FMA, MMSE, MBI, LOTCA

Table 1 (continued)

Author (year)	Country	Study design (blindness)	Type of stroke (I/H)	Age (mean ± SD)	Affect limb (L/R)	Duration of disease (mean ± SD)	Intervention	Intervention duration (number of sessions)	Outcomes
Ju et al. (2022)	China	RCT	EG:30 (17/13) CG_1:30 (14/16) CG_2:30 (18/12)	EG:46.1 ± 6.8 CG_1:44.3 ± 6.6 CG_2:49.5 ± 5.5	N/A	EG:14.6 ± 3.5(d) CG_1:14.0 ± 3.9(d) CG_2:13.5 ± 2.4(d)	EG: rTMS + MI[s] + CR CG_1: MI + CR CG_2:CR	Qd, 5 d/w, 4 weeks (20)	FMA-UE, FTHUE-HK, CL, CMCT

I infarction, *H* hemorrhage, *L* left, *R* right, *SD* standard deviation, *RCT* randomized controlled trials, *DB* double-blind, *SB* single blind, *EG* experimental group, *CG* control group, *MI* motor imagery, *rTMS* repetitive transcranial magnetic stimulation, *tDCS* transcranial direct current stimulation, *FMA* Fugl-Meyer assessment, *FMA-UE* Fugl-Meyer assessment of upper extremity, *FTHUE* functional test for the hemiplegic upper extremity, *MBI* modified Barthel index, *RMT* resting motor threshold, *rTMS* repetitive transcranial magnetic stimulation, *NIHSS* national institute of health stroke scale, *No* serum nitric oxide, *ET-1* endothelin-1, *MEP-CL* cortical latency of motor evoked potential, *CMCT* central motor conduction time, *TUTG* time up and go test, *BBS* Berg Balance Scale, *MFES* modified falls efficacy scale, *MAS* motor assessment scale, *DLPFC* dorsolateral prefrontal cortex, *WMFT* wolf motor function test, *MAL-AOU* motor activity log-amount of use, *MAL-QOM* motor activity log-quality of movement, *MMSE* minimum mental state examination, *MoCA* montreal cognitive assessment, *NA* not available, *LOTCA* Loewenstein occupational therapy cognitive assessment, *FTHUE-HK* Hong Kong version of the hemiplegic upper limb functional test, *m* months, *s* simultaneously, *d* day, *BBT* box and blocks test, *ARAT* action research arm test, *DTI* diffusion tensor imaging, *CBF* cerebral blood flow, *MEP* motor evoked potential, *ERD* event-related desynchronization, *SICI* short intra-cortical inhibition, *ReHo* regional homogeneity, *FC* functional connectivity, *ALFF* amplitude of low-frequency fluctuation, *Qd* quaque die, *w* weeks, *d* days

Quantitative summary: rehabilitation effects of MI combined with NIBS compared with MI alone or NIBS alone

According to the objective of this meta-analysis and the protocol published in PROSPERO, a quantitative analysis of the primary variable function was performed. There were 13 studies that addressed the primary outcome measures, i.e., 13 studies involving FMA-UE [25–31, 33, 35, 36, 38] and 10 studies involving MBI [25, 31–37]. The secondary outcomes were investigated by 6 studies, the level of functional activity of upper limb movements by 4 studies [25, 26, 31, 35], the cortical latency of motor evoked potentials by 3 studies [31, 34, 38], and the central motor conduction time by 2 studies [34, 38].

Motor function of the upper limbs

Eleven studies used the FMA-UE as the monitoring scale to improve upper limb motor function in stroke patients. As shown in Fig. 3, the body structure and function improvement in the MI + NIBS group was significantly higher than in the control group (MD = 5.43; 95% CI 4.34–6.53; $P < 0.00001$). No statistical heterogeneity was observed in the forest plots ($I^2 = 0\%$; $P = 0.91$). According to Table 3**,** eight studies in the MI + NIBS group achieved improvements greater than the Minimal Clinically Important Difference (MCID) of 12.4 [42], whereas no control group observed improvements reaching the MCID threshold. The overall average MCID for the MI + NIBS group was 12.32, and for the control group, it was 7.62.

Activities of daily living

Ten studies used the modified Barthel index in people with stroke to assess their ability to perform daily activities. Overall, the MI + NIBS group had a significant improvement in activity levels in comparison to the control group (MD = 11.07; 95% CI 6.33–15.80; $P < 0.00001$) (Fig. 4). The forest plot shows significant heterogeneity between studies ($I^2 = 94\%$; $P < 0.00001$).

Functional activity of upper limb movements

Six studies assessed the functional activity of upper limb movements. Three studies used WMFT, and 3 studies used ARAT. Overall, the MI + NIBS group induced a significant improvement in the functional activity of upper limb movements in comparison to the control group (SMD = 0.82; 95% CI 0.58–1.06; $P < 0.00001$) (Fig. 5). The forest plot shows that statistical heterogeneity was not observed ($I^2 = 0\%$; $P = 0.93$).

Neurophysiological index

MEP-CL Four studies reported on the cortical latency of motor-evoked potentials. There was no significant difference between the MI + NIBS group and the control group (MD = −0.29; 95% CI −0.64–0.06; $P = 0.11$) (Fig. 6A). No statistical heterogeneity was observed in the forest maps ($I^2 = 0\%$; $P = 0.53$).

CMCT Only two studies reported central motor conduction time. Compared with the control group, the conduction time was significantly shorter in the MI + NIBS group (MD = −1.11; 95% CI −1.63 to −0.59; $P < 0.0001$) (Fig. 6B). No statistical heterogeneity was observed in the forest maps ($I^2 = 0\%$; $P = 0.66$).

Adverse events

Regarding adverse events, NIBS combined with MI therapy can be considered a safe treatment. Among the included studies, only Kashoo et al. [26] reported that

Table 2 Detailed Interventions reported in the meta-analysis

Study	Classification	NIBS parameters	MI parameters	Stimulation timing	Type of control group	Follow-up	Adverse events
Pan et al. (2019)	Uncertain (3–12 months)	1 Hz over the M1 of the contralesional hemisphere, 90% RMT 1, 500 pulses 30 min	Audio-based MI 30 min	Simultaneously	rTMS	2 weeks	None
Kashoo et al. (2022)	Chronic (> 6 months)	Anode: affected hemisphere C3/C4 Cathode: contralateral supraorbital region 35 cm^2, 1.5 mA × 30-min tDCS	Visual assisted MI 30 min	Simultaneously	MI	No follow-up	Tingling sensation (n = 8) Itching under electrodes (n = 5)
Hong et al. (2017)	Chronic (> 9 months)	Anode: ipsilesional M1 Cathode: contralateral M1 35 cm^2, 1.0 mA × 20-min tDCS	BCI-MI 40 min	NIBS first, then MI	MI	4 weeks	Not mentioned
Ang et al. (2015)	Chronic (> 9 months)	Anode: ipsilesional M1 Cathode: contralateral M1 1.0 mA × 20-min tDCS	BCI-MI 60 min	NIBS first, then MI	MI	2 weeks	Not mentioned
Chew et al. (2020)	Chronic (> 9 months)	Anode: ipsilesional M1 Cathode: contralateral M1 35 cm^2, 1.0 mA × 20-min tDCS	BCI-MI 20 min	NIBS first, then MI	MI	4 weeks	Not mentioned
Hu et al. (2021)	Chronic (> 12 months)	Anode: ipsilesional M1 Cathode: contralateral M1 1.0 mA × 20-min tDCS	BCI-MI 40 min	NIBS first, then MI	MI	4 weeks	Not mentioned
Huang et al. (2023)	Uncertain	1 Hz for 8 s duration bursts,90% RMT, intertrain intervals of 3 s, repeat 82 times, 15 min	Verbal guidance MI 50 min	NA	rTMS	No follow-up	Not mentioned
Zhou et al. (2018)	Subacute (1–3 months)	Anode: ipsilesional M1 Cathode: contralateral shoulder 35 cm^2, 2.0 mA × 20-min tDCS	Verbal guidance MI 80 min	Simultaneously	MI	No follow-up	Not mentioned
Li et al. (2022)	Acute (< 4 weeks)	1 Hz for 20 pulses/sequence, 30 sequences/time, pause 5-s, 100%RMT, 10 min	Verbal guidance 30 min	Simultaneously	MI	No follow-up	Not mentioned

