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A Meta-Analysis of Non-Invasive Brain Stimulation Therapies for Motor Function Recovery in Stroke Patients

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Abstract: In recent years, there have been reports suggesting that non-invasive brain stimulation (NIBS) can improve post-stroke complications. Non-invasive brain stimulation therapies include transcranial direct current stimulation (tDCS), transcranial magnetic stimulation (TMS), and intermittent theta burst stimulation (iTBS), among others. Clinically, a combination of one or more of these therapies is often used. However, it remains unclear which method is the most effective and safest for the recovery of limb function after a stroke. The aim of this study is to integrate various research findings to investigate the effects of non-invasive brain stimulation on the recovery of limb motor function in all stroke survivors.

Keywords: Transcranial Direct Current Stimulation (tDCS), Magnetic Stimulation, Transcranial Magnetic Stimulation (TMS), Stroke Rehabilitation, meta-analysis

1. Introduction

It is estimated that stroke is the second leading cause of death worldwide, affecting approximately 13.7 million people, with around 5.5 million deaths annually [1]. Stroke is also the third most common cause of disability globally [2], with a disability rate as high as 70% in aging China [33]. Over 50% of chronic stroke patients experience motor function impairments [27], with about 10% showing significant reductions in motor function [3], typically affecting arm and leg movements on one side of the body. This is due to brain lesions caused by stroke [24] that damage the upper motor neurons in the cortical motor area, leading to a loss of higher central inhibition of spinal reflexes, resulting in increased spinal reflexes and muscle tone abnormalities characterized by muscle rigidity, increased tendon reflexes, and voluntary movement disorders [25]. The excitability of the affected cortical area is significantly reduced, while excitability in the unaffected hemisphere is increased due to an imbalance in interhemispheric interactions [28]. In Traditional Chinese Medicine (TCM), stroke is classified as "stroke" [30], caused by factors such as deficiency, fire, wind, phlegm, qi, blood, and stasis leading to obstruction of brain vessels or hemorrhage, resulting in sudden coma. According to its symptoms, stroke can be classified into common patterns such as "wind yang disturbance," "qi deficiency and blood stasis," "yin deficiency and wind movement," and "wind-phlegm obstruction" [31]. Among these, the wind-phlegm-obstruction pattern is the most common in ischemic stroke [32], with the pathogenesis involving phlegm disturbing the clear orifices and meridian obstruction, clinically presenting as limb numbness [30]. Motor function impairments in the limbs are the most common sequelae of stroke, significantly reducing daily living activities and quality of life [4], and requiring caregivers to invest more time and effort, creating a significant caregiving burden [5]. Therefore, exploring optimal treatment measures has become a clinical focus.

Research indicates that increasing excitability on the affected side or decreasing excitability on the unaffected side can promote recovery of upper limb motor function after stroke [28]. Non-invasive brain stimulation (NIBS) has a bidirectional effect on excitability and can either increase excitability on the affected side or decrease it on the unaffected side to promote upper limb motor function recovery. NIBS is an emerging method to enhance rehabilitation outcomes after stroke [7]. As a non-invasive and safe technique, it has garnered increasing attention due to its potential therapeutic effects on brain activity [8]. NIBS therapies include transcranial direct current stimulation (tDCS) [9], transcranial magnetic stimulation (TMS) [10,11], and intermittent theta burst stimulation (iTBS). Among these, tDCS and rTMS are more commonly used. tDCS regulates cortical excitability by

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stimulating the central nervous system, with anodal tDCS usually increasing cortical excitability and cathodal tDCS decreasing it [27]. Specifically, it involves placing electrodes on the scalp to modulate the resting membrane potential of neurons, thereby altering cortical excitability [12]. Many studies place the anodal electrode on the affected side's primary motor cortex (M1) to increase excitability, and the cathodal electrode on the unaffected side's M1 to decrease excitability, thereby alleviating the excitability imbalance between the hemispheres after stroke [28]. This promotes synaptic plasticity and the acquisition of motor functions [26]. rTMS uses changing currents through coils to generate a pulsed magnetic field that passes through the skull without attenuation to stimulate the cortical area, inducing depolarization in neurons and generating evoked potentials to excite neurons [13]. Studies show that high-frequency rTMS (3–20 Hz) and intermittent TBS (iTBS) increase cortical excitability, while low-frequency rTMS (<1 Hz) decreases it [28]. Clinically, a combination of one or more therapies is commonly used to treat limb function disorders after stroke [14,15,16]. However, these studies vary not only in the choice of NIBS methods [9,10,11,14] but also in the frequency and stimulation sites used [17,18,19], and the most effective and safest method for limb function recovery after stroke remains unknown.

