Neurology Asia 2024; 29(4) : 985 – 1007

Age and method-specific differences in the efficacy of non-invasive brain stimulation in patients' post-stroke limb spasticity: a meta-analysis

[1]Xiaorong Cao, [2]Wei Xu, [1]Mengbei Yu

[1]*Department of Rehabilitation Medicine, Ningbo Yinzhou No.2 Hospital, China;* [2]*Operating Room, Ningbo Yinzhou No.2 Hospital, China*

Abstract

Objective: The aim of this study was to evaluate the effectiveness of two non-invasive brain stimulation (NIBS) methods, repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), on spasticity in post-stroke patients with respect to patient age and muscle type. *Methods:* This meta-analysis was performed according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines. PUBMED (MEDLINE), Web of Science, Cochrane Library, and ExcerptaMedica Database (EMBASE) were searched for all randomized controlled trials (RCTs) published before December 2023. *Results*: In patients with spasticity after stroke, both rTMS (SMD: -0.56, $CI_{95\%}$: -0.81, -0.31, P<0.0001) and tDCS (SMD: -0.74, $CI_{95\%}$: -0.89, -0.59, P=0.005) significantly reduced the modified Ashworth Scale (MAS) compared with the control group. rTMS and tDCS were more effective in patients < 60 years than those > 60 years. Both rTMS and tDCS were effective against upper limb spasticity, particularly in patients aged < 60 years. Chronicity of stroke did not affect the benefit of rTMS to reduce spasticity although tDCS was more effective at 2 months after stroke onset. The reduction in spasticity in patients with supratentorial lesions was demonstrated by tDCS. The effectiveness of rTMS in spasticity reduction was not affected by the stimulation rate, but the use of tDCS at < 2 mA significantly decreased spasticity. Anodal stimulation (tDCS) reduced spasticity after stroke, especially in patients < 60 years of age. Other therapies, such as robotic therapy, the use of virtual reality, and electroacupuncture, were less effective against spasticity than conventional physical therapy combined with tDCS. The effectiveness of rTMS in spasticity reduction was not affected by the level of development, although tDCS was more successful in developing countries. *Conclusions*: Our findings suggest that NIBS should consider age, methods, and muscle type when treating patients with limb spasticity after stroke.

Keywords: Non-invasive brain stimulation, spasticity, transcranial magnetic stimulation, transcranial direct current stimulation, meta-analysis

INTRODUCTION

Post-stroke spasticity (PSS), a neurological sign that accompanies the classic syndrome of increased muscle tone, occurs in up to 25% of stroke survivors.[1] Spasticity can cause problems, such as pain, muscle spasms, abnormal joint positioning, and ankylosis and can further reduce motor function in stroke patients and cause great difficulty in daily activities.[2] Hence, interventions for PSS reduction are especially critical. Methods that can improve spasticity after stroke include electrical muscle stimulation, botulinum toxin injection, oral spasticity medication, and wearable exoskeletons.[3,4] Nevertheless, the common side effects of drugs and the obtrusive nature of topical medicines are unsavory, thereby constraining their efficacy.

Recently, non-invasive brain stimulation (NIBS) has been studied for the treatment of various neurological diseases. Among different NIBS strategies, repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) are most regularly utilized to treat patients with PSS.[5,6] These techniques noninvasively induce changes in the underlying cerebral cortex and permanent neuroplastic changes.[7] The mechanism of action of NIBS involves changes in the excitability of the motor

Address correspondence to: Mengbei Yu, Department of Rehabilitation Medicine, Ningbo Yinzhou No.2 Hospital, 315192, China. Email: annie32211@sina.com
Date of Submission: 2 February 2024; Date of Acceptance: 29 August 2024
https://doi.org/10.54029/2024eiu

cortex of the brain and indirectly decreasing the excitability of motor neurons in the spinal cord via the H-reflex.[8]

rTMS techniques utilize various frequencies of electromagnetic currents via a magnetic coil administered to the scalp to regulate cortical excitability.[9] tDCS modifies transmembrane electrical potentials by passing low-amplitude direct currents through scalp electrodes.[9] This acts through anodal or cathodal stimulation to either increase or decrease cortical excitability.[10] These modalities can stimulate or depress cortical activity to increase adaptive patterns or reduce maladaptive patterns, respectively. It is possible for tDCS and rTMS to modify cortical activity after the stimulation has ended[11]; although inter-individual responses and stimulation parameters may vary greatly.[12] Subsequently, the effects of NIBS on spasticity after stroke may be conflicting. For example, some studies have shown the advantageous effects of NIBS (rTMS and tDCS) in the treatment of PSS, whereas other studies have not reported significant benefits of NIBS in reduction of muscle spasms.[13-15]

There is limited information on the effectiveness of different NIBS techniques (i.e., rTMS and tDCS) for PSS in relation to patient characteristics (i.e., age). In this meta-analysis, we hypothesized that the efficacy of NIBS for treating patients with PSS may vary depending on patient age and the methods used.

METHODS

Literature search strategy

This meta-analysis conformed to the PRISMA guidelines for systematic reviews and meta–analyses (Figure 1).[16] According to the PICO guidelines, there are four categories: populations; interventions; controls; and outcomes. All articles included in this meta-analysis were retrieved according to the PICO guidelines.[17] The inclusion criteria were population (patients diagnosed as stroke patients by clinical examination and with PSS); intervention (NIBS); control (Sham stimulation); results (MAS); and research type (RCT). The research language was limited to English. PUBMED (MEDLINE), Web of Science, Cochrane Library, and Embase were the electronic databases that the two authors independently searched. Using MeSH terms such as "stroke", "noninvasive brain stimulation", "spasm", and "spasticity", we searched the database for pertinent articles published by November 2023. In the event of disagreement during the article inclusion process, a third author was consulted to resolve the issue.

Study selection

The article search strategy is illustrated in Figure 1. We retrieved 2,482 publications in the first search. The two authors screened the titles and abstracts to identify relevant research articles and then further reviewed the full text to determine the research articles included in the meta-analysis. Any disagreements during the inclusion process were resolved by the third author.

Quality assessment

The Quality in Prognostic Studies (QUIPS) tool was used to evaluate the potential for bias in studies.[18,19] According to the Cochrane Methods Prognosis Group, the QUIPS tool is an effective method for prognostic research as it addresses all types of bias that are commonly found in studies.[18,19] To assess the probability of bias in a study, two team members evaluated each study individually and independently to determine whether it was low, moderate, or high. A third author was consulted to resolve any conflicts in the assessment. The QUIPS tool encompasses measures of prognostic factors, outcomes measurements, statistical analysis and reporting, study confounding, research participation, and study attrition.[18,19] An additional method for assessing publication bias was the use of funnel plot analysis (Egger's regression test).

Data extraction

All studies that met the inclusion criteria were accompanied by relevant experimental design information and outcome analysis. All data were extracted, including study characteristics (author, year of publication, and sample size), treatment parameters (stimulation method, stimulation parameters, stimulation duration), country classification, stroke chronicity, lesion location, and main outcome measure (MAS).

Statistical analysis

In this meta-analysis, we estimated a pooled estimate and 95% confidence interval ($CI_{95\%}$) of the standardized mean difference (SMD) between the experimental and control groups after the intervention. Meta-analysis was performed using META-MAR V2.7.0. In the cases of heterogeneity within and between parameters, a random-effects

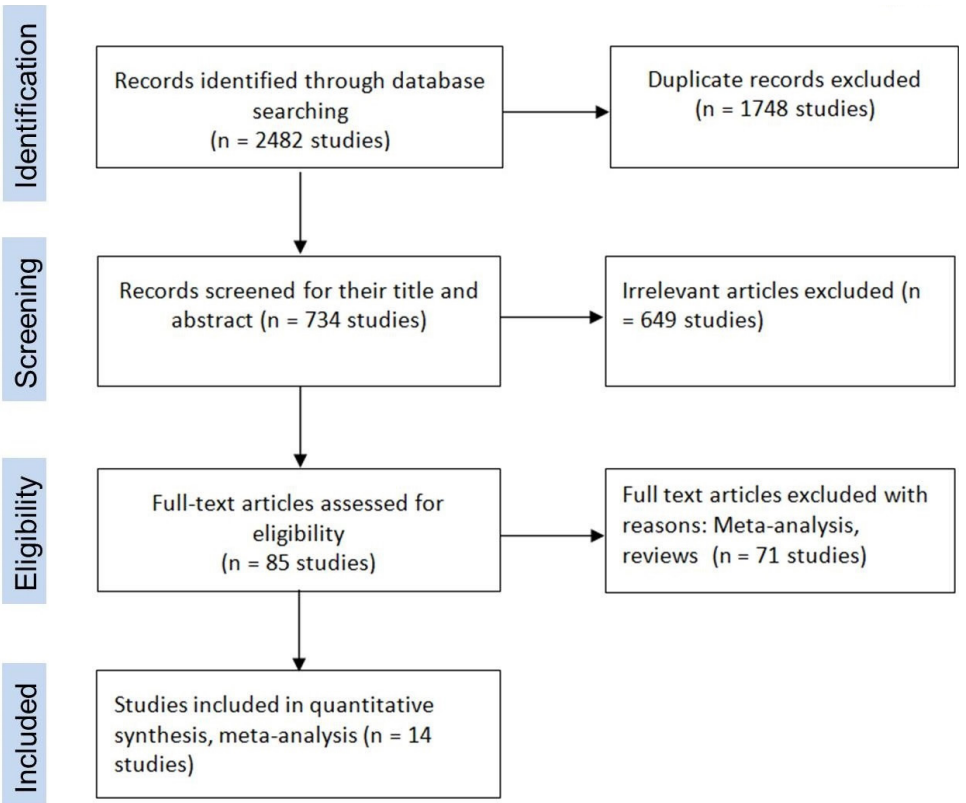


Figure 1. PRISMA flow chart of the selection of studies.

model was used to determine the weighted mean effect size and $CI_{95\%}$, otherwise the fixed-effects model was used. Statistical heterogeneity was estimated using Cochran's Q test and the I^2 index. An I^2 index > 50% and $P < 0.05$ of the Cochran's Q test indicated high heterogeneity. In addition, meta-regression analysis was carried out to assess potential heterogeneity. The results of the meta-analysis are presented as a Forest Plot. Potential publication bias was assessed using funnel plots and Egger's test. The meta-analysis included fewer studies (<10 studies) at the time, which may have resulted in biased results through the use of funnel plot and Egger's tests. Therefore, the QUIPS tool was also employed to assess the potential for bias in the included studies.

RESULTS

Study identification and selection

According to the PRISMA guidelines, we searched the database and found 2,849 studies (Figure 1). After removing duplicates, 895 studies were identified for screening. Of these, 788 studies were considered irrelevant, and out of the remaining 107 studies, another 87 studies were rejected for specific reasons. As a result (Figure 1), 20 studies were included and reviewed in the current meta-analysis.[20-39] This meta-analysis included eight rTMS[20-27] (including 11 independent experiments) and 12 tDCS[28-39] (including 14 independent experiments) research papers. The outcome measure in all studies was MAS. Information about all studies and the details of each study are provided in Table 1. In terms of study design, all papers in this study were RCTs.