Table 2 (continued)

Study	Classification	NIBS parameters	MI parameters	Stimulation timing	Type of control group	Follow-up	Adverse events
Ren et al.-A (2023)	Subacute (1–3 months)	Anode: ipsilesional M1 Cathode: contralateral M1 35 cm^2, 1.0 mA × 30-min tDCS	Verbal guidance 30 min	NA	MI	No follow-up	Not mentioned
Ren et al.-B (2023)	Subacute (1–3 months)	Anode: ipsilesional M1 Cathode: contralateral M1 35 cm^2, 1.0 mA × 30-min tDCS	Verbal guidance 30 min	NA	tDCS	No follow-up	Not mentioned
Che et al. (2017)	Acute (< 2 weeks)	Anode: affected shoulder Cathode: contralateral M1 2.0 mA × 20-min Anode: ipsilesional M1 Cathode: unaffected shoulder for another 2.0 mA × 20-min	Verbal guidance-MI, 40 min	Simultaneously	tDCS	No follow-up	Not mentioned
He et al. (2020)	Uncertain	Anode: ipsilesional M1 Cathode: contralateral M1 1.5 mA × 30-min tDCS	Verbal guidance 20 min, 2/d	Simultaneously	tDCS	No follow-up	Not mentioned
Ju et al. (2022)	Acute (< 1 month)	1 Hz for 600-s duration bursts, pause1s,90%RMT, 1200 pulses, 20 min	Verbal guidance 20 min	Simultaneously	MI	No follow-up	Not mentioned
Jia et al.-A (2023)	Uncertain (< 6 months)	1 Hz over the M1 of the contralesional hemisphere, 80%RMT, 20 min	Graded MI 30 min	NA	rTMS	No follow-up	None
Jia et al.-B (2023)	Uncertain (< 6 months)	1 Hz over the M1 of the contralesional hemisphere, 80% RMT, 20 min	Graded MI 30 min	NA	MI	No follow-up	None

NIBS non-invasive brain stimulation, *MI* motor imagery, *M1* motor cortex, *rTMS* repetitive transcranial magnetic stimulation, *tDCS* transcranial direct current stimulation, *RMT* resting motor threshold, *C3/C4* EEG International Standard 10–20 anchor points, *NA* not available

6 people in the real-tDCS group experienced tingling sensations over the scalp, 5 suffered itching, and 2 people in the control group had tingling sensations over the scalp. These mild adverse reactions did not affect the patients' participation in the experiment. There is still a need for studies that actively assess adverse events, as 6 of the studies included in this review reported no adverse events, and 7 did not mention adverse events.

Follow up

Only 5 studies reported post-intervention follow-up. Compared with the control group, FMA-UE results in the MI + NIBS group were significantly higher than those in the control group at 2–4 weeks after the intervention (MD = 4.48; 95% CI 1.45–7.52; $P = 0.004$) (Fig. 7). No statistical heterogeneity was observed in the forest maps ($I^2 = 0\%$; $P = 0.59$).

Table 3 Mean change in FMA-UE scores (with standard deviations) and participant numbers in the MI combined with NIBS group versus MI Only or NIBS Only (control groups) for the included studies

Study	Combined			Control		
	m	sd	n	m	sd	n
Ang et al.	0.90	3.00	10	2.80	4.00	9
Che et al.	13.25	12.87	41	7.41	11.85	39
Chew et al.	0.90	3.00	10	2.80	4.00	9
Hong et al.	2.17	11.98	9	4.63	12.15	9
Hu et al.	0.90	3.00	10	2.90	4.20	8
Ju et al.	12.64	12.28	30	7.40	10.65	30
Jia et al.-A	16.11	9.03	19	10.78	6.18	18
Jia et al.-B	16.11	9.03	19	10.22	6.72	19
Kashoo et al.	7.60	0.86	32	2.40	0.87	32
Pan et al.	13.33	8.33	21	7.47	11.07	21
Ren et al.-A	15.21	6.19	28	10.07	4.80	28
Ren et al.-B	15.21	6.19	28	9.07	5.66	28
Zhou et al.	18.87	6.06	32	11.49	21.96	31
Overall	12.32	9.85	289	7.62	10.79	281

MI motor imagery, *FMA-UE* Fugl-Meyer assessment of the upper extremity, *NIBS* non-invasive brain stimulation, *sd* standard deviations, *n* number, *m* mean

Subgroup analysis

Subgroup analyses (defined according to the stage of stroke, the parameters of MI, the time of MI, the type of NIBS (LF-rTMS or HF-rTMS or bi-tDCS or c-tDCS or a-tDCS), the stimulation time of NIBS, stimulation timing for NIBS and MI were shown in Fig. 8**.**

Motor function of the upper limbs

Considering the stage of stroke, we found significant results in acute and subacute subgroups: (1) acute (MD = 6.17; 95% CI 3.25–9.09; $P < 0.001$; $I^2 = 0\%$); (2) subacute (MD = 5.52; 95% CI 4.10–6.93; $P < 0.001$; $I^2 = 0\%$). We also found no significant results in the chronic subgroup: (3) chronic (MD = 0.68; 95% CI −3.61–4.97; $P = 0.76$; $I^2 = 0\%$).

For the type of NIBS, the results were significant in both LF-rTMS (MD = 6.16; 95% CI 4.09–8.23; $P < 0.001$; $I^2 = 0\%$), bi-tDCS (MD = 5.01; 95% CI 3.55–6.48; $P < 0.001$; $I^2 = 0\%$) and a-tDCS (MD = 5.64; 95% CI 2.91–8.36; $P < 0.001$; $I^2 = 0\%$).

For the time of NIBS, the results were significant for both subgroups: (1) > 20 min (MD = 5.73; 95% CI 4.52–6.94; $P < 0.001$; $I^2 = 0\%$). (2) ≦20 min (MD = 4.04; 95% CI 1.61–6.63; $P = 0.002$; $I^2 = 0\%$).

For the type of MI, the results were significant in both the general video and audio-assisted MI group (MD = 5.77; 95% CI 4.55–6.99; $P < 0.001$; $I^2 = 0\%$) and GMI group (MD = 5.76; 95% CI 2.64–8.87; $P < 0.001$; $I^2 = 0\%$). No significant results were found in the brain-computer interface-based motor imagery (BCI-MI) group (MD = 0.68; 95% CI -3.61–4.97; $P = 0.76$; $I^2 = 0\%$).

For the time of MI, significant results were found for both subgroups: (1) > 30 min (MD = 4.99; 95% CI 2.79–7.19; $P < 0.001$; $I^2 = 0\%$) and (2) ≦30 min (MD = 5.58; 95% CI 4.32–6.84; $P < 0.001$; $I^2 = 0\%$).

For stimulation timing for NIBS and MI, significant results were found for both subgroups: (1) NIBS first (MD = 4.00; 95% CI 1.48–6.52; $P = 0.002$; $I^2 = 0\%$) and (2) simultaneous use (MD = 6.50; 95% CI 4.10–8.90; $P < 0.001$; $I^2 = 0\%$).

The above-reported results on body structure/function domain were shown in (Fig. 8A).

Activities of daily living

For the stage of stroke, significant results were found in acute and subacute subgroups: (1) acute (MD = 10.7; 95% CI 4.59–16.8; $P < 0.001$; $I^2 = 54\%$); (2) subacute (MD = 8.12; 95% CI 5.58–10.36; $P < 0.001$; $I^2 = 0\%$). As 5 studies included chronic and subacute phases, we could not select results for the chronic phase alone.

For the type of NIBS, the results were significant in both LF-rTMS (MD = 12.12; 95% CI 10.17–14.06; $P < 0.001$; $I^2 = 5\%$), bi-tDCS (MD = 12.12; 95% CI 2.70–21.55; $P = 0.01$; $I^2 = 97\%$) and a-tDCS (MD = 5.91; 95% CI 1.68–10.14; $P = 0.006$;).