Shao Jinhui and others believe that physical stimulation still has certain side effects and recurrence rates, whereas acupuncture and massage therapy have high efficacy and can achieve noticeable results within 1 to 3 months [29]. Acupuncture, an important external treatment in TCM, has a lower treatment cost and relatively simple clinical operation, and has recently proven effective in treating post-stroke complications. Scalp acupuncture using the Jiaozhi method in specific functional areas has shown good clinical outcomes, improving recovery in neurological function and motor function in post-stroke hemiplegia patients [30]. Therefore, this study also includes research on acupuncture treatment for post-stroke hemiplegia patients for analysis.

Previous meta-analyses [20] have confirmed that rTMS can promote motor recovery in stroke patients, but the comprehensive results of meta-analysis, heterogeneity analysis, and study quality assessment indicate that the effects confirmed are only effective for lower limb motor function. The mechanisms of rTMS in stroke recovery have not been elucidated. Another meta-analysis [34] confirmed that acupuncture can effectively improve spastic hemiplegia of the upper limb after stroke, but due to variations in acupuncture tools, stimulation methods, and intensities, and a small sample size for some therapies, a systematic evaluation of a single therapy was not feasible. Recent high-quality original studies [21,22,23,35] have been published, making it necessary to integrate different studies to explore the effects of non-invasive brain stimulation and acupuncture on limb motor function and muscle strength recovery in stroke survivors.

2. Method

2.1. Search Strategy

We searched for English-language randomized clinical trials published from the inception of PubMed and Embase databases up to September 2021. The search strategy combined subject headings with free terms, aiming to explore the impact of non-invasive brain stimulation on the recovery of limb motor function after stroke. The following keywords were used for database searches: "stroke" or "stroke rehabilitation" or "apoplexy" or "cerebrovascular disorder," "transcranial direct current stimulation" or "transcranial magnetic stimulation" or "TMS" or "rTMS" or "tDCS" or "noninvasive brain stimulation."

2.1. Inclusion and Exclusion Criteria

To ensure the quality of the articles, we screened them according to unified inclusion standards from five aspects. The specific criteria are as follows:

2.1.1. Study Population

Inclusion Criteria:

1. Age $\geq$ 18 years
2. No other rehabilitation treatments taken and voluntarily joined, signed informed consent.
3. Patients diagnosed with stroke confirmed by head CT or MRI scans or by a physician. Acceptable diagnostic criteria include the stroke diagnostic standards set by the Fourth National Conference on Cerebrovascular Diseases or other internationally recognized standards.

Exclusion Criteria:

1. Presence of serious organic diseases such as heart, lung, liver, or kidney diseases.
2. Presence of cognitive or psychiatric disorders or communication barriers.
3. Patients in the acute phase of stroke.

2.1.2. Intervention Measures

The intervention group uses non-invasive brain stimulation methods such as transcranial magnetic stimulation, transcranial electrical stimulation, or repetitive transcranial magnetic stimulation. These methods can be used alone or in combination with two or more therapies. There are no specific limitations on the frequency, stimulation sites, or duration of the stimulation.

Subgroup Analysis: Patients with stroke are grouped according to the time of starting non-invasive brain stimulation after stroke onset, and the effectiveness of non-invasive brain stimulation treatment is analyzed in relation to the time of starting the treatment.

2.1.3. Control Measures

The control group receives sham stimulation.

2.1.4. Outcome Indicators

The degree of recovery of limb motor function after stroke is measured using recognized tools such as the ARAT, FM, MAL, GAS, and FMA-UE scales; quality of life (QOL) after stroke; and activities of daily living (ADL) abilities.

2.1.5. Study Types

All studies are randomized controlled trials, including both crossover and parallel designs.

2.2. Literature Quality Assessment Method

Two trained researchers independently assessed the quality of the literature using the risk of bias assessment tool provided by Cochrane systematic reviews. The assessed aspects include: bias due to randomization process (selection bias), bias due to deviations from intended interventions (performance bias), bias in outcome assessment (detection bias), bias due to missing outcome data (attrition bias), bias in reporting research results (reporting bias), and other biases. Based on the information from the literature, the risk of bias items are categorized as low risk, high risk, or unclear. Finally, based on the comprehensive evaluation results, decisions are made to include, exclude, or cautiously include the literature. If the literature lacks specific descriptions of random sequence generation and allocation concealment, attempts will be made to contact the authors to obtain relevant information before conducting the quality assessment; if contact fails, it will be categorized as unclear. When inconsistencies occur in quality assessment results, a third researcher will make the judgment.