Overall effects of rTMS and tDCS

The meta-analysis showed that the overall effect of treatment with rTMS or tDCS was significant in PSS reduction (SMD: -0.69, $CI_{95\%}$: -0.82, -0.56, $P < 0.001$, Figure 2). The heterogeneity was low between the rTMS studies ($I^2 = 0$, $P = 0.61$; Figure 2A); while, it was high between the tDCS studies (I^2: 87%, $P < 0.01$; Figure 2B).

Effects of rTMS

Subgroup analysis revealed that rTMS reduced spasticity (SMD: -0.56, $CI_{95\%}$: -0.81, -0.31, P <

Table 1: Research characteristics of rTMS and tDCS studies

Study	Country	Stroke onset	Lesion location	Stimulation rate/intensity	Participant				Mean Severity, MAS (SD)			
					Intervention		Control		Intervention	Control	Intervention	Muscle
					Age Mean (SD)	No. (M/F)	Age Mean (SD)	No. (M/F)				
Barros Galvao 2014[24]	Brazil	> 6 mo	Ischemic or hemorrhagic hemispheric stroke	1500 pulse, 1 Hz, 10 sessions, 1 session/d	57.4 (12.0)	10 (6/4)	64.6 (6.8)	10 (7/3)	2.5 (0.5)	2.4 (0.5)	LF-rTMS	Wrist
Aşkın 2017[23]	Turkey	28.4± 15.3 mo	Hemisphere Right/left Dominant/non-dominant	1200 pulses, 1 Hz, 10 sessions, 5 d/wk	56.8 (11.5)	20 (14/6)	58.8 (12.0)	20 (15/5)	3.2 (0.8)	2.8 (0.8)	LF-rTMS	Upper limb
Chervyakov 2018a[22]	USA	5.1-4.8 mo	Middle cerebral artery	1 Hz, 10 sessions, 5 d/wk	54.2 (11.1)	11 (5/6)	61.4 (11.4)	10 (5/5)	1.2 (0.9)	1.4 (1.0)	HF-rTMS	Arm
Chervyakov 2018b[22]	USA	5.8-4.6 mo	Middle cerebral artery	10 Hz, 10 sessions, 5 d/wk	58.6 (10.4)	13 (10/3)	61.4 (11.4)	10 (5/5)	1.8 (0.8)	1.4 (1.0)	LF-rTMS	Arm
Chervyakov 2018c[22]	USA	7.4-5.9 mo	Middle cerebral artery	A combination of 1 and 10 Hz, 10 sessions, 5 d/wk	60.7 (9.6)	8 (6/2)	61.4 (11.4)	10 (5/5)	1.5 (0.9)	1.4 (1.0)	HF-rTMS	Arm
Chen 2019[20]	Taiwan	≥ 6 mo	Supratentorial, Infratentorial	50 Hz, 10 sessions, 1 session/d	52.9 (11.1)	11 (7/4)	52.6 (8.3)	11 (7/4)	3.9 (2.1)	4.1 (1.6)	iTBS	Upper limb
Chen 2021[21]	Taiwan	5.0± 4.4 mo	Cerebral cortex: Cortical M1 involvement Subcortical	1200 pulses, 50 Hz	54.4 (10.6)	12 (8/4)	49.0 (9.6)	11 (10/1)	0.9 (0.5)	0.9 (0.7)	LF-rTMS	Upper limb
Gottlieb 2021[26]	Germany	NR	Middle cerebral artery	1 Hz, 10 sessions, 5 d/wk	63.9 (10.9)	14 (9/5)	62.4 (11.5)	14 (3/11)	1.9 (1.4)	1.7 (1.3)	LF-rTMS	Upper limb
Xu 2021[27]	China	2 wk to 6 mo	NR	550 pulses, 1 Hz, 5 sessions/wk	79.5 (1.5)	22 (17/5)	68.9 (3.1)	22 (15/7)	2.3 (0.5)	2.4 (0.5)	LF-rTMS	Upper limb

Study	Country	Stroke onset	Lesion location	Stimulation rate/intensity	Participant				Mean Severity, MAS (SD)		Intervention	Muscle
					Intervention		Control		Intervention	Control		
					Age Mean (SD)	No. (M/F)	Age Mean (SD)	No. (M/F)				
Kuzu 2021a[25]	Turkey	16.4± 2.5 mo	Cerebral Cortical Subcortical	1200 pulses, 1 Hz, 10 sessions	56.3 (11.5)	7 (4/3)	65.0 (4.6)	6 (2/4)	1.8 (0.4)	2.3 (0.6)	LF-rTMS	Upper limb
Kuzu 2021b[25]	Turkey	14.5± 1.6 mo	Cerebral Cortical Subcortical	600 pulses, 50 Hz	61.3 (9.8)	7 (6/1)	65.0 (4.6)	6 (2/4)	2.1 (0.6)	2.3 (0.6)	LF-rTMS	Upper limb
Hesse 2012a[29]	Germany	3.4±1.8 wks	Ischemic supratentorial	2.0 mA, 30 sessions	63.9 (10.5)	32 (20/12)	65.6 (10.3)	32 (21/11)	1.6 (2.9)	1.4 (2.7)	tDCS (Anodal plus Robot-Assisted Arm Training)	Upper limb
Hesse 2012b[29]	Germany	3.8± 1.4 wks	Ischemic supratentorial	2.0 mA, 30 sessions	65.4 (8.6)	32 (18/14)	65.6 (10.3)	32 (21/11)	1.0 (1.8)	1.4 (2.7)	Cathodal plus Robot-Assisted Arm Training	Upper limb
Wu 2013[33]	China	2-12 mo	Cerebral cortex: Primary sensorimotor cortex	1.2 mA, 20 sessions, 5 d/wk, 20 sessions	45.9 (11.2)	45 (34/11)	49.3 (12.6)	45 (35/10)	2.0 (0.8)	2.0 (0.5)	Cathodal stimulation plus conventional physical therapy	Wrist
Lee 2014a[30]	Korea	17.4± 9.4 d	Cerebral Cortex Subcortex	2.0 mA, 15 sessions, 5 sessions/wk)	63.1 (10.3)	19 (10/9)	60.3 (11.3)	20 (9/11)	0.5 (0.4)	0.5 (0.4)	Cathodal stimulation plus occupational therapy	Upper limb
Lee 2014a[30]	Korea	16.9± 5.5 d	Cerebral Cortex Subcortex	2.0 mA, 15 sessions, 5 sessions/wk	63.1 (10.3)	20 (12/8)	60.6 (14.1)	20 (9/11)	0.5 (0.4)	0.5 (0.4)	Cathodal stimulation plus virtual reality	Upper limb

Study	Country	Stroke onset	Lesion location	Stimulation rate/ intensity	Participant				Mean Severity, MAS (SD)		Intervention	Muscle
					Intervention		Control		Intervention	Control		
					Age Mean (SD)	No. (M/F)	Age Mean (SD)	No. (M/F)				
Viana 2014[32]	Brazil	31.9 ±18.2 mo	NR	2.0 mA, 15 sessions	56.0 (10.2)	10 (9/1)	55.0 (12.2)	10 (7/3)	1.5 (0.7)	1.5 (0.5)	Anodal stimulation plus virtual reality	Upper limb
Andrade 2017[28]	Brazil	1.8± 1.6 mo	Cerebral Cortical/ subcortical	0.7 mA, 10 sessions	54.1 (3.7)	40 (22/18)	54.8 (4.3)	20 (12/8)	3.3 (0.4)	3.6 (0.5)	Anodal stimulation plus constraint-induced movement therapy	Upper limb
Mazzoleni 2019[31]	Italy	25± 7 d	Supratentorial	2.0 mA, 30 sessions	67.5 (16.3)	20 (8/12)	68.7 (15.8)	19 (7/12)	1.1 (1.9)	1.6 (2.3)	Anodal stimulation plus wrist robot-assisted rehabilitation	Wrist
Qu 2009[34]	China	5± 6.1 mo	Primary sensorimotor cortex	0.5 mA, 1 session/d, 5 d/wk, 20 sessions	45 (12.5)	25	45 (12.5)	25	2.0 (0.8)	2.0 (0.8)	Cathodal stimulation plus exercise training	Upper limb
Wang 2019[35]	China	1.6± 0.9 years	Primary motor cortex	0.5 mA, 1 session/d, 5 d/wk, 20 sessions	51.9 (11.3)	30	51.9 (11.3)	30	16.0 (12.3)	16.0 (12.3)	Anodal stimulation plus conventional rehabilitation	Upper limb
Zhang 2019[36]	China	4.5± 1.6 mo	Cerebral cortex	2.0 mA, 1 session/d, 6 d/wk, 24 sessions	48.2 (6.5)	36	48.2 (6.5)	36	2.1 (0.3)	2.1 (0.3)	Dual stimulation plus Robot-Assisted Arm Training	Upper limb