For the time of NIBS, the results were significant for both subgroups: (1) > 20 min (MD = 12.61; 95% CI 5.04–20.19; $P = 0.001$; $I^2 = 96\%$). (2) ≦20 min (MD = 9.90; 95% CI 6.87–12.92; $P < 0.001$; $I^2 = 54\%$).

For the type of MI, the results were significant in both the general video and audio-assisted MI group (MD = 12.61; 95% CI 5.04–20.19; $P = 0.001$; $I^2 = 96\%$)

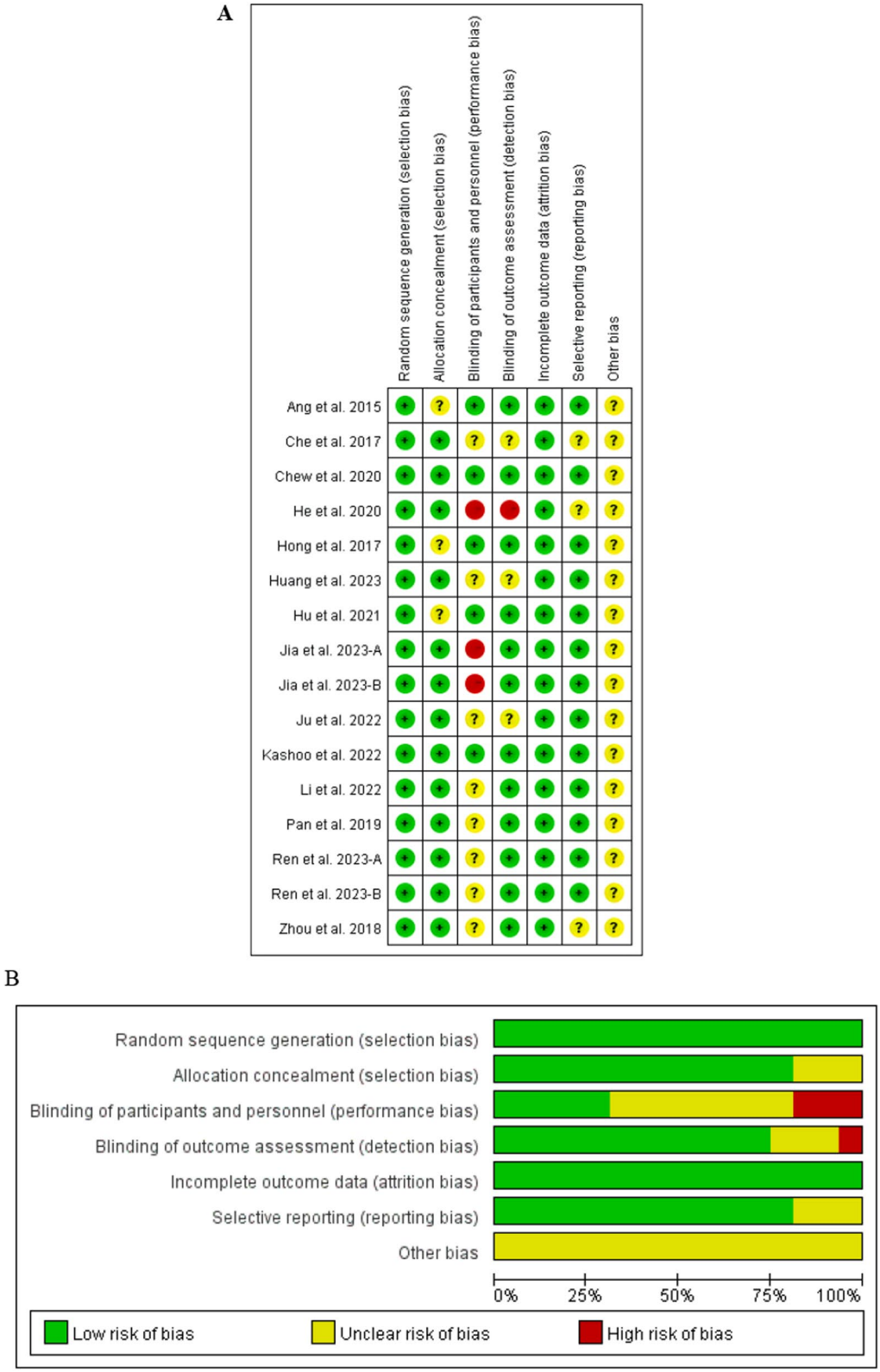


Fig. 2 **A** Risk of bias summary. **B** Risk of bias graph

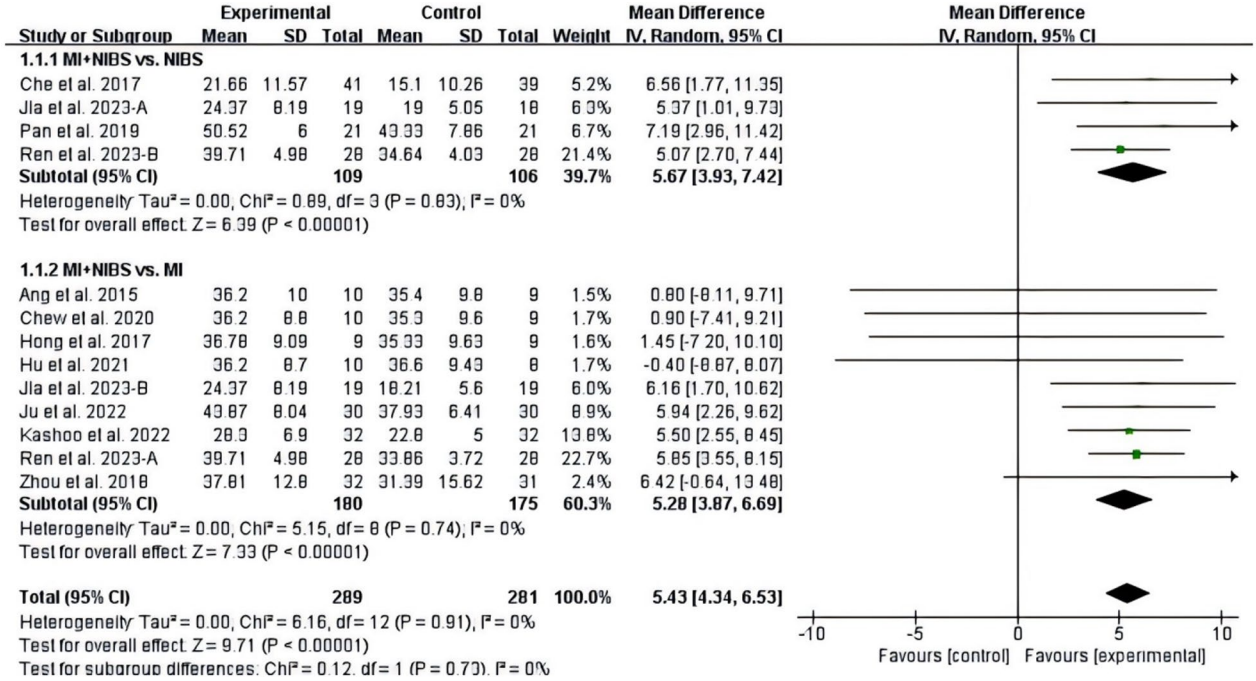


Fig. 3 Forest plot of trails comparing NIBS + MI vs. NIBS alone or MI alone for motor function of the upper limbs