2.3. Data Extraction and Analysis

Two experienced reviewers independently completed the data extraction. (1) Basic Information: first author's name, publication date, baseline characteristics of study subjects, sample size; (2) Intervention and Control Group Measures: specific form, frequency, site, number of interventions, duration of each intervention, follow-up time, etc.; (3) Outcome Indicators: degree of recovery of limb motor function.

Meta-analysis was performed using RevMan 5.3 software. For the continuous data of limb motor function recovery, effect measures (95% confidence intervals (CI) and p-values) are calculated using mean and standard deviation. The heterogeneity among studies is assessed, and if there is no significant heterogeneity ($P > 0.1$, $I^2 < 50\%$), a fixed-effects model is used to calculate the combined effect size. If heterogeneity is present ($P < 0.1$, $I^2 > 50\%$), but clinical judgment indicates consistency among groups, a random-effects model is used to combine effect sizes and subgroup analysis is performed to identify sources of heterogeneity. If heterogeneity is too large, only descriptive analysis will be done. To assess the stability of outcome indicators, sensitivity analysis is conducted by comparing the differences between combined effect sizes through sequential exclusion of included studies.

3. Result & discussion

Initially, 9,345 articles were retrieved. After removing 3,837 duplicate articles and applying the inclusion and exclusion criteria, a total of 14 articles were selected for the meta-analysis. The literature screening process is illustrated in Figure 1 (middle) and Figure 2 (English).

The data extracted from the included articles include: name of the corresponding author, country, year of publication; patient characteristics (average age, number); type, location, intensity, and dose of stimulation; evaluation scales and time; follow-up duration. A total of 448 stroke patients received either electrical stimulation or magnetic stimulation treatment, with 265 in the experimental group, aimed at improving motor function outcome measures. The average age of the study participants ranged from 60.3 to 70.3 years. All stroke patients included in the articles were in the chronic phase. In terms of experimental methods, all included studies were randomized controlled trials. The main features and quality assessment of the included studies are detailed in Table 1 and Figure 5.

Two studies investigated tDCS, with 106 patients receiving this intervention; eight studies investigated rTMS, with 190 patients receiving this intervention; one study investigated TMS, with 14 patients receiving this intervention; two studies investigated rTMS combined with iTBS, with 106 patients receiving this intervention; and one study investigated rPMS, with 32 patients receiving this intervention.