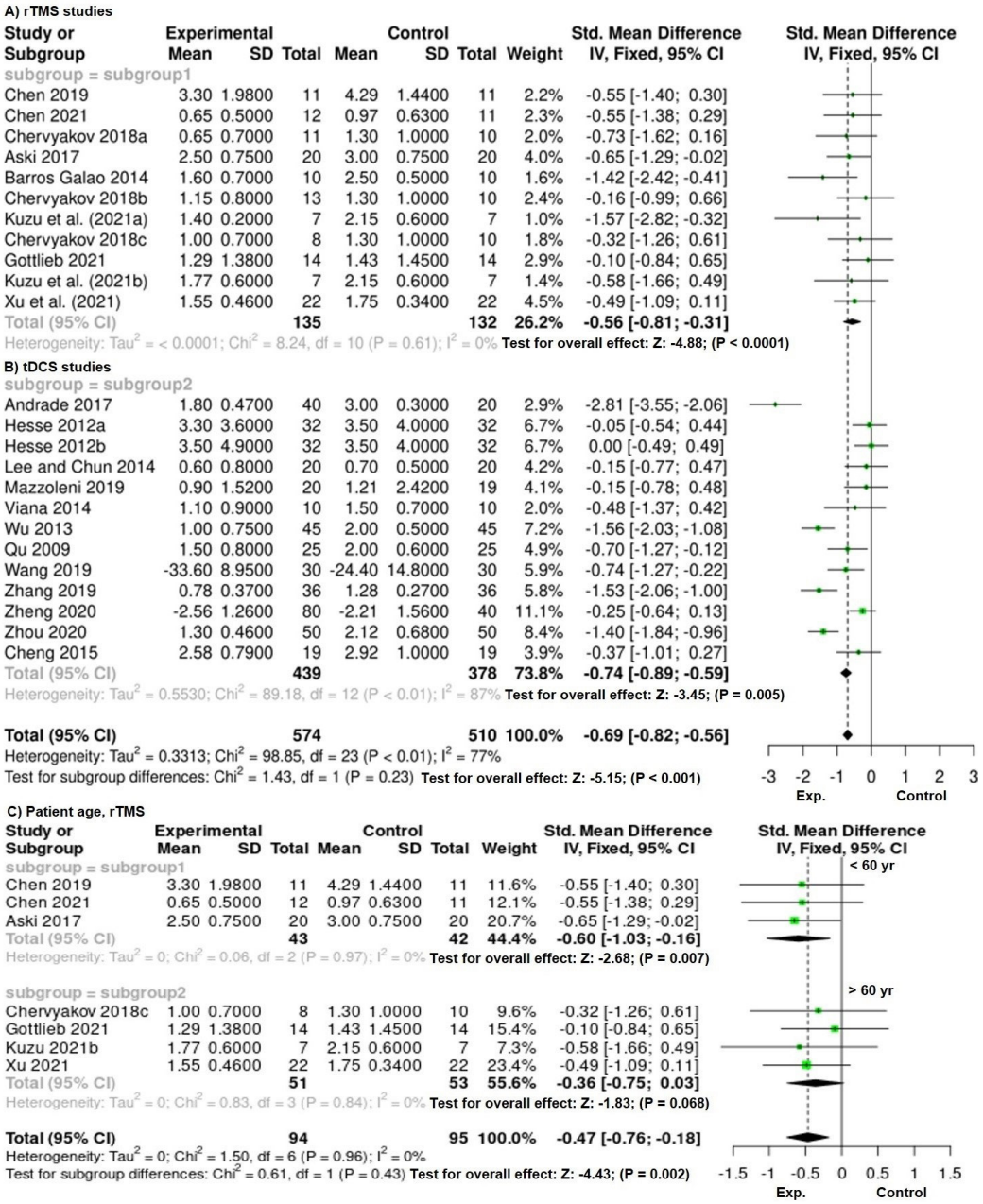
Study	Country	Stroke onset	Lesion location	Stimulation rate/ intensity	Participant				Mean Severity, MAS (SD)		Intervention	Muscle
					Intervention		Control		Intervention	Control		
					Age Mean (SD)	No. (M/F)	Age Mean (SD)	No. (M/F)				
Zheng 2020[37]	China	4.4± 2.8 mo	NR	1.5 mA, 1 session/d, 6 d/wk, 36 sessions	48.9 (2.2)	80	48.9 (2.2)	40	1.5 (0.2)	1.5 (0.2)	Dual stimulation or (dual stimulation plus electro-acupuncture)	Upper limb
Zhou 2020[38]	China	2.6± 1.2 mo	NR	1.0 mA, 1 session/d, 40 sessions	55.2 (8.8)	50	55.2 (8.8)	50	2.8 (0.8)	2.8 (0.8)	Anodal stimulation plus conventional rehabilitation	Upper limb
Cheng 2015[39]	China	49.6± 17.8 d	Primary motor cortex	1.2 mA, 1 session/d, 6 d/wk, 36 sessions	59.2 (7.3)	19	59.2 (7.3)	19	3.9 (1.0)	3.9 (1.0)	Dual stimulation plus conventional rehabilitation training	Upper limb

MAS: modified Ashworth Scale; SD: standard deviation; M: male; F: female; rTMS: repetitive transcranial magnetic stimulation; tDCS: transcranial direct current stimulation; LF: low-frequency; HF: high-frequency; mo: month; d: day, wk: week.

0.0001, Figure 2A). As shown in Figure 2C, rTMS was more effective in MAS reduction in patients aged < 60 years (SMD: -0.60, $CI_{95\%}$: -1.03, -0.16, P = 0.007) than that in patients aged > 60 years (SMD: -0.36, $CI_{95\%}$: -0.75, 0.03, P = 0.068). rTMS had significant benefits in improving upper limb function after stroke (SMD: -0.54, $CI_{95\%}$: -0.84, -0.25, P = 0.003; Figure 3A). Furthermore, rTMS was more effective in improving upper limb function in patients < 60 years of age (SMD: -0.60, $CI_{95\%}$: -1.03, -0.16, P = 0.007) than in patients > 60 years of age (SMD: -0.37, $CI_{95\%}$: –0.80, 0.06, P = 0.089; Figure 3B). The effect of rTMS on MAS reduction was greater in developing countries (SMD: -0.76, $CI_{95\%}$: -1.29, -0.23, P < 0.0001) than in developed (SMD: -0.38, $CI_{95\%}$: -0.65, -0.12, P = 0.029; Figure 3C). Subgroup analysis revealed that stroke chronicity did not change the effect of rTMS on MAS reduction in patients (Figure 4A); however, the effect size was greater at > 6 months after stroke onset (SMD: -0.76, $CI_{95\%}$: -1.12, -0.39, P < 0.0001) than it was < 6 months (SMD: -0.47, $CI_{95\%}$: -0.85, -0.09, P = 0.014; Figure 4A). In terms of lesion location, the use of rTMS was more effective in MAS reduction in patients with hemispheric stroke (SMD: -0.87, $CI_{95\%}$: -1.41, -0.34, P < 0.001) than in patients with lesions in the middle cerebral artery or cerebral cortex or subcortex (Figure 4B). The stimulation rate of rTMS did not change the effect of treatment on MAS in patients; rTMS at 1 Hz (SMD: -0.65, $CI_{95\%}$: -0.97, -0.33, P < 0.0001) and 50 Hz (SMD: -0.56, $CI_{95\%}$: -1.08, -0.03, P = 0.036) significantly reduced MAS (Figure 4C).

Effects of tDCS

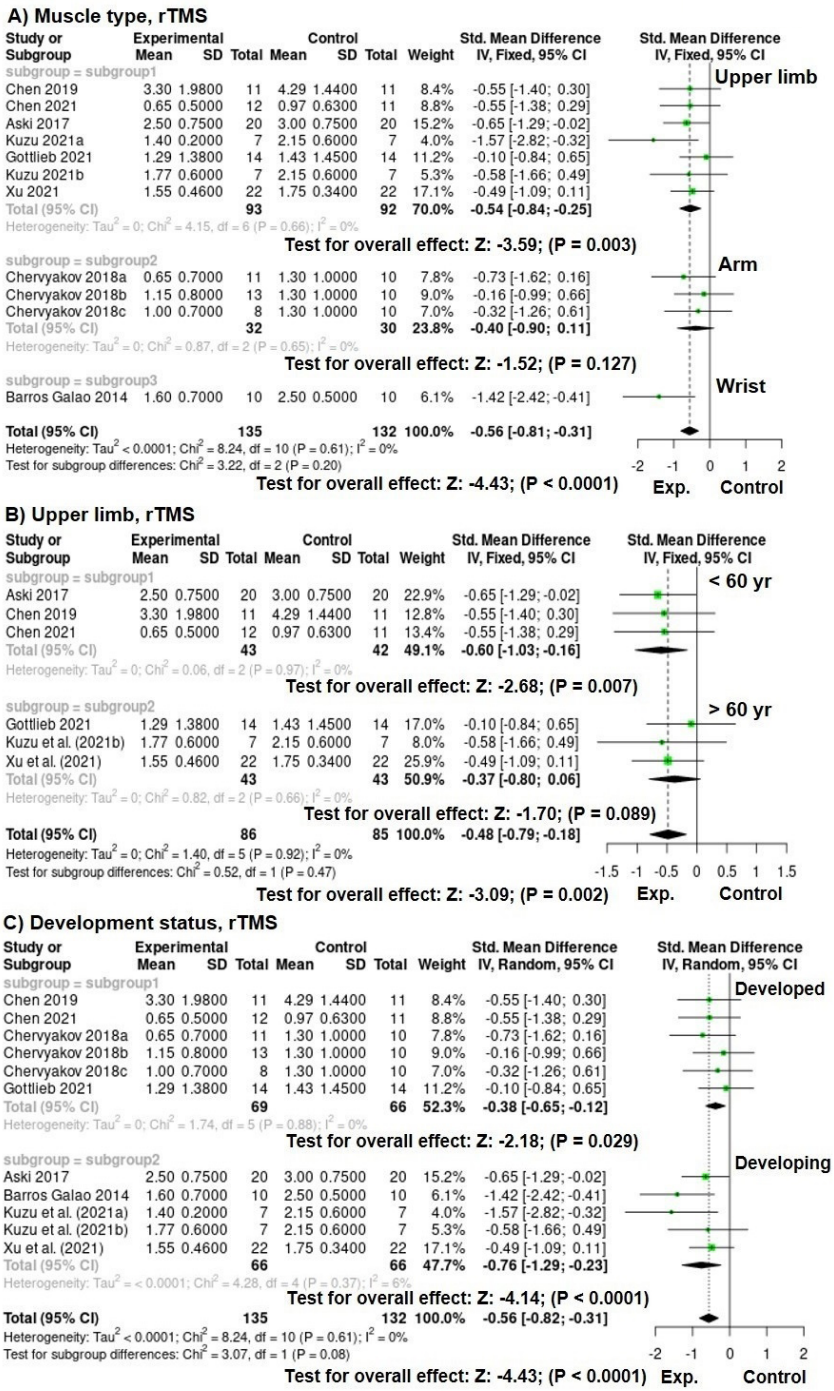
The use of tDCS significantly decreased MAS in patients with PSS (SMD: -0.74, $CI_{95\%}$: -0.89, -0.59, P = 0.005, Figure 2B), particularly in patients < 60 years (SMD: -1.09, $CI_{95\%}$: -1.70, -0.47, P = 0.003, Figure 5A). In terms of muscle recovery, subgroup analysis revealed that the effect of tDCS on spasticity reduction was significantly higher for upper limb function (SMD: -0.76, $CI_{95\%}$: -1.32, -0.20, P = 0.012, Figure 5B), particularly in patients < 60 years (SMD: -1.02, $CI_{95\%}$: -1.72, -0.33, P < 0.01, Figure 5C). Subgroup analysis revealed that the stimulation type (anodal, cathodal, or dual stimulation) did not change the effect of tDCS on PSS. However, the effect of anodal stimulation was greater (SMD: -0.93, $CI_{95\%}$: –2.01, 0.15, P = 0.076; Figure 6A). It was found that patient age did not change the effect of tDCS on spasticity; however, anodal stimulation



yr: year, Exp: experiment

Figure 2. Forest plot analysis. The overall effect of (A) repetitive transcranial magnetic stimulation (rTMS) and (B) tDCS on post-stroke spasticity. (C) Effect of rTMS on post-stroke spasticity according to patient age. Articles pertaining to patients who were < 60 years or older in both the experimental and control groups were included.

reduced spasticity in patients < 60 years (SMD: -1.36, $CI_{95\%}$: –2.99, 0.27, P = 0.077; Figure 6B). We found that the effect of tDCS was greater at > 2-6 (SMD: -0.96, $CI_{95\%}$: -1.93, 0.01, P < 0.05) or > 6 (SMD: -0.67, $CI_{95\%}$: -2.16, 0.81, P < 0.01) months after stroke onset than when it was < 2 months (SMD: -0.57, $CI_{95\%}$: -1.70, 0.56, P = 0.253; Figure 7A). Regarding supratentorial lesions, the use of tDCS significantly reduced spasticity (SMD: -1.11, $CI_{95\%}$: –1.94, -0.28, P =



yr: year, Exp: experiment

Figure 3. Forest plot analysis. Effect of repetitive transcranial magnetic stimulation (rTMS) on post-stroke spasticity in relation to (A) muscle type, (B) upper limb according to patient age (Articles pertaining to patients who were < 60 years or older in both the experimental and control groups were included), and (C) country classification (developed or developing).