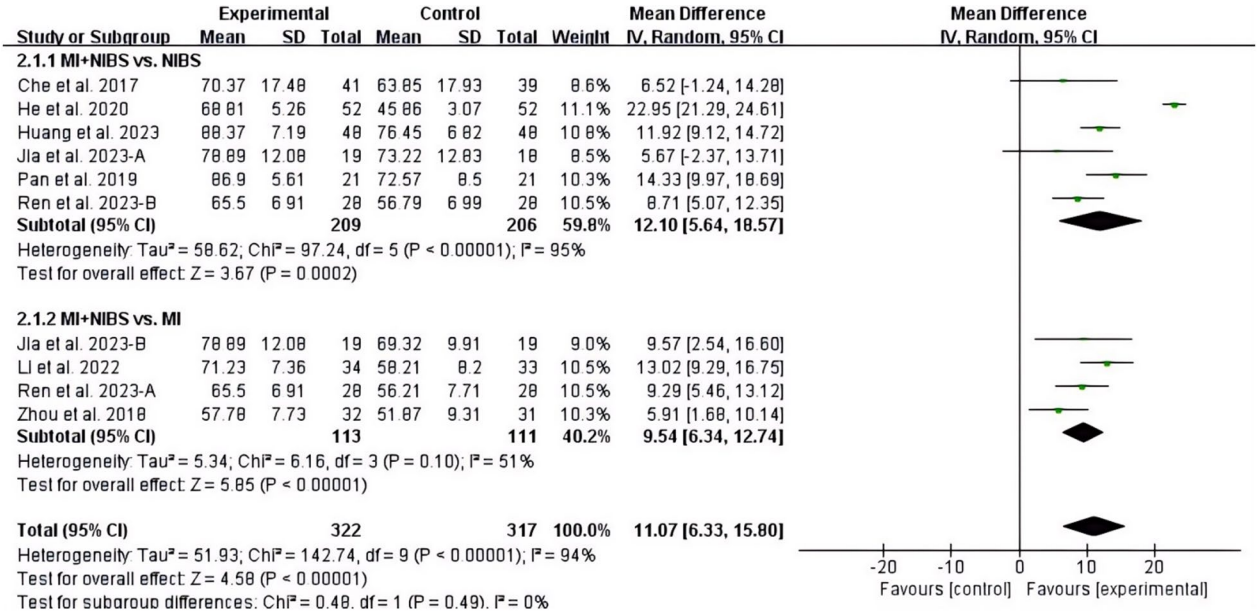


Fig. 4 Forest plot of trails comparing NIBS + MI vs. NIBS alone or MI alone for the ability to perform activities of daily living

and GMI group (MD = 9.09; 95% CI 6.87–12.92; $P < 0.001$; $I^2 = 54\%$). No studies used BCI for motor imagery.

For the time of MI, significant results were found for both subgroups: (1) > 30 min (MD = 12.12; 95% CI 3.13–21.11; $P = 0.008$; $I^2 = 97\%$) and (2) ≦30 min (MD = 10.66; 95% CI 8.37–12.96; $P < 0.001$; $I^2 = 33\%$).

For stimulation timing for NIBS and MI, MI combined with NIBS interventions was performed simultaneously in all studies, and MBI scores in the MI + NIBS group

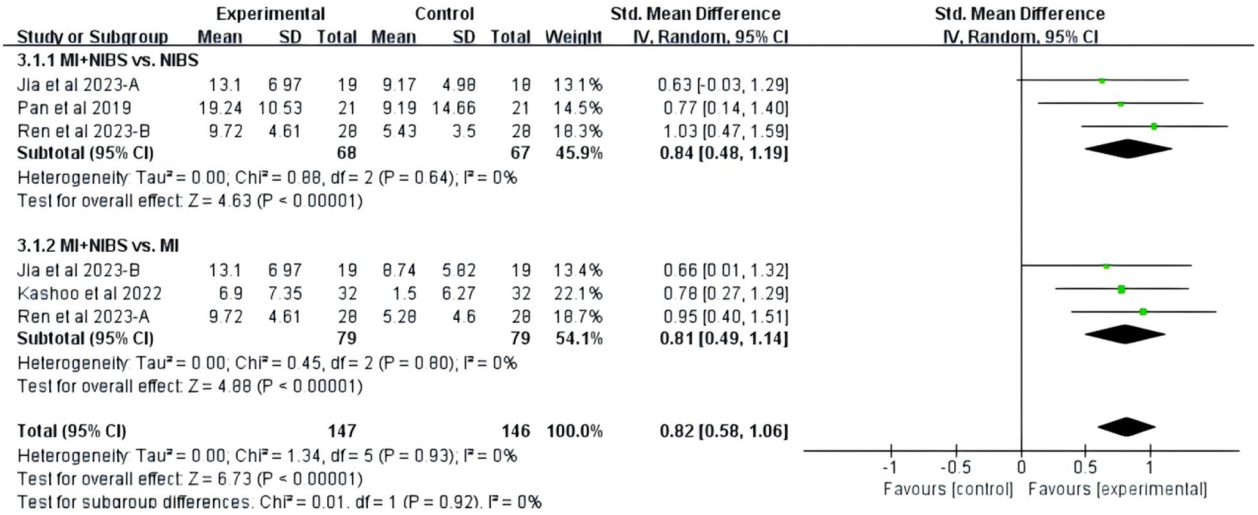


Fig. 5 Forest plot of trails comparing NIBS + MI vs. NIBS alone or MI alone for functional activity of upper limb movements

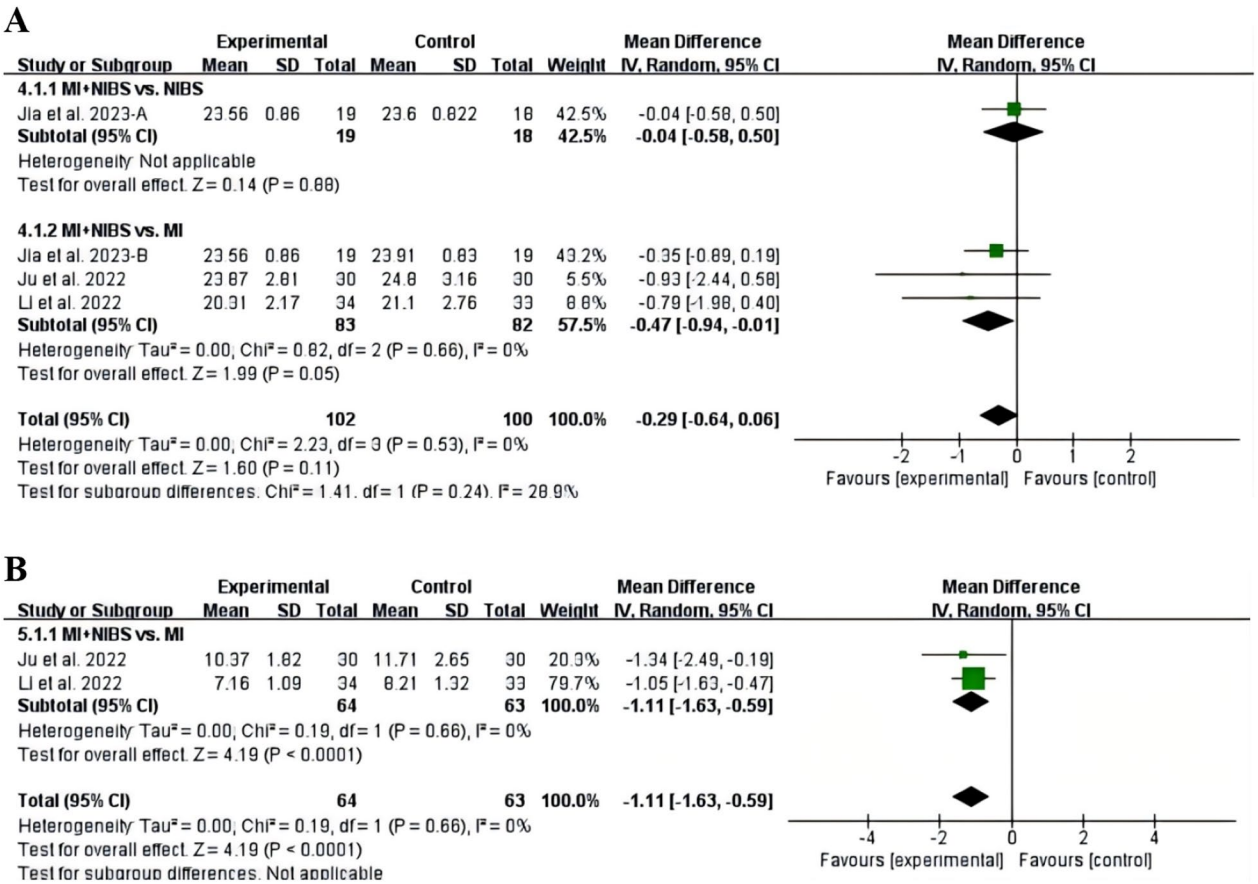


Fig. 6 Forest plot of trails comparing NIBS + MI vs. MI alone or NIBS alone for neurophysiological index. **A** Motor-evoked potential cortical latency (MEP-CL) and **B** central motor conduction time (CMCT)