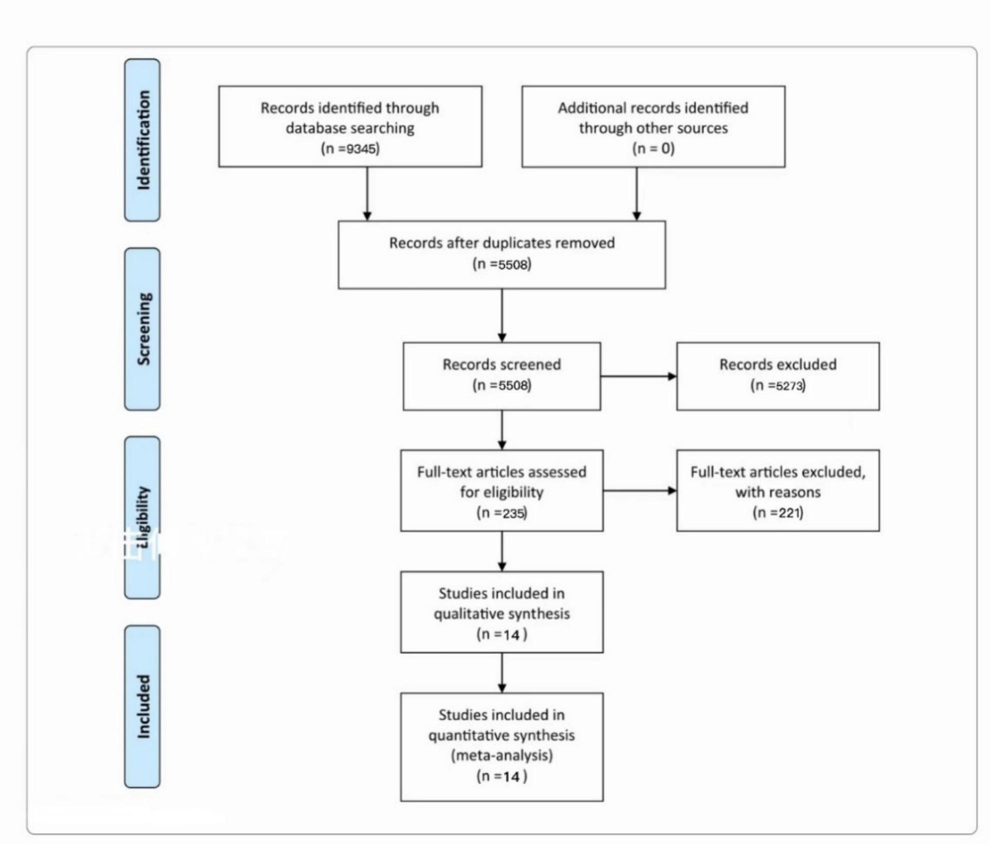

Figure 1 PRISMA flow diagram

Table 1 Characteristics of studies included in this meta-analysis

author/year	country	N(Invention/ Control group)	age(years)Mean ± SD	Intervention	Control	Protocol	Outcome	Measurement time points	Follow-up
Chang/2015	Korea	7/7	66.5 ± 8.6	TMS(+)	TMS(-)	Cortical stimulation:once a workday over affected the vertex over four weeks;Electrode size:A Magstim Novametrix 200 magnetic stimulator with a 9 cm mean diameter circular coil.	MI，FAC	4 weeks	6 months
Chen/2020	China	16/16	47.3 ± 13.3	rPMS	sham rPMS	Cortical stimulation:For muscle groups with spasticity(low frequency of 5 Hz,total of 750 stimuli),for their antagonistic muscles(high frequency of 20 Hz,total of 5100 stimuli);Sham stimulation:a second coil to the patients'upper limbs with a real coil operated nearby on a chair to produce a simulated voice;Electrode size: inner diameter of 25 mm and external diameter of 120 mm, with a pulse width of 280 µs.	MAS,MTS, FM	/	/
Conforto/2012	Brazil	15/15	55.8 ± 13.3	rTMS	sham rTMS	Cortical stimulation:once a workday over the scalp on the optimal site for the nonparetic APB in the contralesional hemisphere over two weeks (1HZ for 25 minutes,total of 1500 stimuli);Sham stimulation:the coil was held perpendicularly to the vertex. Patients were comfortably seated, wore earplugs, and were instructed to remain at rest during TMS.	JTT,AS,FM,MRS，PF	2 weeks	1 month
Del Felice/2016	Italy	5/5	62	Sham Stimulation+tDCS(-)	Sham Stimulation+ Dual tDCS	Cathodal stimulation:once a workday over the unaffected primary M1 over one week (1.0 mA for 20 minutes);Dual stimulation:once a workday over the cM1 and anode over M1 over one week(1.0 mA for 20 minutes);Sham stimulation:applying the same current at the beginning and ending of stimulation(for 30 seconds).	MRC,MAS, AS	1 week	8 weeks

Table 1 (Continued)

author/year	country	N(Invention/ Control group)	age(years)Mean ± SD	Intervention	Control	Protocol	Outcome	Measurement time points	Follow-up
Etoh/2013	Japan	9/9	59.7 ± 11.0	sham rTMS+motor training	motor training+ sham rTMS	Cortical stimulation:once a workday over the unaffected abductor pollicis brevis (APB) muscle over four weeks (1HZ for 4 minutes,total of 240 stimuli);Sham stimulation:a region 5-cm posterior to the contralesional motor cortex (1HZ for 4 minutes);Rehabilitation training: 40 minutes of repetitive facilitation exercises every workday,1–2 h of voluntary training.	FM,ARAT, MAS	20 days	/
Rastgoo/2016	Iran	17/17	52.2 ± 11.4	rTMS+sham rTMS	sham rTMS+rTMS	Cortical stimulation:once a workday over unaffected lower extremity motor area over 1 week(1HZ,total of 1000 stimuli).	MMAS,FM	5 days	1 week
Hesse/2011	Germany	64/32	65 ± 9.8	tDCS(-)+AT tDCS(+)+AT	sham tDCS(+) +AT	Anodal stimulation: once a workday over affected primary motor cortex over six weeks (2.0 mA for 20 minutes);Cathodal stimulation: once a workday over non-affected primary motor cortex over six weeks (2.0 mA for 20 minutes);Sham stimulation: the positions of the electrodes either followed that of anodal or cathodal stimulation (0 mA for 20 minutes);Electrode size: 35 cm2 Robot-Assisted;Arm Training: 400 repetitions each of two different bilateral movements for 20 minutes over six weeks;Rehabilitation training: 45 minutes of individual physiotherapy sessions every workday, 30 minutes of individual occupational therapy.	FM,MRC, AS,Barthel Index	6 weeks	3 months
Takeuchi/2005	Japan	10/10	59.0 ± 9.6	rTMS+motor training	sham rTMS+motor training	Cortical stimulation:once a workday over the contralesional M1(1HZ for 25 minutes,20 times);Sham stimulation:perpendicularly to the scalp of the contralesional M1 (1HZ for 25 minutes,20 times);Electrode size: 70-mm figure-8 coil;motor training:pinching of 60 minutes,pinching of 15 minutes for 7 days.	FM	/	/