0.017; Figure 7B). tDCS did not affect spasticity in patients with lesions in cerebral cortex/subcortex (SMD: -0.06, $CI_{95\%}$: –0.23, 0.12, P = 0.721; Figure 7B). Regarding tDCS intensity, an intensity of < 2.0 mA significantly reduced spasticity (SMD: -1.10, $CI_{95\%}$: –1.90, -0.29, P = 0.015; Figure 7C), whereas tDCS with an intensity of 2.0 mA had no effect (SMD: -0.39, $CI_{95\%}$: –1.02, 0.24, P = 0.171; Figure 7C). Subgroup analysis revealed that the combination of tDCS with conventional physical therapy (SMD: -1.25, $CI_{95\%}$: –2.15, -0.35, P = 0.016) outperformed other combinations with virtual reality and robot-assisted therapy in spasticity reduction (Figure 8A). The effect of tDCS in spasticity reduction was greater in developing countries (SMD: -1.09, $CI_{95\%}$: -1.70, -0.47, P = 0.003) than in developed (SMD: -0.07, $CI_{95\%}$: -0.19, 0.04, P = 0.621; Figure 8B).

Publication bias and heterogeneity

The risk of bias in each of the 20 studies was evaluated using the QUIPS tool (Table 2). Nineteen studies had moderate to high risk of bias. The study's confounding was found to be the most concerning aspect of bias (Table 2). Moreover, the meta-regression tests showed significant heterogeneity among tDCS studies (P < 0.0001, Table 3B). Because of this high heterogeneity levels in tDSC studies, several subgroup analyses were performed to address potential heterogeneity. Egger's linear regression test showed that publication bias was unlikely in tDCS studies included in meta- and subgroup analysis (Table 3A). Moreover, the symmetric funnel plots indicated a well-behaved dataset in which publication bias is unlikely in tDCS or rTMS studies (Figure 9 and Figure 10).

Table 2: Risk of bias according to the QUIPS tool

Study	Partici-pation	Attrition	Prognostic Factor	Outcome	Statistical Analysis and Reporting	Study Con-founding	Risk of bias: + = high, +/– = moderate, - = low
Barros Galvao 2014[24]	High	Moderate	Moderate	Low	Moderate	High	+
Aşkın 2017[23]	Moderate	Moderate	Low	Low	Low	High	+/-
Chervyakov 2018[22]	High	High	Moderate	Low	High	High	+
Chen 2019[20]	High	Low	Low	Low	Low	High	+/-
Chen 2021[21]	High	Moderate	Low	Low	Low	High	+/-
Gottlieb 2021[26]	High	High	Low	Low	Moderate	High	+
Xu 2021[27]	Moderate	Moderate	Moderate	High	High	High	+
Hesse 2012[29]	Low	Low	Low	Low	Low	Moderate	-
Kuzu 2021[25]	High	Moderate	Low	Low	Low	High	+/-
Wu 2013[33]	Low	Moderate	Low	Low	Low	High	+/-
Lee 2014[30]	Moderate	High	Low	Low	Moderate	High	+/-
Viana 2014[32]	High	Moderate	Low	Low	Moderate	High	+/-
Andrade 2017[28]	Moderate	Moderate	Low	Low	Moderate	High	+/-
Mazzoleni 2019[31]	Moderate	Low	Low	Low	Moderate	High	+/-
Qu 2009[34]	High	High	Moderate	Moderate	Moderate	High	+
Wang 2019[35]	High	High	Low	Low	Moderate	Moderate	+/-
Zhang 2019[36]	High	Moderate	Low	Low	Moderate	Moderate	+/-
Zhou 2020[38]	Moderate	Moderate	Low	Moderate	Moderate	High	+
Cheng 2015[39]	High	High	Moderate	Moderate	High	High	+
Zheng 2020[37]	Low	Moderate	Low	Low	Moderate	High	+/-
Overall: High risk	11/20	6/20	0/20	1/20	3/20	17/20	7/20
Overall: Moderate	6/20	11/20	5/20	3/20	11/20	3/20	12/20
Overall: Low risk	3/20	3/20	15/20	16/20	6/20	0/20	1/20

Table 3: Heterogeneity and publication bias

A) Publication bias			B) Heterogeneity	
Variable	Egger's Regression Test		Meta regression	
	t	p-value	Q	p-value
rTMS	-1.70	0.122	6.32	0.612
tDCS	-0.69	0.506	67.88	0.0001
Intensity, tDCS	-0.47	0.645	74.60	0.0001
Stimulation rate, rTMS	-1.88	0.096	6.799	0.450
Chronicity, tDCS	-0.69	0.506	67.88	0.0001
Chronicity, rTMS	-1.58	0.157	5.428	0.711
Lesion location, tDCS	-0.68	0.514	44.02	0.0001
Lesion location, rTMS	-1.78	0.112	4.845	0.563
Age, tDCS	-0.47	0.645	56.77	0.0001
Age, rTMS	0.21	0.849	0.884	0.971
Muscle type, tDCS	-0.47	0.645	86.16	0.0001
Muscle type, rTMS	-1.70	0.122	5.023	0.755
Stimulation type, tDCS	-0.47	0.645	86.977	0.0001

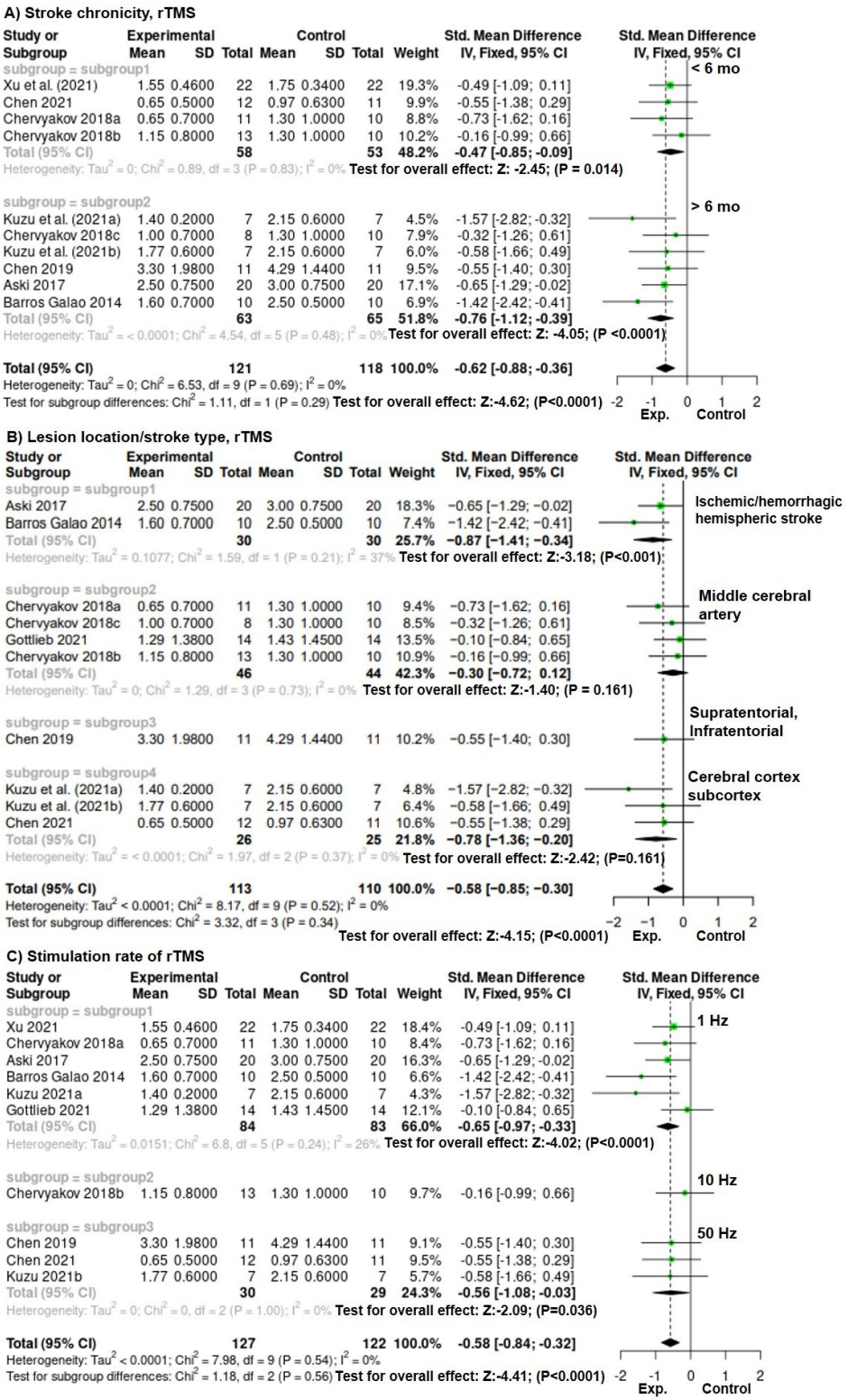
rTMS: repetitive transcranial magnetic stimulation; tDCS: transcranial direct current stimulation

Figure 4. Forest plot analysis. Subgroup analysis of (A) stroke chronicity, (B) lesion location, and (C) stimulation rate regarding repetitive transcranial magnetic stimulation (rTMS).