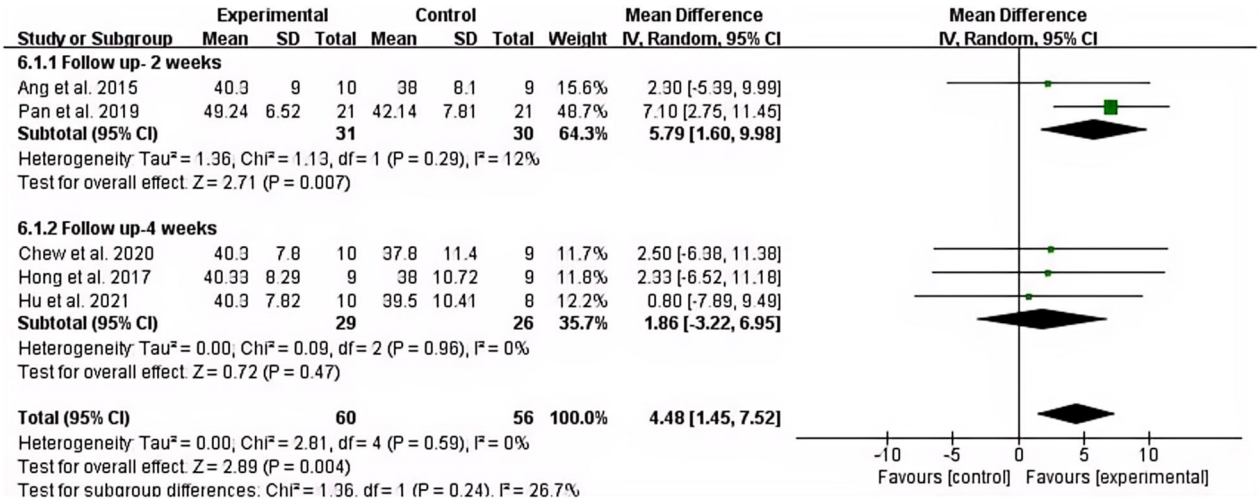


Fig. 7 Forest plot of trails comparing NIBS + MI vs. MI alone or NIBS alone for follow-up

were significantly higher than those in the control group: simultaneously subgroup (MD = 11.48; 95% CI 5.03–17.92; $P < 0.001$; $I^2 = 94\%$).

The above-reported results on activity levels domain were shown in (Fig. 8B).

Functional activity of upper limb movements

For the stage of stroke, significant results were found in subacute (MD = 4.55; 95% CI 3.11–6.00; $P < 0.001$; $I^2 = 0\%$). The remaining 3 studies did not specify the stage of stroke patients included.

For the type of NIBS, significant results were found for both subgroups: (1) LF-rTMS (MD = 4.83; 95% CI 2.18–7.49; $P < 0.001$; $I^2 = 1\%$), (2) bi-tDCS (MD = 4.36; 95% CI 2.75–5.96; $P < 0.001$; $I^2 = 0\%$) and (3) a-tDCS (MD = 5.40; 95% CI 2.05–8.75; $P = 0.002$;).

For the time of NIBS, the results were significant for both subgroups: (1) > 20 min (MD = 4.74; 95% CI 3.32–6.16; $P < 0.001$; $I^2 = 0\%$). (2) ≦20 min (MD = 4.13; 95% CI 1.32–6.95; $P = 0.004$; $I^2 = 0\%$).

For the type of MI, significant results were found for both subgroups: (1) general video and audio-assisted MI (MD = 4.74; 95% CI 3.32–6.16; $P < 0.001$; $I^2 = 0\%$); (2) GMI (MD = 4.13; 95% CI 1.32–6.95; $P = 0.004$; $I^2 = 0\%$). No studies used BCI for MI.

For the time of MI, all studies were completed in 30 min or less (MD = 4.61; 95% CI 3.35–5.88; $P < 0.001$; $I^2 = 0\%$).

For stimulation timing for NIBS and MI, significant results were found for both subgroups: (1) NIBS first (MD = 4.13; 95% CI 1.32–6.95; $P = 0.004$; $I^2 = 0\%$) and (2) simultaneous use (MD = 6.37; 95% CI 2.67–10.07; $P < 0.001$; $I^2 = 15\%$).

The above-reported results on functional activity levels domain were shown in (Fig. 8C).

Sensitivity analysis results

Sensitivity analysis showed a high degree of heterogeneity in the results of daily living activities, which was significantly reduced after excluding the study by He et al. [37], suggesting that the literature caused heterogeneity. Further analysis revealed that the experimental design process was not rigorous, no blinding was used, and the investigators, participants, and evaluators were aware of the specific experimental intervention plan, which could lead to biased results.

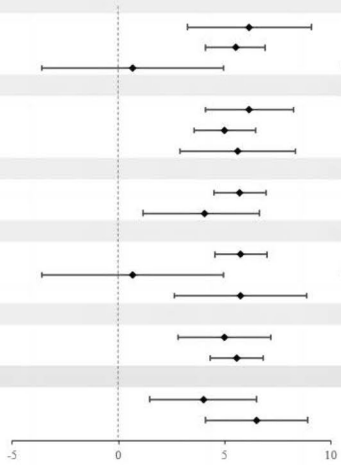
Discussion

Summary of evidence

This systematic review and meta-analysis initially included 14 RCTs. However, two articles were divided into four studies, resulting in 16 studies (886 patients) included in the analysis to investigate the effects of MI combined NIBS on upper limb function after stroke. In addition, its effectiveness in motor function of the upper limbs, activities of daily living, functional activity of upper limb movements, and neurophysiological index (MEP-CL and CMCT) were analyzed. Studies have shown the crucial clinical significance of comparing combination therapy with NIBS alone or MI alone to assess real synergistic effects [26, 31]. This systematic review provided evidence that MI combined with NIBS therapy had positive effects on the recovery of upper limb dysfunction after stroke. Subgroup analysis showed that combinations of the stage of stroke, type of MI, type of NIBS may be key factors that can modulate the effects of MI combined NIBS therapy for upper limb function.

A

Subgroup	Studies	Experimental group, n	Control group, n	MD (95% CI)	P_{within}	I^2_{within}	$P_{between}$	$I^2_{between}$
Motor function of the upper limbs								
Stage of stroke								
Acute	2	71	69	6.17 (3.25 to 9.09)	P<0.001	0%	P=0.09	59%
Subacute	4	120	119	5.52 (4.10 to 6.93)	P<0.001	0%		
Chronic	4	39	35	0.68 (-3.61 to 4.97)	P=0.76	0%		
Type of NIBS								
LF-rTMS	4	89	88	6.16 (4.09 to 8.23)	P<0.001	0%	P=0.67	0%
bi-tDCS	7	136	130	5.01 (3.55 to 6.48)	P<0.001	0%		
a-tDCS	2	64	63	5.64 (2.91 to 8.36)	P<0.001	0%		
Time of NIBS								
>20 minutes	7	188	185	5.73 (4.52 to 6.94)	P<0.001	0%	P=0.25	25.5%
≦20 minutes	6	101	96	4.04 (1.16 to 6.63)	P=0.002	0%		
Type of MI								
General-MI	7	212	209	5.77 (4.55 to 6.99)	P<0.001	0%	P=0.08	60.4%
BCI-MI	4	39	35	0.68 (-3.61 to 4.97)	P=0.76	0%		
GMI	2	38	37	5.76 (2.64 to 8.87)	P<0.001	0%		
Time of MI								
>30 minutes	7	140	133	4.99 (2.79 to 7.19)	P<0.001	0%	P=0.65	0%
≦30 minutes	6	149	148	5.58 (4.32 to 6.84)	P<0.001	0%		
Stimulation timing								
NIBS first	6	77	72	4.00 (1.48 to 6.52)	P=0.002	0%	P=0.16	49.4%
Simultaneously	3	92	90	6.50 (4.10 to 8.90)	P<0.001	0%		