Table 1 (Continued)

author/year	country	N(Invention/ Control group)	age(years)Mean ± SD	Intervention	Control	Protocol	Outcome	Measurement time points	Follow-up
Fregni/2006	America	10/5	56 ± 11.5	rTMS(low-frequency)	sham rTMS	Cortical stimulation:once a workday over the unaffected hemisphere over the primary motor cortex over one week(1HZ for 20 minutes,total of 1200 stimuli);Sham stimulation: the positions of the electrodes followed that of real stimulation (0 HZ for 20 minutes).	JTT	5 days	2 weeks
Higgins/2013	Canada	6/5	67 ± 9.5	rTMS+Task-Oriented Training	Sham rTMS+Task-Oriented Training	Cortical stimulation:once a workday over FDI(1HZ,total of 1200 stimuli);Task-Oriented Training:Each task was repeated on average 10–15 times for a duration of approximately 10 to 15 minutes(90 minutes).	Grip strength,MAL	/	/
Seniow/2012	Poland	20/20	63.5 ± 9.1	rTMS+Motor training	sham rTMS+Motor training	Cortical stimulation:once a workday over FDI over three weeks(1HZ for 30 minutes);Sham stimulation:Patients did not know whether they were receiving real or sham stimulation;Motor training:15 once-daily sessions, 5 days per week for 3 weeks.	WMFT,Fugl-Meyer	3 weeks	3 mooths
Sung/2013	China	43/15	63.2 ± 12.4	rTMS+iTBS+physiotherapy sham rTMS+iTBS+physiotherapy rTMS+sham iTBS+physiotherapy	sham rTMS+sham iTBS+physiotherapy	rTMS+iTBS:once a workday over the contralesional primary motor cortex (M1) and then intermittent theta burst stimulation over the ipsilesional M1 over four weeks(1 HZ,30 to 60 minutes);physiotherapy:one hour for 20 days.	WMFT,FM,MRC	20 days	/
Wang/2014	China	32/16	62.6 ± 12.5	rTMS+iTBS+physiotherapy sham rTMS+iTBS+physiotherapy	sham rTMS+sham iTBS+physiotherapy	Cortical stimulation:once a workday over FDI over four weeks(1HZ for 20 minutes of rTMS,190 seconds of iTBS);physiotherapy:one hour daily, five times per week.	FM, WMFT, MRC	4 weeks	3 months
Rose/2014	USA	11/11	64.7 ± 8	rTMS+physiotherapy	sham rTMS+physiotherapy	Cortical stimulation:over ECR(the extensor carpi radialis) over 4 times per week for 4 weeks(1HZ,total of 1200 stimuli);physiotherapy:one hour daily,4 times per week for 4 weeks.	WMFT,ARAT,MAS,MAL,Grip strength	4 weeks	/

Age：Del Felice/2016：Average age

Fourteen studies were randomized controlled trials and assessed for quality using the RoB 2 Excel Macro Form Manual. The evaluation results are presented with evaluation items as columns and included studies as rows. Among the intention-to-treat group, 7 studies were classified as low risk of bias, and 3 studies were classified as having some risk. In the per protocol group, 4 studies were classified as low risk of bias.

Summarize the proportion of each evaluation item categorized as "low," "uncertain," and "high" risk. Selection bias and attrition bias are considered high risk, implementation bias, measurement bias, and attrition bias are categorized as uncertain risk, and reporting bias and other biases are categorized as low risk.