DISCUSSION

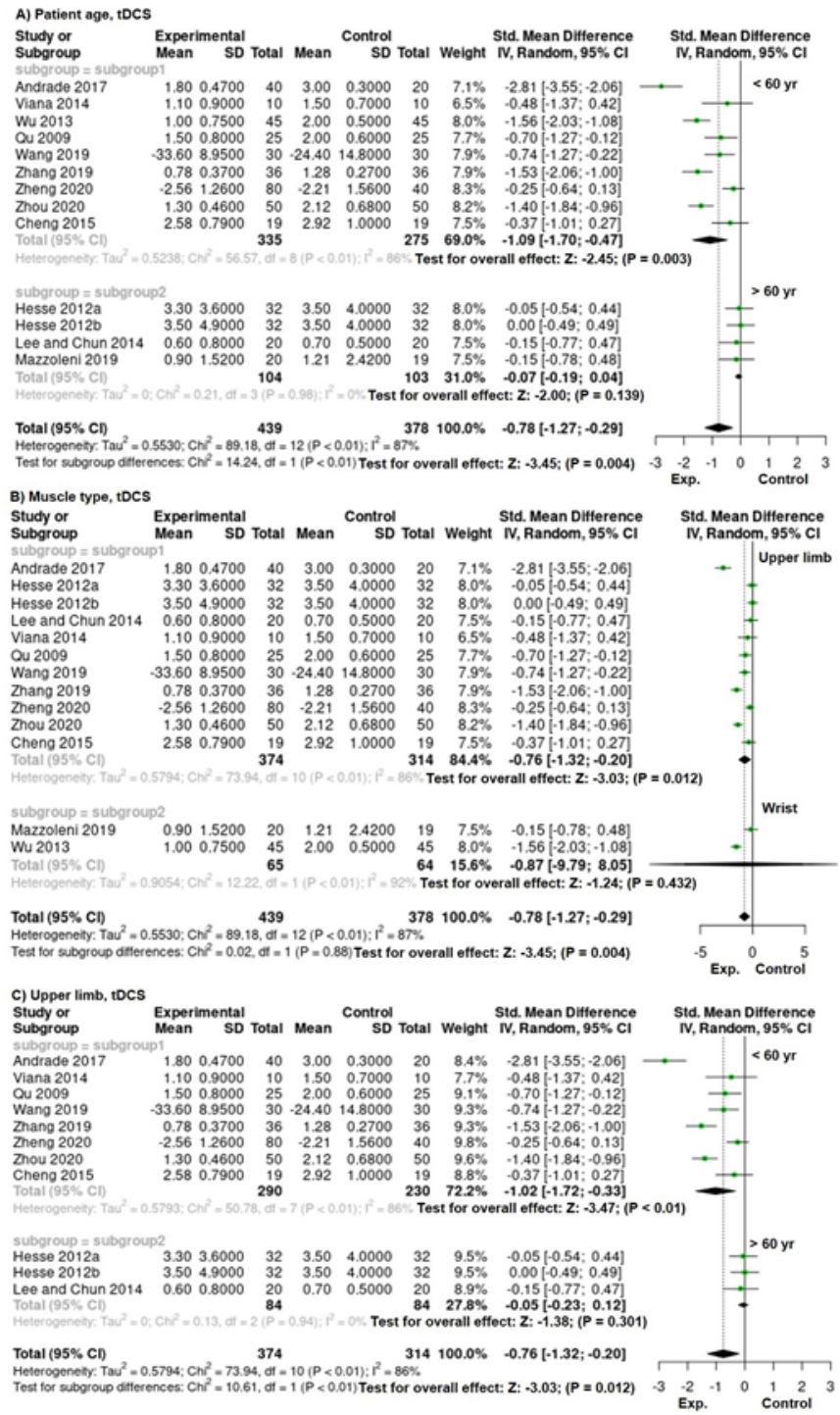
The meta-analysis revealed that the effects of different NIBS on PSS may vary depending on patient age, muscle type, stimulation method, lesion location, and country classification (level of development).

Subgroup analyses showed that both rTMS and tDCS had positive effects on spasticity reduction. Patients with stroke are prone to experiencing long-term disability due to spasticity. The pathophysiology of spasticity is proposed to involve damage to the upper motor neurons, which impairs inhibitory input to the spinal cord. At the spinal cord level, alpha and gamma motor neurons and interneurons exhibit increased excitability because of this phenomenon.[40] Spasticity reduction can be achieved through rTMS in patients with different neurological conditions.[41] By using magnetic signals of varying frequencies, rTMS stimulates specific regions of the central nervous system. By creating an electric field, rTMS stimulates cortical neurons and modifies cortical excitability during stimulation.[42] rTMS is typically applied in an inhibitory mode over the non-lesioned hemisphere to reduce the transcallosal inhibitory effect in the non-lesioned hemisphere on the stroke side.[43] Evidence suggests that rTMS can facilitate the restructuring of abnormal cortical circuits, which may be connected to its therapeutic value.[43] rTMS can modulate specific TMS-evoked EEG potential components (TEPs) that may serve as markers of neuroplastic changes.[44,45] Hamidi *et al*.[46] recorded EEG during a 3-s train of 10 Hz rTMS (30 pulses) delivered to the postcentral gyrus and superior parietal lobule. They demonstrated that successive pulses first decreased and then increased the amplitude of the TMS-evoked brain response. In a study of chronic stroke patients, rTMS reduced F waves, suggesting that rTMS suppresses spinal cord excitability by enhancing inhibitory input from the cerebral cortex to spinal neurons.[47] Helfrich *et al*.[48] reported a decrease in N100, although a rapid increase in N100 was observed after approximately 500 pulses (8 min of stimulation), followed by a stable plateau after this rapid increase. It has been suggested that N100 represents both motor cortical inhibition and modulation of GABAergic inhibition.[45,49] Therefore, the cerebral cortex is stimulated by rTMS, which affects physiological processes in the brain and changes cortical excitability, metabolism, and blood flow.[50] This alters the functioning of neurotransmitters and communication in the brain, leading to the restoration of normal brain function by restoring damaged cells.[50] Therefore, rTMS may reduce limb spasticity in post-stroke patients, induce



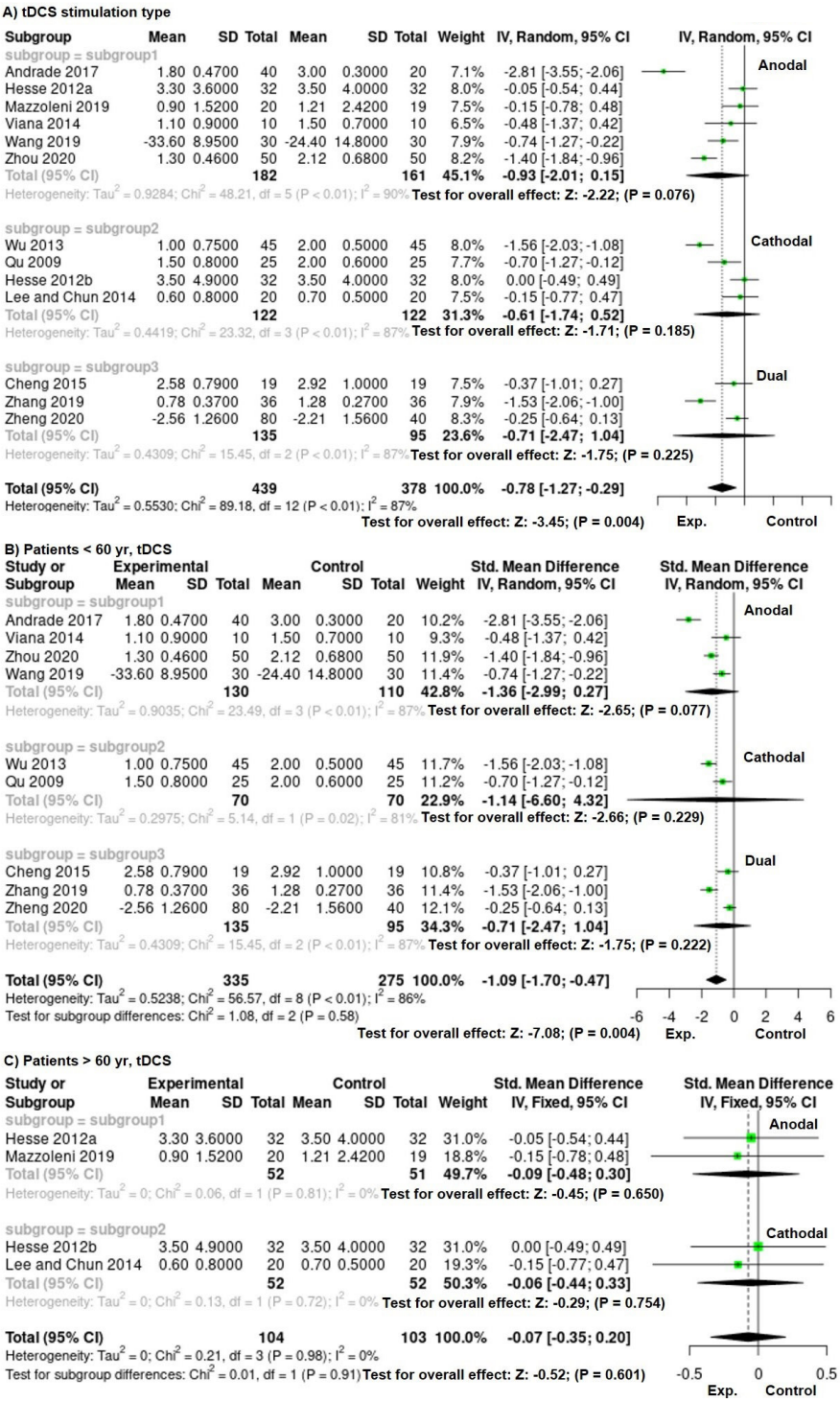
mo: month; Exp: experiment.

Figure 4. Forest plot analysis. Subgroup analysis of (A) stroke chronicity, (B) lesion location, and (C) stimulation rate regarding repetitive transcranial magnetic stimulation (rTMS).



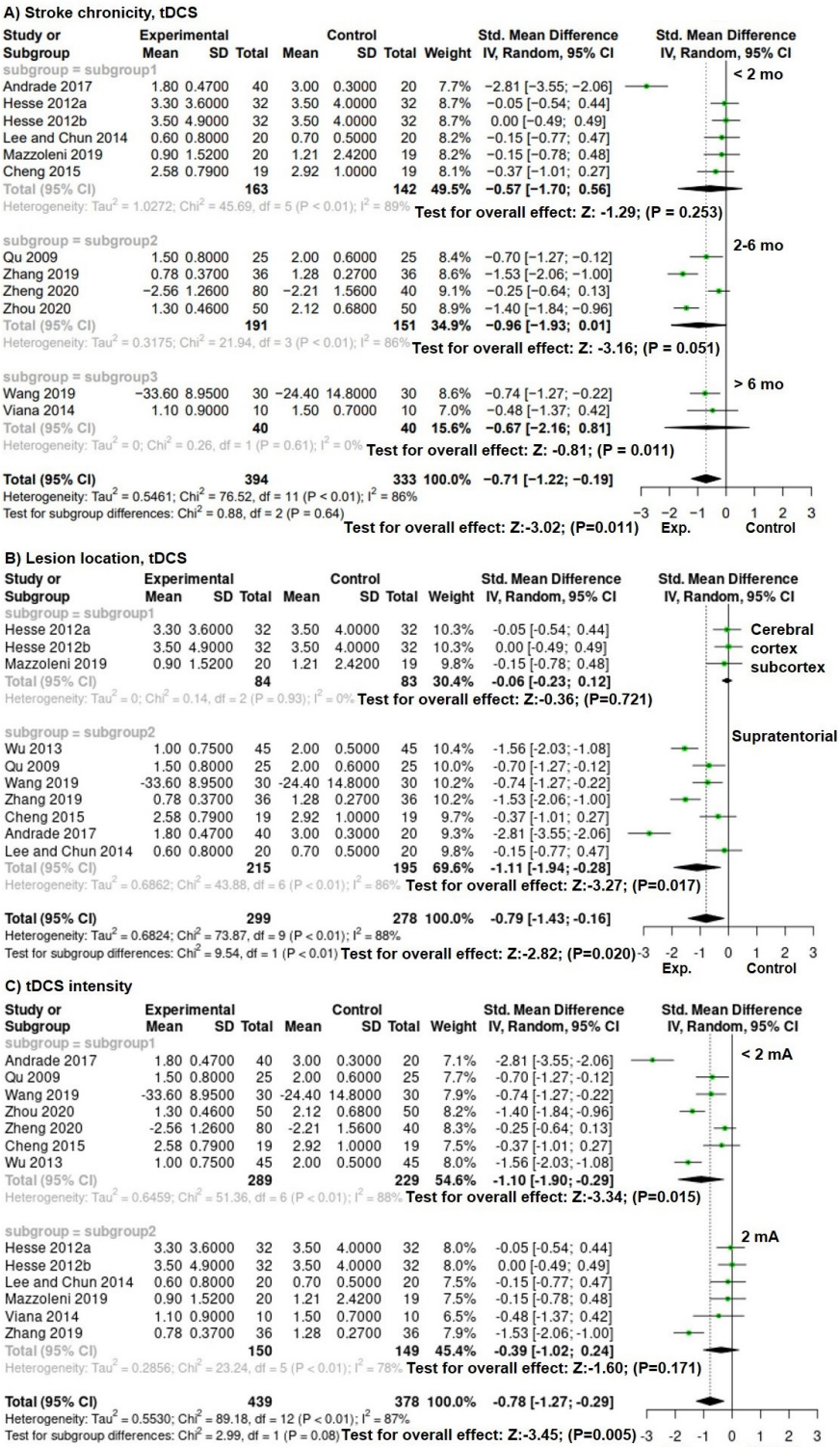
mo: month; Exp: experiment.