B

Subgroup	Studies	Experimental group, n	Control group, n	MD (95% CI)	P_{within}	I^2_{within}	$P_{between}$	$I^2_{between}$
Activities of daily living								
Stage of stroke								
Acute	2	75	72	10.7 (4.59 to 16.8)	P<0.001	54%	P=0.44	0%
Subacute	3	88	87	8.12 (5.88 to 10.36)	P<0.001	0%		
Type of NIBS								
LF-rTMS	5	141	139	12.12 (10.17 to 14.06)	P<0.001	5%	P=0.03	70.9%
bi-tDCS	4	149	147	12.12 (2.70 to 21.55)	P=0.01	97%		
a-tDCS	1	32	31	5.91 (1.68 to 10.14)	P=0.006			
Time of NIBS								
>20 minutes	5	170	168	12.61 (5.04 to 20.19)	P=0.001	96%	P=0.51	0%
≦20 minutes	5	152	149	9.90 (6.87 to 12.92)	P<0.001	54%		
Type of MI								
General-MI	5	170	168	12.61 (5.04 to 20.19)	P=0.001	96%	P=0.51	0%
GMI	5	152	149	9.09 (6.87 to 12.92)	P<0.001	54%		
Time of MI								
>30 minutes	4	173	170	12.12 (3.13 to 21.11)	P=0.008	97%	P=0.76	0%
≦30 minutes	6	149	147	10.66 (8.37 to 12.96)	P<0.001	33%		
Stimulation timing								
Simultaneously	7	218	213	11.48 (5.03 to 17.92)	P<0.001	94%		

C

Subgroup	Studies	Experimental group, n	Control group, n	MD (95% CI)	P_{within}	I^2_{within}	$P_{between}$	$I^2_{between}$
Activities of daily living								
Stage of stroke								
Acute	2	75	72	10.7 (4.59 to 16.8)	P<0.001	54%	P=0.44	0%
Subacute	3	88	87	8.12 (5.88 to 10.36)	P<0.001	0%		
Type of NIBS								
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≦20 minutes	5	152	149	9.90 (6.87 to 12.92)	P<0.001	54%		
Type of MI								
General-MI	5	170	168	12.61 (5.04 to 20.19)	P=0.001	96%	P=0.51	0%
GMI	5	152	149	9.09 (6.87 to 12.92)	P<0.001	54%		
Time of MI								
>30 minutes	4	173	170	12.12 (3.13 to 21.11)	P=0.008	97%	P=0.76	0%
≦30 minutes	6	149	147	10.66 (8.37 to 12.96)	P<0.001	33%		
Stimulation timing								
Simultaneously	7	218	213	11.48 (5.03 to 17.92)	P<0.001	94%		

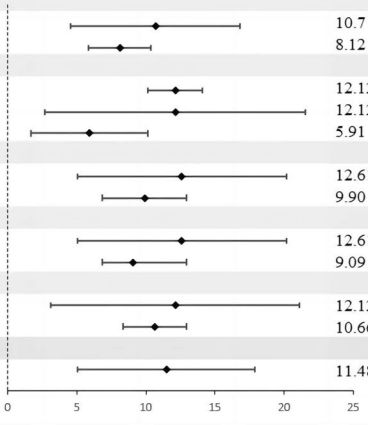

Fig. 8 Subgroup analyses, defined according to the stage of stroke, the type and stimulation time of NIBS, the type and stimulation time of MI, and stimulation timing for MI and NIBS. **A** FMA-UE results. **B** MBI results. **C** WMFT and ARAT results

Clinical effects of MI and NIBS

Our findings were similar to a recent meta-analysis published by Monteiro et al. [7]. Although their study protocol presented a high degree of heterogeneity, the results indicated that training of motor imagery at least twice a week in the three weeks after stroke was effective in improving the motor performance of patients, suggesting that when motor imagery is used as a supplement to traditional rehabilitation techniques, it is an effective technique for treating post-stroke patients. However, a meta-analysis by Aprigio et al. [42] reviewing 412 stroke patients from 13 studies, including 232 in the intervention group and 180 in the control group. They evaluated motor function based on ARAT and FMA, finding no favorable results for MI training after stroke, which is inconsistent with this study. These previous studies focused only on the results of MI alone and not on the effect of MI combined with NIBS, which is different from our study.

Non-invasive brain stimulation has shown promising clinical results, leading to increased demand for an evidence-based review of its clinical effects [43]. Several systematic review studies have analyzed the effects of tDCS and rTMS on motor function recovery in stroke patients. According to the results by Keser et al. [44], evidence-based guidelines support Level A (definite efficacy) for the use of LF-rTMS of the primary motor cortex for hand motor recovery in the post-acute stage of stroke. A guideline and meta-analysis of the use of tDCS in the treatment of neurological and psychiatric disorders by Fregni et al.[45] found that when tDCS was combined with other therapies to treat subacute and chronic strokes, patients showed improvement, and tDCS enhanced the effect of adjuvant therapy. However, the effect size and duration of the effect are usually limited, and the true clinical impact needs to be further determined through different study designs.

Overall findings

The upper limb function (FMA-UE, WMFT, ARAT)

FMA-UE is the most commonly used tool to evaluate upper limb motor function after stroke [46], and 13 articles in our study chose this scale as the basis for improving upper limb motor function. The results showed that after the intervention, the FMA-UE score of the combined group was significantly higher than that of the control group, indicating that the improvement of upper limb motor function of the combined group was significantly better than that of the control group. No significant heterogeneity was observed in the results of FMA-UE, indicating that the results were robust and reliable. Furthermore, the MCID serves as a metric to ascertain whether the change in outcome scores due to interventions is meaningful and constitutes a significant clinical improvement for patients [47]. However, the clinical significance of FMA-UE scores may differ across various patient groups and research settings, necessitating a case-by-case analysis [48]. For example, in the case of stroke patients with moderate to severe damage, an increase of 12.4 points in the FMA-UE score is typically regarded as signifying a meaningful clinical improvement [47]. The results of this systematic review and meta-analysis showed that MCID in the combined group exceeded 12.4 in eight studies, and no improvement to the MCID was observed in the control group, suggesting that only MI or only NIBS has limited clinical effect despite the intervention. We observed that the study populations failing to achieve the MCID were all chronic phase patients more than one-year post-onset. Moreover, a previous study has indicated that for chronic stroke patients, particularly those with residual severe upper limb hemiplegia, the MCID for FMA-UE scores has not been clearly defined, necessitating further research to determine the MCID value for this group [49]. Current evidence suggests that MI combined with NIBS is recommended for patients with severe injury, and MI combined with NIBS is not only statistically effective, but also clinically beneficial to patients.

Regarding functional activity of upper limb movements (such as WMFT and ARAT), 3 studies evaluated WMFT, and 3 evaluated ARAT. Similar to FMA-UE changes, these scores also showed better improvement in the combined treatment group compared to MI alone or NIBS alone. Similarly, no significant heterogeneity was observed, suggesting that the results were robust and reliable, and that MI combined with NIBS was more effective in improving the functional activity performance of the upper limbs in stroke patients.

Activity daily living (MBI)

MBI is the most commonly used measure of activities of daily living (ADL) after stroke, which shows the degree of independence of the patient and provides a quantitative estimate of the level of independence [50]. Ten studies in this study used MBI assessment criteria for activities of daily living. Similar to the results of FMA-UE, the MBI score of the combined group was significantly higher than that of the control group after the intervention, suggesting that the combined group was better than the control group in improving the ability of stroke patients to perform activities of daily living.