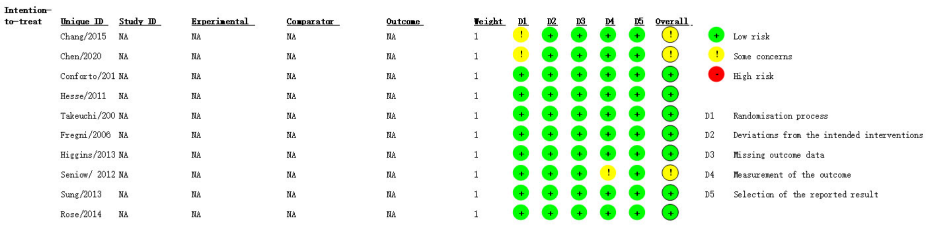

Figure 2 Risk of bias graph

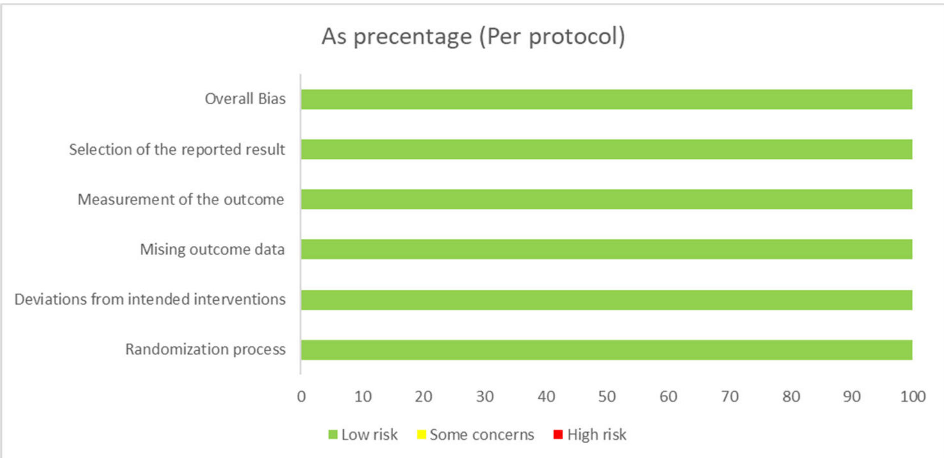

Figure 3 Risk of bias summary

A total of 2 studies tested the effects of transcranial direct current stimulation (tDCS).

Participants: A total of 106 stroke patients (66 males and 40 females) were surveyed. The time post-stroke varied (from 4 weeks to 3 years), and the location of the lesions was inconsistent (45 right-sided and 51 left-sided).

Study Design: Both studies investigated the efficacy of real tDCS compared to sham stimulation. One study administered active stimulation for 20 minutes per session (with a total of 30 sessions), while the other study administered active stimulation for 20 minutes per session (with a total of 5 days of treatment). All studies assessed parameters before and after the intervention. Both studies also conducted additional follow-up evaluations 8 weeks to 3 months after the intervention.

Stimulation Protocol: One trial studied bilateral tDCS (combining anodal tDCS on the same hemisphere and cathodal tDCS on the opposite hemisphere) and cathodal tDCS. Another study placed the anodal tDCS over the hand area of the lesioned hemisphere.

Real vs. Sham Stimulation: Data from the forest plots indicate that tDCS yielded negative results for upper limb motor function in stroke patients. According to the study results, cathodal tDCS on the contralesional hemisphere had a better impact on the assessment parameters compared to bilateral tDCS, and it was more effective in reducing distal upper limb spasticity. Neither anodal nor cathodal tDCS improved the effects of bilateral arm training.

Eight studies tested magnetic stimulation (TMS), repetitive peripheral magnetic stimulation (rPMS), repetitive transcranial magnetic stimulation (rTMS), and intermittent theta-burst stimulation (iTBS) for improving upper limb motor function in stroke patients. One study tested the effect of TMS on lower limb motor function improvement.

Participants: A total of 259 patients (173 males and 77 females) were included. The time post-stroke varied (from 16 days to 11 years), as did stroke etiology (45 ischemic, 41 hemorrhagic), stroke location (75 subcortical, 84 cortical), and lesion side (81 right-sided, 53 left-sided).