Figure 5. Forest plot analysis. Effect of transcranial direct current stimulation (tDCS) on post-stroke spasticity based on the (A) patient age, (B) muscle type, and (C) upper limb and patient age. Articles pertaining to patients who were < 60 years or older in both the experimental and control groups were included.



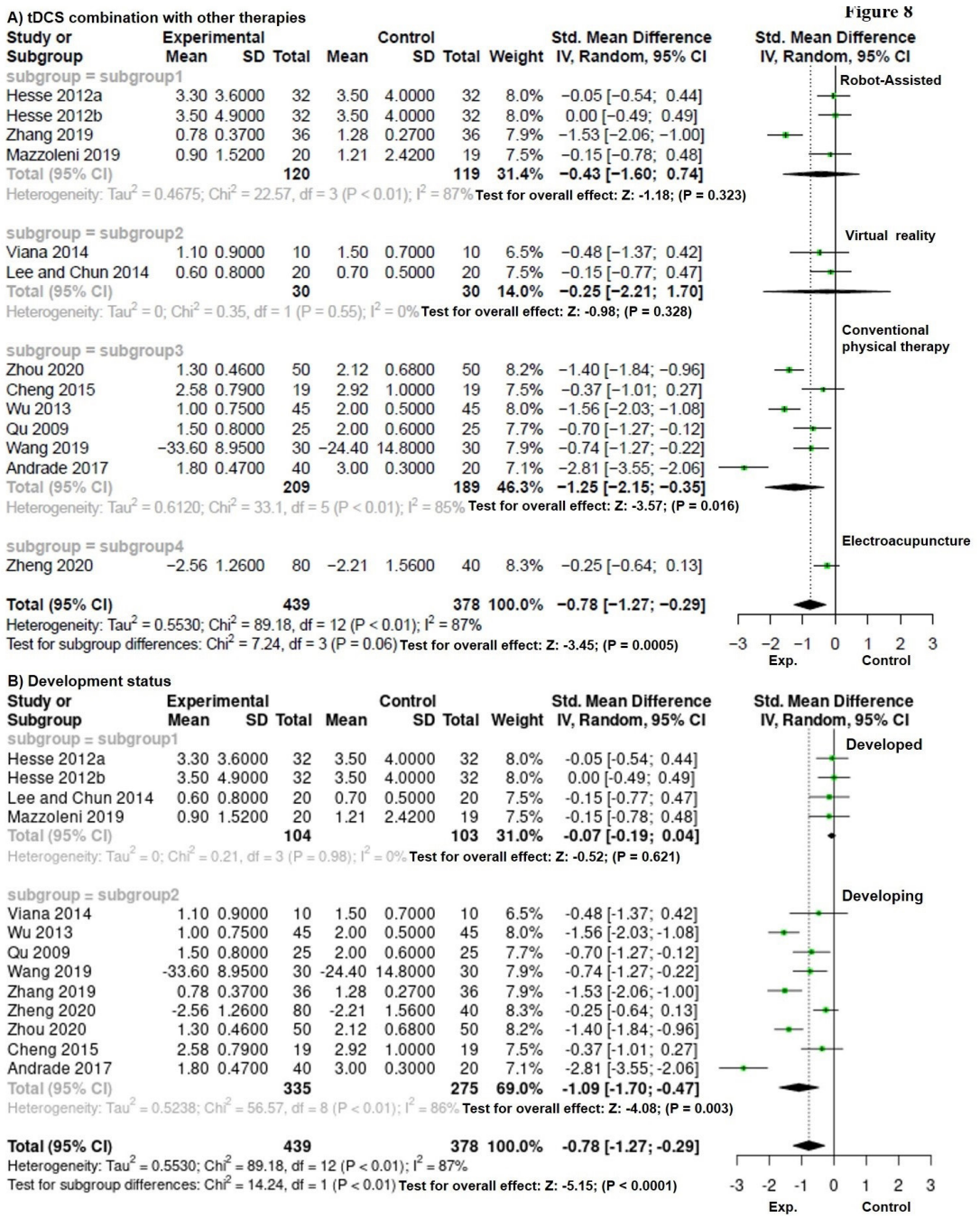
Exp: experiment.

Figure 6. Forest plot analysis. Effect of transcranial direct current stimulation (tDCS) on post-stroke spasticity in terms of (A) stimulation type (anodal, cathodal, and dual), (B) stimulation type and patient age (< 60 years), and (C) stimulation type and patient age (> 60 years).



Exp: experiment.

Figure 7. Forest plot analysis. Subgroup analysis of (A) stroke chronicity, (B) lesion location, and (C) intensity regarding repetitive transcranial direct current stimulation (tDCS).



Exp: experiment.

Figure 8. Forest plot analysis. (A) Effect of transcranial direct current stimulation (tDCS) combination with other therapies and (B) country classification (developed or developing) on post-stroke spasticity.

brain plasticity and brain network reorganization, and enhance the recovery of the primary and secondary motor cortex.[51]

Subgroup analysis revealed that the stimulation rate [both low-frequency (≤ 1 Hz) and high-frequency (≥ 5 Hz)] did not affect the positive effect of rTMS on PSS, with a greater effect from low-frequency rTMS (-0.65 versus -0.56). A previous study revealed that chronic stroke patients who experienced 1 Hz rTMS over the

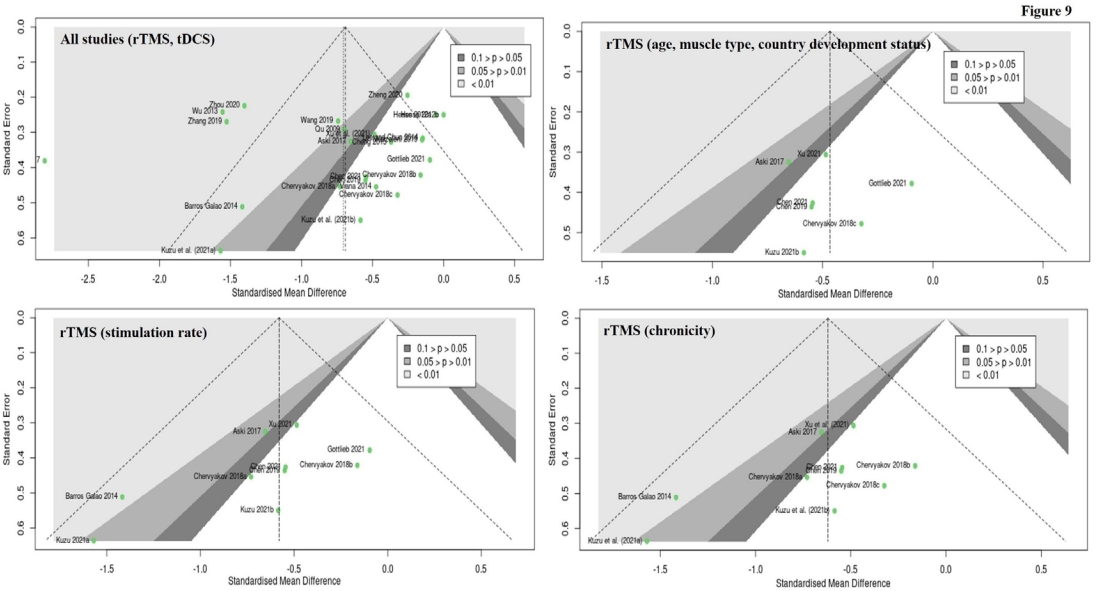


Figure 9. Funnel plot symmetry suggesting the absence of publication bias in the studies included in various meta- and subgroup analysis.

unaffected motor cortex had better upper limb function.[52] Motor function in chronic stroke patients is likely to be enhanced by either excitatory HF-rTMS of the ipsilesional primary motor cortex (M1) or inhibitory LF-rTMS of the contralesional M1.[23] This mechanism may enhance motor skills. The chronic phase of stroke is more likely to be affected by LF-rTMS in the unaffected hemisphere.[53] In patients with chronic stroke, LF-rTMS has been found to enhance the activation of damaged cortex and decrease interhemispheric inhibition, which is associated with improved function.[23] The use of LF-rTMS and HF-rTMS together can regulate the excitability of both hemispheres, leading to more effective therapeutic effects.[54] Nevertheless, there are no consistent standards for various stimulatory methods.

As mentioned above, tDCS had a positive effect on PSS reduction. tDCS applies a low-amplitude direct current via scalp electrodes, which alters the transmembrane potential and increases or decreases cortical excitability through anodal or cathodal stimulation, respectively.[55] In contrast to TMS, which has applications in both neurostimulation and neuromodulation, tDCS appears to be a neuromodulatory intervention.[56] The resting membrane potential of neurons is regulated by the tDCS current.[56] The three primary mechanisms of tDCS-induced neurophysiology include (a) enhancement of local cerebral blood flow, (b) stimulation of synaptic efficiency, and (c) activation of neurotrophic factors.[56] Anodal tDCS leads to subthreshold depolarization, which improves excitability in the affected hemisphere, whereas cathodal tDCS causes hyperpolarization and decreases excitability in the unaffected hemisphere. This may normalize the bihemispheric imbalance of transcallosal inhibition following stroke.[56] Following stroke, functional recovery can be improved by both anodal and cathodal stimulation, which regulates neurogenesis, increases the recruitment of oligodendrocyte precursor cells, and divides microglia.[56] tDCS has therapeutic effects on the functional recovery and survival of cortical neurons in subacute stroke models.[56] The goal of tDCS is to provide a subthreshold stimulus that modulates the probability of neuron firing by hyperpolarizing or depolarizing brain tissue without directly depolarizing the neurons. The meta-analysis showed that tDCS enhanced functional recovery after stroke by modulating neuronal activity and promoting neuroplasticity.