Cortical excitability (MEP-CL and CMCT)

When the motor cortex is stimulated by TMS, motor-evoked potentials are generated, and the latency of MEP can represent motor cortical excitability and

corticospinal cord pathway integrity. CMCT is also a commonly used parameter of motor evoked potentials, which is the conduction time from motor cortical neurons to spinal cord motor neurons, mainly reflecting motor neuron and spinal cord anterior horn cell function [51, 52]. Only 4 studies in this systematic review reported using MEP-CL, and 2 studies evaluated CMCT. Interestingly, despite the theoretical similarity of MEP-CL and CMCT, the results of this study showed an inconsistent trend, contrary to our expectations, as some previous studies have shown that MI and NIBS increase corticospinal excitability [43, 53]. Similarly, Chen et al. [54] found that the duration of MEP-CL and CMCT in the experimental group was significantly shortened compared with the control group when discussing the impact of rTMS combined with motor learning training procedures (MRP) on stroke patients. The inconsistency between the two indexes in this study may be due to individual differences of the patients, trial design differences, as well as objective factors such as the position of the coil and the machine, which cannot be accurately measured to obtain the motor-evoked potential index under the same standard, and the motor evoked potential itself tends to fluctuate in different time states of the same patient. In addition, the small sample size may also be one of the reasons for this result. It is recommended to conduct a large sample size randomized controlled trial in the future to determine the effect of MI combined with NIBS on cortical excitability in stroke patients.

Phases of stroke during the intervention

For stroke patients at different stages, the effect of MI combined with NIBS seems to be different. For example, when compared with single therapy, MI combined with NIBS therapy is more effective at improving the FMA-UE score in the acute and subacute stages, but the effect is not significant for stroke patients in the chronic stage. Similar studies have also reached similar conclusions. For example, Ahmed et al. [55] conducted a meta-analysis of 1120 subjects and found that compared with false stimulation, NIBS combined with other therapies effectively improved the FMA-UE score of acute/subacute stroke, but could not change the FMA-UE score of chronic stroke. Brain plasticity is higher in the acute and subacute phases after stroke, which may be why MI combined with NIBS is more effective in these phases.

Taking into account the stage of the disease and the extent of the injury in the rehabilitation process are essential for developing a more accurate and effective program [56]. Given the limited training options for severely impaired chronic patients, we suggest that early intervention is important, so that the damaged neural network can still be reorganized, which may stabilize in chronic patients [57]. Second, chronic patients can be more personalized to their level of injury, such as different types of NIBS (HF-rTMS or LF-rTMS or a-tDCS or c-tDCS) and different types of MI (GMI or MI-BCI) to find the best treatment for the individual. Severely impaired patients may need more intensive or longer treatment, and other rehabilitation methods such as rehabilitation robots [58] and constraint-induced movement therapy [59] may be combined to improve the effectiveness of training. In addition, new technologies such as virtual reality have also explored for the training of MI combined with NIBS [60], which can help severely impaired chronic stroke patients obtain more immersive MI training through virtual reality, reduce fatigue, increase participation, and improve treatment effect.

Differences in types of MI

Considering the type of MI, 7 studies used general video and audio-guided MI, which provides a standardized guide to MI in which patients typically watch video materials and listen to audio instructions to perform specific actions, such as shrugging shoulders, raising hands, making fists, etc. It is simple and intuitive, using familiar sensory inputs to promote MI [25]. With the development of brain-computer interface technology, it provides a visual window for MI. Four studies used BCI real-time feedback-guided MI, which is performed by collecting changes in sensorimotor rhythms that occur in the brain during MI [30]. Since there is a gap in the individual motor imagery ability, MI-BCI can provide visual, auditory and tactile feedback help, so that patients may benefit more from MI training. Two studies used graded MI, which gradually increases the difficulty of MI tasks according to the patient's ability and stage of recovery, from simple MI to more complex and closer to daily living skills, based on personal experience and memory [31, 32].

Despite the advanced nature of MI-BCI technology, its effect in this study is not beyond the video and audio-guided MI and graded MI methods. Notably, no patients with BCI blindness were reported in any of the included MI-BCI studies, which prevented them from effectively using the BCI system and thus did not achieve a prefetch effect. However, the studies included did not employ a uniform assessment tool to quantify the participants' MI abilities. This difference may have influenced the interpretation of the findings to some extent. Thus, for future research, it is advisable to utilize standardized assessment instruments to measure MI capabilities. This will facilitate a more precise evaluation of the performance of MI-BCI systems and provide a more consistent baseline for comparing results across different studies. In light of the current evidence, it is recommended that video and

audio-guided MI and graded MI be given priority in clinical practice, while continuously delving into the optimization of BCI technology.

Differences in types of NIBS

Clinically, different studies have used different types of NIBS to stimulate stroke patients. Our results showed that MI, whether combined with tDCS or rTMS, can significantly improve upper limb motor function (FMA-UE score), functional activity level (WMFT, ARAT score), activity of daily living (ADL score), and corticospinal excitability (CMCT). Similar findings were reported by a recent meta-analysis by Kang et al. [61], which evaluated the effectiveness of NIBS in improving the force production capability in paretic limbs and concluded that tDCS and rTMS regiments (increased cortical excitability of the affected cerebral hemisphere by a-tDCS and HF-rTMS; reducing the excitability of the contralateral cerebral cortex by c-tDCS and LF-rTMS) successfully improved paretic limb force production capabilities.

In addition, subgroup analysis in this study showed differences in MBI outcomes between LF-rTMS and bi-tDCS and a-tDCS subgroups, i.e., the type of NIBS had a significant interaction with the effect of MI combined with NIBS therapy, and the effect of LF-rTMS and a-tDCS was better than that of bi-tDCS. LF-rTMS in the unaffected cerebral hemispheres has been reported to be more effective in the chronic phase of stroke (grade B recommendation) [62]. A recent meta-analysis showed that HF-rTMS increased cortical excitability in the affected hemisphere at the stimulation site and improved impaired upper extremity motor function in stroke patients [63]. Research by Lefebvre et al. [64] suggests that when using tDCS, people should pay attention to which brain regions should be targeted and which stimulation types should be used. As shown in the Muffel et al. [23] study, which included 24 stroke patients randomly divided in two groups treated with bi-tDCS or a-tDCS, bi-tDCS showed a significantly greater beneficial effect on improving motor and sensory function compared with a-tDCS. The differences in therapeutic effects may be due to the fact that rTMS and tDCS are two distinct types of stimulation with different technological mechanisms, stimulation parameters, and targeted brain regions. However, due to the small number of studies extracted and the variability of reported stimulus parameters, we could not perform a sub-analysis to elucidate stimulus parameters for different NIBS, which limited our understanding of the positive changes in motor function promoted by NIBS. Neuroimaging data (fMRI) should be acquired prior to, during, and following treatment to elucidate the underlying neural mechanisms mediating treatment effects. Moreover, MRI-neuronavigation may address potential discordance between coil/electrode placement and region of interest, potentially improving treatment efficacy [65].

Stimulation timing and after-effect

Regarding stimulation time, the current MI training was about 30 min, and the NIBS time was about 20 min, which was taken as a classification in our study. These results may suggest that the time of MI and NIBS is not a direct factor affecting the effect, and it is necessary to conduct a more extensive study in the future to explore the best intervention duration of MI and NIBS to maximize the time and economic benefits of patients and make more people benefit from them. On the other hand, we note that most of the included studies reported only the total duration of MI in their intervention protocols, without specifying the repetition time and exact number of times to perform MI tasks, impeding the development of more structured protocols for MI.

This study showed that compared with a single therapy, stroke patients' upper limb motor function could be better improved regardless of the stimulation timing of MI and NIBS in the combination group. NIBS can promote motor recovery by activating or inhibiting activity in cortical areas, particularly when combined with appropriate motor training, they can optimize changes in brain plasticity and thus play a greater role in the recovery of motor function after stroke [66]. Kang et al. [67] also obtained similar conclusions, which could be explained by the priming stimulation mechanism. This theory suggests that "the brain that has been primed by prior activation is generally more responsive to the accompanying or subsequent training". However, some preliminary evidence seems to support the notion that applying NIBS prior to activity execution can more effectively enhance motor performance, and that NIBS can prime cortical excitability for subsequent motor training tasks, thereby optimizing the processes of motor learning involved in standard rehabilitation therapies, leading to more pronounced and longer lasting functional gains [68–71]. As demonstrated by Cabral et al. [69] and Jo et al. [70], the absence of tDCS-induced effects when tDCS is applied during or after motor training may be due to the induction of meta-plasticity plasticity and the activation of homeostatic regulation mechanisms. Conversely, Jin et al. [72] proposed that applying tDCS during motor training may be more conducive to motor recovery. We speculate that different NIBS protocols (HF-rTMS, LF-rTMS, a-tDCS, c-tDCS, or bi-tDCS) may lead to inter-individual differences in therapeutic outcomes, and therefore their efficacy might vary. Consequently, the optimal timing of NIBS (ie, before vs during MI) is still open to question. In the future, the successful implementation of combined

NIBS and MI will critically rely on improved understanding of their functional interactions and associated effects on neural plasticity. Greater understanding of the mechanisms of action of each approach is necessary in order to optimize their combined use in rehabilitation and realize the promise of a more effective means to promote functional recovery after stroke.