Study Design: All studies investigated the efficacy of magnetic stimulation (TMS), repetitive peripheral magnetic stimulation (rPMS), low-frequency repetitive transcranial magnetic stimulation (rTMS), and intermittent theta-burst stimulation (iTBS) compared to sham stimulation. The duration of active stimulation ranged from 10 to 30 minutes (190 to 5100 pulses). All trials used pre- and post-intervention assessments. Four trials conducted additional follow-up evaluations from six weeks to six months after the intervention.

Stimulation Protocol: Three studies applied rTMS to the contralesional hemisphere. Two trials administered bilateral stimulation (TMS applied to both the same hemisphere and the opposite hemisphere; left hemisphere stimulation used counterclockwise current, and right hemisphere stimulation used clockwise current). Two studies tested contralesional hemisphere rTMS combined with iTBS on the ipsilesional hemisphere. One trial applied repetitive peripheral magnetic stimulation (rPMS) to the muscles. One study used low-frequency rTMS on the contralesional hemisphere.

Real vs. Sham Stimulation: Post-intervention data indicated significant improvements in observed parameters with magnetic stimulation (TMS), repetitive peripheral magnetic stimulation (rPMS), low-frequency repetitive transcranial magnetic stimulation (rTMS), and intermittent theta-burst stimulation (iTBS). Repetitive transcranial magnetic stimulation (rTMS) produced the largest effect. Repetitive peripheral magnetic stimulation (rPMS) also demonstrated good efficacy.

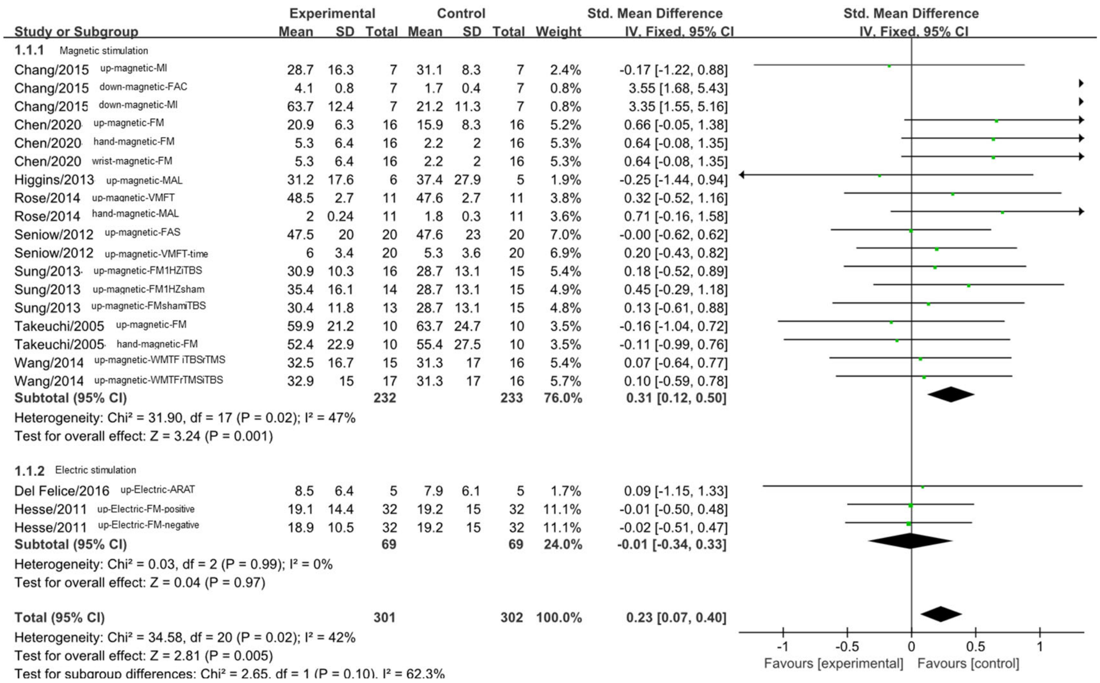

Figure 4 Statistical analysis of electrical and magnetic stimulation.