Subgroup analysis showed that the effect of tDCS on PSS reduction was not influenced by the type of stimulation. The effects of anodal rDCS were greater than those of cathodal rDCS or dual stimulation. Anodal stimulation effectively activates motor-evoked potentials, whereas cathodal stimulation inhibits them.[29] Anodal polarization increases excitability and cathodal stimulation decreases cortical excitability.[33] These changes are observed during tDCS and continue for up to an hour after termination. Hummel *et al*.[57]

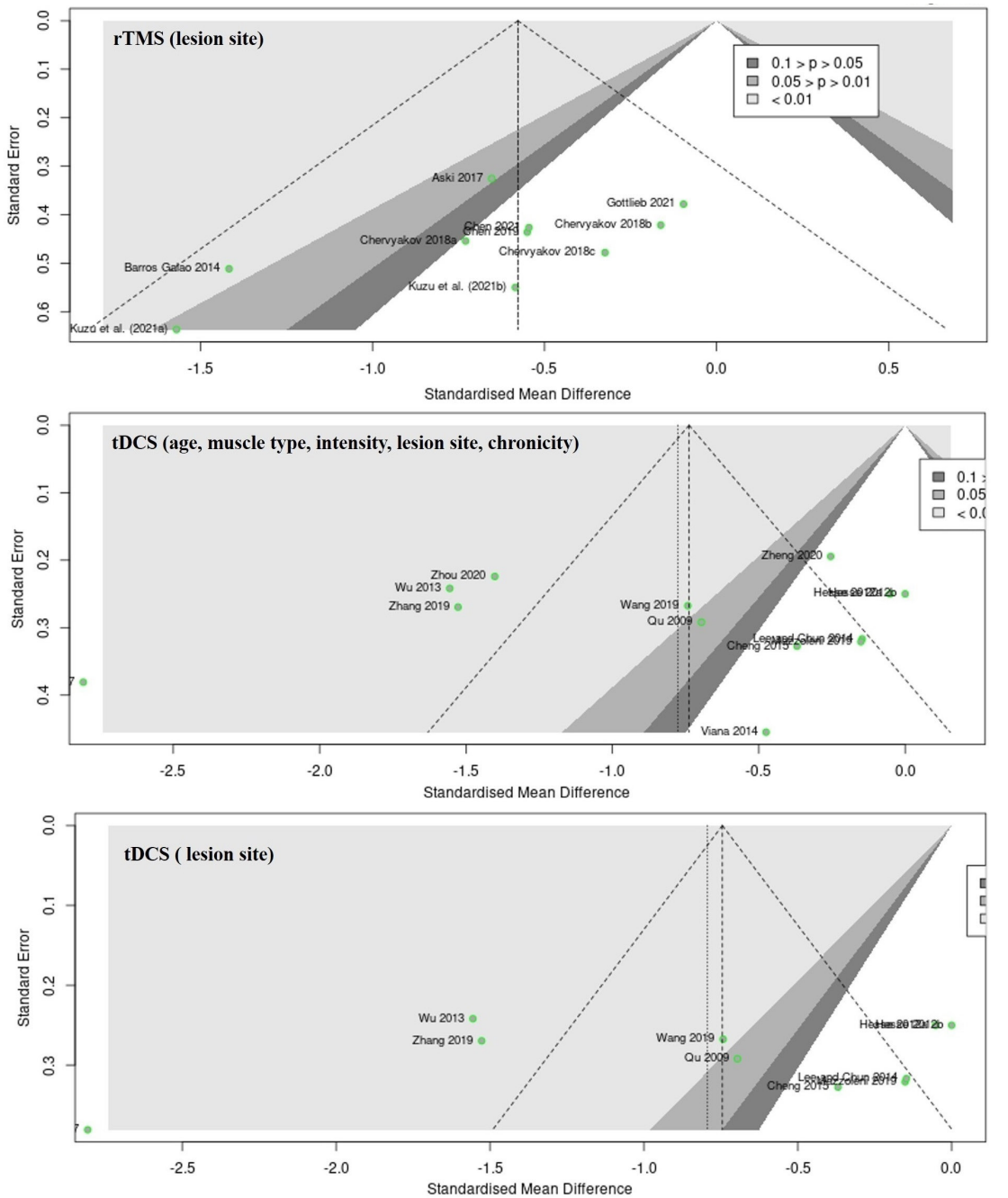


Figure 10. Funnel plot symmetry suggesting the absence of publication bias in the studies included in various meta- and subgroup analysis.

proved that motor performance in chronic stroke survivors was temporarily improved by activation of the affected hemisphere by anodal tDCS. Anodal stimulation of the affected hemisphere appears to be more effective than cathodal rDCS for improving motor performance.

Subgroup analysis revealed that tDCS at current levels of > 2.0 mA significantly reduced spasticity, whereas a current level of 2.0 mA showed no significant effect on post-stroke spasticity. Similar to our findings, the reversal of excitatory effects on corticospinal excitability was observed at higher intensities (≥ 1 mA).[58] Specific changes in intracortical physiology, including increased inhibition and reduced excitatory mechanisms, are linked to this phenomenon.[58] Higher intensities

and longer stimulation times may increase calcium influx into more neurons to induce plasticity.[58] On the other hand, the use of low-intensity electrical current in tDCS is intended to regulate the charge distribution of the membrane potential of nerve cells by applying it to the target brain area.[59] This leads to depolarization or hyperpolarization, thereby altering the excitability of the cerebral cortex.[59] The results indicated that low-intensity tDCS can improve post-stroke spasticity.

Subgroup analysis revealed that upper limb (except arms) function was improved by rTMS and tDCS. The application of low-frequency rTMS to the unaffected hemisphere was more effective than the application of high-frequency rTMS to improve upper limb motor function.[25] Upper extremity dysfunction is common in stroke patients, and permanent upper extremity motor deficits limit activities of daily living in many cases.[60] Bradnam *et al*.[61] reported that cathodal tDCS improved upper extremity control only in patients with mild stroke and worsened it in patients with moderate and severe stroke. Upper limb function was improved by rTMS and tDCS in individuals with stroke, as indicated by the data.

Subgroup analysis showed that the benefits of rTMS-reduced spasticity reduction were not affected by stroke chronicity. Regarding tDCS, the study found that this method was more effective in reducing spasticity two months after stroke onset.[62] A meta-analysis and systematic review demonstrated that tDCS is an effective treatment for chronic post-stroke aphasia.[63] The timing of NIBS use after stroke can affect patient recovery. For example, promising results were observed after repeated tDCS, which improved patients' motor and somatosensory function in the first month after stroke. Interestingly, comparable positive outcomes have been observed in patients with chronic stroke.[63] There is a proposed model of functional recovery in chronic stroke that involves maladaptive changes in M1-γ-aminobutyric acid-mediated inhibition in both the ipsilateral and contralateral lesions.[64] The use of bihemispheric tDCS therapy improved upper limb motor functions in patients with chronic stroke.[65] These findings are consistent with our findings showing the benefits of tDCS in improving upper limb function. This study provides promising results for the rehabilitation of PSS and indicates a potential tool to reduce spasticity in acute and chronic stroke.

The meta-analysis revealed that tDCS significantly reduced plasticity in patients with supratentorial lesions. Although the frequency of spasticity after stroke varies significantly between 4.0% and 42.6%, research on the effects of brain lesions on patients with stroke is limited.[66] In patients with stroke, damage to the anterior putamen and thalamus is associated with a poorer prognosis of upper limb function.[67] Using magnetic resonance imaging, Kyoung *et al*.[67] found that the progression of upper-limb spasticity was associated with lesions in the superior corona radiata, posterior limb of the internal capsule, posterior corona radiata, thalamus, putamen, premotor cortex, and insula.[68] However, supratentorial brain lesions in motor network regions are at low risk of developing post-stroke spasticity if their volume is less than 0.5 cm^3. Post-stroke spasticity was accompanied by significantly higher volume of brain lesions (> 3 cm^3) and involvement of motor network areas.[68] Thus, the prevalence of spasticity after stroke varies widely and depends on the characteristics of the lesion.

Subgroup analysis showed that both rTMS and tDCS reduced PSS in patients aged < 60 years (mean: 54.6 years) compared with patients aged > 60 years (mean: 66.4 years). Furthermore, subgroup analysis revealed that the beneficial effects of rTMS and tDCS on upper limb function were greater in patients aged < 60 years. Aging is linked to extensive qualitative and quantitative changes in the motor cortex.[69] For example, the occurrence of cortical atrophy, reduced cortical excitability, reduced cortical plasticity, and neurochemical abnormalities is believed to be linked to advanced age.[69] People over 65 years of age have been shown to have a 43% volumetric reduction in the size of the perikaryon of premotor cortex neurons compared to adults less than 45 years of age.[70] Cortical thinning also accompanies aging, with areas close to the primary motor cortex (e.g., the precentral gyrus) showing marked atrophy.[71] Furthermore, older adults exhibit significantly greater intracortical inhibition and less intracortical facilitation than younger adults.[72] The results indicated the need to improve NIBS techniques for older adults.

Subgroup analysis revealed that the combination of tCDS and conventional physical therapy reduced spasticity, whereas other adjuvant therapies, including virtual reality and robot-assisted therapy, did not reduce spasticity. The possibility of combining physical therapy modalities is an advantages of tDCS.[28] Previous studies have demonstrated that physical rehabilitation can promote alterations in sensory-motor cortical

activation and corticospinal conductivity in patients after stroke, in addition to promoting significant clinical improvement.[73] Plow et al.[74] emphasized that physical rehabilitation plus tDCS can facilitate cortical activity and restore interhemispheric balance, representing an important adjuvant therapy for functional recovery. Previous study revealed that tDCS is not an effective combination approach when physical therapy alone has a significant impact.[75] The findings indicate that combining tDCS and physical therapy can reduce spasticity in post-stroke patients.

Interestingly, subgroup analysis revealed that the use of rTMS and tDCS was more advantageous for reducing spasticity in post-stroke patients from developing countries than in those from developed countries. In terms of the effectiveness of tDCS in post-stroke rehabilitation, there are still significant disparities between developed and developing countries.[62] However, it is not clear why this method was more effective in developing countries than in developed countries. One explanation is that variability in responses is linked to interpersonal factors in tCDS studies.[62] The lack of collaboration with international teams is a notable limitation despite the fact that many scientists are actively working on tDCS for stroke treatment. The area would benefit from increased collaboration and communication in future research.

As our society ages rapidly, it is critical for the scientific community to better understand age-related differences in the effectiveness of NIBS. Therefore, appropriate treatment targets and effective interventions need to be developed to improve the decline in muscle function after stroke, especially in the elderly. In addition, in future studies, it is necessary to gather long-term follow-up data to evaluate the persistence of the therapeutic effects of rTMS and tDCS on PSP. Zhang et al assessed the immediate and longer-lasting effects (> 1 month) and found that tDCS and rTMS over the primary motor cortex decreased spasticity with no statistical significance after 1 month.[76]

In conclusion, these findings suggest a more complex or distinct interaction between stimulation parameters, patient age, lesion site, and induced plasticity.

DISCLOSURE

Data availability: All data generated or analyzed during this study are included in the published article.