It is also worth mentioning the post-intervention follow-up, which was found in a total of 5 included studies. The subgroup analysis showed that the intervention effect varied at different time points. At the 2-week follow-up, the functional improvement of MI combined with NIBS therapy was still better than that of single therapy, indicating that this functional improvement was maintained in the short term. However, four weeks after the end of the intervention, there was no difference in the effects between the two, suggesting that the advantage of the combination therapy was lost. The reason for this fact may be that the initial effect of MI combined with NIBS is more pronounced, and the intervention time in the study is relatively short, which leads to the effect not being maintained for a long time. In addition, differences in individual characteristics and study design, as well as follow-up methods, may affect the assessment of long-term effects. Although the combination of MI and NIBS has shown positive effects in the follow-up, how to maintain this effect is still a challenge, and it is necessary to explore long-term effective intervention strategies.

Clinical implications and recommendations

MI combined with NIBS therapy can effectively improve the upper limb motor function and activities of daily living in acute and subacute stroke patients with severe injury, and this improvement has clinical significance. The safety of treatment and combination of various types provides patients with more personalized rehabilitation options, and the short-term effect is significant.

It is important to note that this systematic review and meta-analysis included only Asian studies, which may limit the generality of MI combined with NIBS in the treatment of upper limb function recovery after stroke. We speculate that different regional research priorities, genetic and cultural differences may be responsible for this phenomenon. Non-invasive treatment methods may be preferred in Asia, and the healthcare system and resource allocation differ from those in Western countries, which may affect the implementation and effectiveness of treatment [73]. It is suggested that future studies of NIBS combined with MI should be conducted on a global scale to improve the generality and applicability of the conclusions and to explore the influence of geography and culture on treatment outcomes in order to design personalized rehabilitation strategies for different regions.

As it has been highlighted in numerous studies, there are several issues regarding combining MI and NIBS that still need to be addressed. Personalized selection of the specific types of MI and NIBS is essential, as the appropriate combination of these factors can lead to synergistic effects that enhance therapeutic outcomes. Considering the individual differences in MI abilities, standardized assessment tools are required to evaluate and teach effective imagery techniques. We should educate patients on how to recognize and report any discomfort or side effects to ensure the safety of treatment. In the future, developing is necessary remote rehabilitation platforms that allow patients to conduct MI combined with NIBS training at home, thereby increasing the accessibility of treatment. At the same time, further promotion of its integration with other rehabilitation technologies, such as virtual reality, augmented reality, and electromyography biofeedback, will enhance patient engagement and therapeutic outcomes [74]. Through the collection and analysis of treatment data, the therapy protocol can be continuously optimized to enhance its general effectiveness, and advanced imaging techniques such as functional near-infrared spectroscopy and multimodal functional magnetic resonance imaging can be used to objectively monitor changes in brain activity after treatment to provide direct evidence of treatment effectiveness, thereby enhancing the medical community and patients' acceptance of this treatment regimen. Additionally, conducting long-term studies are essential to assess the long-term effects of MI combined with NIBS treatment. This not only helps in understanding the sustainability of the therapeutic effects but also evaluates its impact on patients' quality of life and social participation. Therefore, taking these aspects into comprehensive consideration will provide patients with more comprehensive, safer, and more effective treatment options.

Limitations

The present study has some limitations. First, the number of included studies was small, with only 7 articles in English and 7 in Chinese. Second, the research design of the included articles in this study was quite different, and the methods of allocation hiding and blinding were different in the included population, some of which were not mentioned in the article. Third, due to the small number of studies addressing the electrophysiology indicators and the different equipment used in different studies, understanding the role of MI combined with NIBS in promoting cortical excitability is limited. Fourth, routine rehabilitation varied slightly across studies in addition to the set intervention. Fifth, there was a high degree of

heterogeneity in MBI evaluation results, which diminished the power of the findings and their implications for clinical practice. Sixth, it remained unclear whether age, injury severity, and injury type affect the outcome of MI combined with NIBS. These factors should be considered when forming a uniform sample to determine whether these factors are essential for movement improvement after combination therapy. Finally, the monitored study outcomes differed across studies, limiting the ability to compare outcomes and the inconsistencies in the results.

Conclusion

The combination of MI and NIBS may be a promising therapeutic approach to enhance upper limb motor function, functional activity, and activities of daily living after stroke. Our findings provide preliminary evidence for the effectiveness of MI in combination with NIBS in improving upper limb motor dysfunction in stroke patients and encourage further high-quality research in this area. Despite some limitations, we believe the findings and recommendations provided in this review may help select the most appropriate combination regimen to maximize upper limb motor function restoration in stroke patients.

Abbreviations

tDCS	Transcranial direct current stimulation
rTMS	Repetitive transcranial magnetic stimulation
NIBS	Non-invasive brain stimulation
MI	Motor imagery
FMA-UE	Fugl-Meyer assessment of upper extremity
MBI	Modified Barthel Index
WMFT	Wolf motor function test
ARAT	Action research arm test
MEP-CL	Cortical latency of motor evoked potential
CMCT	Central motor conduction time
MD	Mean differences
SMD	Standard mean differences
CI	Confidence intervals
ASA	American Stroke Association
LF-rTMS	Low frequency rTMS
HF-rTMS	High frequency rTMS
bi-tDCS	Bilateral-transcranial direct current stimulation
a-tDCS	Unilateral anodal transcranial direct current stimulation
c-tDCS	Unilateral cathodal transcranial direct current stimulation
BCI-MI	Brain computer interface based motor imagery
I	Infarction
H	Hemorrhage
L	Left
R	Right
SD	Standard deviation
RCT	Randomized controlled trials
DB	Double-blind
DLPFC	Dorsolateral prefrontal cortex
SB	Single blind
EG	Experimental group
CG	Control group
CR	Control group
FTHUE	Functional test for the hemiplegic upper extremity
RMT	Resting motor threshold
NIHSS	National institute of health stroke scale
No	Serum nitric oxide
ET-1	Endothelin-1
TUTG	Time up and go test
BBS	Berg balance scale
MFES	Modified falls efficacy scale
MAS	Motor assessment scale
MAL-AOU	Motor activity log-amount of use
MAL-QOM	Motor activity log-quality of movement
MMSE	Minimum mental state examination
MoCA	Montreal cognitive assessment
MCID	Minimal clinically important difference
MRP	Motor relearning procedures
NA	Not available
LOTCA	Loewenstein occupational therapy cognitive assessment
FTHUE-HK	Hong Kong version of the hemiplegic upper limb functional test
m	Month
s	Simultaneously
d	Day
BBT	Box and blocks test
ARAT	Action research arm test
DTI	Diffusion tensor imaging
CBF	Cerebral blood flow
MEP	Motor evoked potential
ERD	Event-related desynchronization
SICI	Short intra-cortical inhibition
ReHo	Regional homogeneity
FC	Functional connectivity
ALFF	Amplitude of low-frequency fluctuation
NA	Not available

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Author contributions

WDZ and XLL carried out the studies, participated in collecting data, and drafted the manuscript. MYG and ZSL carried out the literature search and data extraction. WBL, QQZ and PYL and statistical analysis and quality evaluation. YY and WBL participated in acquisition, analysis, or interpretation of data and draft the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request. For any specific inquiries regarding the data or materials used in this study, please contact the corresponding author.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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