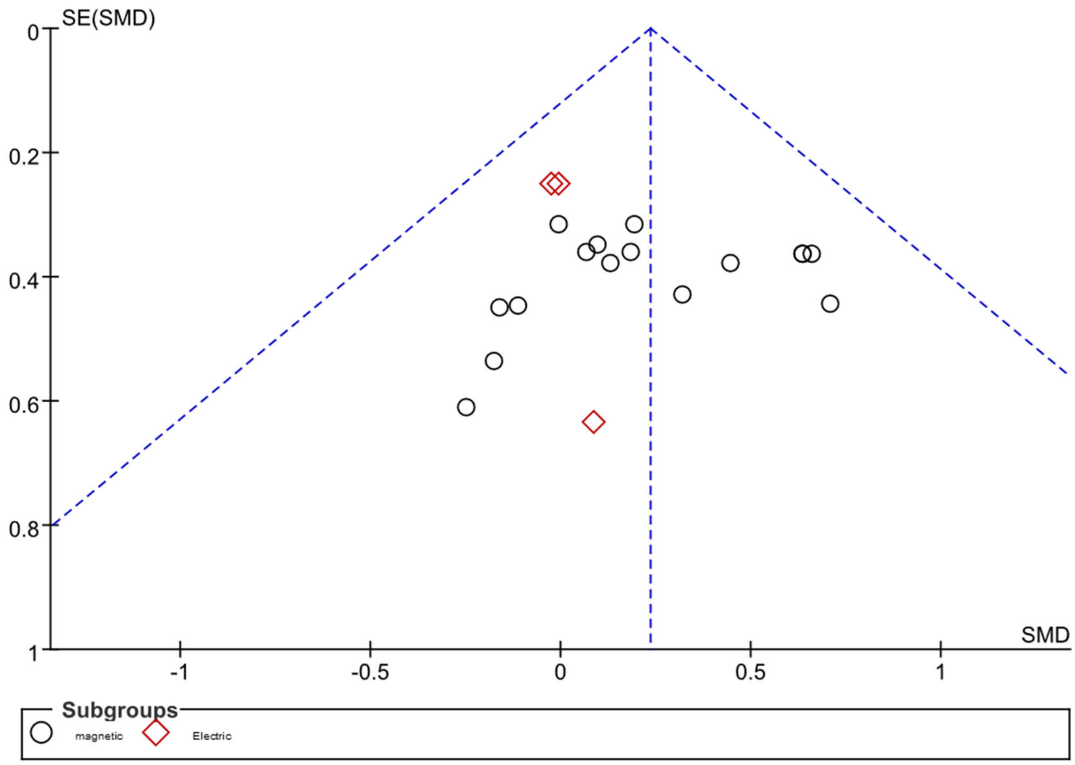

Figure 5 Data bias analysis

4. Conclusion

This review investigated the efficacy of various neuromodulation techniques, specifically transcranial direct current stimulation (tDCS) and magnetic stimulation (TMS), in improving motor function in stroke patients.

For electrical stimulation, the findings from the two studies on tDCS revealed mixed results. Although tDCS is a widely studied and promising technique, the evidence indicates that its effectiveness in enhancing upper limb motor function in stroke patients remains inconclusive. Specifically, while bilateral tDCS and cathodal tDCS applied to the contralesional hemisphere were evaluated, the results showed that neither approach significantly improved motor function compared to sham stimulation. Moreover, the study outcomes suggested that cathodal tDCS on the contralesional hemisphere was somewhat more effective than bilateral tDCS in reducing distal upper limb spasticity, but the overall impact on functional recovery was limited. Thus, further research is needed to clarify the optimal tDCS protocols and their potential benefits in stroke rehabilitation.

In contrast, the review of magnetic stimulation techniques, including TMS, repetitive peripheral magnetic stimulation (rPMS), repetitive transcranial magnetic stimulation (rTMS), and intermittent theta-burst stimulation (iTBS), demonstrated more promising results. The eight studies reviewed provided evidence that these techniques could substantially improve upper limb motor function in stroke patients. Among these, rTMS showed the most significant effects, suggesting that it might be particularly effective in enhancing motor recovery. Repetitive peripheral magnetic stimulation (rPMS) also demonstrated good efficacy, indicating its potential utility in stroke rehabilitation. The variations in stimulation protocols and patient characteristics across studies, however, underscore the need for more standardized and controlled trials to establish optimal treatment regimens.

In summary, while tDCS showed limited and inconsistent benefits, magnetic stimulation techniques, particularly rTMS, have shown more robust and positive effects on upper limb motor function post-stroke. The variability in patient demographics, stroke characteristics, and intervention protocols highlights the complexity of stroke rehabilitation and the necessity for personalized treatment approaches. Future research should focus on refining neuromodulation techniques, exploring their mechanisms of action, and determining the most effective protocols for different patient populations. By advancing our understanding of these neuromodulation strategies, we can enhance rehabilitation outcomes and improve the quality of life for stroke survivors.

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