Conflict of interest: None

REFERENCES

1. Wissel J, Schelosky LD, Scott J, *et al*. Early development of spasticity following stroke: a prospective, observational trial. *J Neurol* 2010;257:1067-72. doi: 10.1007/s00415-010-5463-1.
2. Bavikatte G, Subramanian G, Ashford S, *et al.* Early identification, intervention and management of post-stroke spasticity: expert consensus recommendations. *J Cent Nerv Syst Dis* 2021;13:11795735211036576. doi: 10.1177/11795735211036576.
3. Bethoux F. Spasticity management after stroke. *Phys Med Rehabil Clin N Am* 2015;26:625-39. doi: 10.1016/j.pmr.2015.07.003.
4. Nam HS, Koh S, Kim YJ, *et al.* Biomechanical reactions of exoskeleton neurorehabilitation robots in spastic elbows and wrists. *IEEE Trans Neural Syst Rehabil Eng* 2017;25:2196-203. doi: 10.1109/TNSRE.2017.2714203.
5. Chen YT, Li S, DiTommaso C, *et al.* Possible contributions of ipsilateral pathways from the contralesional motor cortex to the voluntary contraction of the spastic elbow flexors in stroke survivors: a TMS study. *Am J Phys Med Rehabil* 2019;98:558-65. doi: 10.1097/PHM.0000000000001147.
6. Molero-Chamizo A, Salas Sánchez Á, Álvarez Batista B, *et al*. Bilateral motor cortex tDCS effects on post-stroke pain and spasticity: a three cases study. *Front Pharmacol* 2021;12:624582. doi: 10.3389/fphar.2021.624582.
7. Hara T, Shanmugalingam A, McIntyre A, *et al*. The effect of non-invasive brain stimulation (NIBS) on attention and memory function in stroke rehabilitation patients: a systematic review and meta-analysis. *Diagnostics* (Basel) 2021;11:227. doi: 10.3390/diagnostics11020227.
8. Mori F, Koch G, Foti C, *et al.* The use of repetitive transcranial magnetic stimulation (rTMS) for the treatment of spasticity. *Prog Brain Res* 2009;175:429-39. doi: 10.1016/S0079-6123(09)17528-3.
9. Wassermann EM, Lisanby SH. Therapeutic application of repetitive transcranial magnetic stimulation: a review. *Clin Neurophysiol* 2001;112:1367-77. doi: 10.1016/s1388-2457(01)00585-5.
10. Brunoni AR, Nitsche MA, Bolognini N, *et al.* Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions. *Brain Stimul* 2012;5:175-95. doi: 10.1016/j.brs.2011.03.002.
11. Fregni F, Pascual-Leone A. Technology Insight: noninvasive brain stimulation in neurology—perspectives on the therapeutic potential of rTMS and tDCS. *Nature Rev Neurol* 2007;3:383-93. doi: 10.1038/ncpneuro0530.
12. López-Alonso V, Cheeran B, Río-Rodríguez D, *et al.* Inter-individual variability in response to non-invasive brain stimulation paradigms. *Brain Stimul* 2014;7:372-80. doi: 10.1016/j.brs.2014.02.004.
13. Naghdi S, Ansari NN, Rastgoo M, *et al.* A pilot study on the effects of low frequency repetitive transcranial magnetic stimulation on lower extremity spasticity and motor neuron excitability in patients after stroke.

J Bodyw Mov Ther 2015;19:616-23. doi: 10.1016/j.jbmt.2014.10.001.
14. Theilig S, Podubecka J, Bösl K, *et al.* Functional neuromuscular stimulation to improve severe hand dysfunction after stroke: does inhibitory rTMS enhance therapeutic efficiency? *Exp Neurol* 2011;230:149-55. doi: 10.1016/j.expneurol.2011.04.010.
15. Wu D, Qian L, Zorowitz RD, *et al*. Effects on decreasing upper-limb poststroke muscle tone using transcranial direct current stimulation: a randomized sham-controlled study. *Arch Phys Med Rehabil* 2013;94:1-8. doi: 10.1016/j.apmr.2012.07.022.
16. Page MJ, McKenzie JE, Bossuyt PM, *et al*. Updating guidance for reporting systematic reviews: development of the PRISMA 2020 statement. *J Clin Epidemiol* 2021;134:103-12. doi: 10.1016/j.jclinepi.2021.02.003.
17. da Costa Santos CM, de Mattos Pimenta CA, Nobre MR. The PICO strategy for the research question construction and evidence search. *Rev Lat Am Enfermagem* 2007;15:508-11. doi: 10.1590/s0104-11692007000300023.
18. Grooten WJA, Tseli E, Äng BO, *et al.* Elaborating on the assessment of the risk of bias in prognostic studies in pain rehabilitation using QUIPS-aspects of interrater agreement. *Diagn Progn Res* 2019;3:5. doi: 10.1186/s41512-019-0050-0.
19. Riley RD, Moons KGM, Snell KIE, *et al.* A guide to systematic review and meta-analysis of prognostic factor studies. *BMJ* 2019;364:k4597. doi: 10.1136/bmj.k4597.
20. Chen YJ, Huang YZ, Chen CY, *et al*. Intermittent theta burst stimulation enhances upper limb motor function in patients with chronic stroke: a pilot randomized controlled trial. *BMC Neurol* 2019;19:69. doi: 10.1186/s12883-019-1302-x.
21. Chen YH, Chen CL, Huang YZ, *et al.* Augmented efficacy of intermittent theta burst stimulation on the virtual reality-based cycling training for upper limb function in patients with stroke: a double-blinded, randomized controlled trial. *J Neuroeng Rehabil* 2021;18:91. doi: 10.1186/s12984-021-00885-5.
22. Chervyakov AV, Poydasheva AG, Lyukmanov RH, *et al*. Effects of navigated repetitive transcranial magnetic stimulation after stroke. *J Clin Neurophysiol* 2018;35:166-72. doi: 10.1097/WNP.0000000000000456.
23. Aşkın A, Tosun A, Demirdal ÜS. Effects of low-frequency repetitive transcranial magnetic stimulation on upper extremity motor recovery and functional outcomes in chronic stroke patients: a randomized controlled trial. *Somatosens Mot Res* 2017;34:102-7. doi: 10.1080/08990220.2017.1316254.
24. Barros Galvão SC, Borba Costa dos Santos R, Borba dos Santos P, *et al.* Efficacy of coupling repetitive transcranial magnetic stimulation and physical therapy to reduce upper-limb spasticity in patients with stroke: a randomized controlled trial. *Arch Phys Med Rehabil* 2014;95:222-229. doi: 10.1016/j.apmr.2013.10.023.
25. Kuzu Ö, Adiguzel E, Kesikburun S, *et al*. The effect of sham controlled continuous theta burst stimulation and low frequency repetitive transcranial magnetic stimulation on upper extremity spasticity and functional recovery in chronic ischemic stroke patients. *J Stroke Cerebrovasc Dis* 2021;30:105795. doi: 10.1016/j.jstrokecerebrovasdis.2021.105795.
26. Gottlieb A, Boltzmann M, Schmidt SB, *et al.* Treatment of upper limb spasticity with inhibitory repetitive transcranial magnetic stimulation: a randomized placebo-controlled trial. *NeuroRehabilitation* 2021;49:425-34. doi: 10.3233/NRE-210088.
27. Xu D, Cao H, Fan Y, *et al*. Comparative analysis of the effect of low-frequency repeated transcranial magnetic stimulation and extracorporeal shock wave on improving the spasm of flexor after stroke. *Evid Based Complement Alternat Med* 2021;7769581. doi: 10.1155/2021/7769581.
28. Andrade SM, Batista LM, Nogueira LL, *et al.* Constraint-induced movement therapy combined with transcranial direct current stimulation over premotor cortex improves motor function in severe stroke: a pilot randomized controlled trial. *Rehabil Res Pract* 2017;6842549. doi: 10.1155/2017/6842549.
29. Hesse S, Waldner A, Mehrholz J, *et al.* Combined transcranial direct current stimulation and robot-assisted arm training in subacute stroke patients: an exploratory, randomized multicenter trial. *Neurorehabil Neural Repair* 2011;25:838-46. doi: 10.1177/1545968311413906.
30. Lee SJ, Chun MH. Combination transcranial direct current stimulation and virtual reality therapy for upper extremity training in patients with subacute stroke. *Arch Phys Med Rehabil* 2014;95:431-8. doi: 10.1016/j.apmr.2013.10.027.
31. Mazzoleni S, Tran VD, Dario P, *et al*. Effects of transcranial direct current stimulation (tDCS) combined with wrist robot-assisted rehabilitation on motor recovery in subacute stroke patients: a randomized controlled trial. *IEEE Trans Neural Syst Rehabil Eng* 2019;27:1458-66. doi: 10.1109/TNSRE.2019.2920576.
32. Viana RT, Laurentino GE, Souza RJ, *et al*. Effects of the addition of transcranial direct current stimulation to virtual reality therapy after stroke: a pilot randomized controlled trial. *NeuroRehabilitation* 2014;34:437-46. doi: 10.3233/NRE-141065.
33. Wu D, Qian L, Zorowitz RD, *et al*. Effects on decreasing upper-limb poststroke muscle tone using transcranial direct current stimulation: a randomized sham-controlled study. *Arch Phys Med Rehabil* 2013;94:1-8. doi: 10.1016/j.apmr.2012.07.022.
34. Qu YP, Wu DY, Tu XQ, *et al*. Effects of transcranial direct current stimulation on relieving upper-limb spasticity after stroke (in Chinese). *Chin J Cerebrovasc* 2009;6:586-9.
35. Wang RF, Zhang KQ, Wu WY, *et al*. Clinical study of transcranial direct current electrical stimulation combined with exercise therapy on limb dysfunction in stroke patients (in Chinese). *J CZ Med Colg* 2019;33:353-6.
36. Zhang Y, Wang J. Effects of transcranial direct current electrical stimulation combined with upper limb robots in upper limb motor function and surface electromyogram signal in patients with cerebral infraction during convalescence (in Chinese). *J HB Med Univ* 2019;40:561-4.

37. Zheng S, Peng L and Mu JP. Effect of transcranial direct current stimulation combined with staging acupuncture on upper limb motor function in stroke patients with hemiplegia (in Chinese). *China Med Her* 2020;17:86-9.
38. Zhou JS, Lv X, Zhang LL, *et al*. Application of transcranial direct current stimulation combined with conventional adjuvant therapy in the rehabilitation of upper limb function in stroke patients with hemiplegia (in Chinese). *Mod Pract Med* 2020;32:579-80.
39. Cheng P, Jin H, Zheng J, *et al*. Clinical research on transcranial direct current stimulation and electrical acupuncture therapy for upper limb spasticity after stroke (in Chinese). *Chin Arch Tradit Chin Med* 2015;33:1673-717.
40. Mukherjee A, Chakravarty A. Spasticity mechanisms for the clinician. *Front Neurol* 2010;1:149. doi. org/10.3389/fneur.2010.00149.
41. Machado GC, Maher CG, Ferreira PH, *et al*. Efficacy and safety of paracetamol for spinal pain and osteoarthritis: systematic review and meta-analysis of randomised placebo controlled trials. *BMJ* 2015;350: h1225. doi: 10.1136/bmj.h1225.
42. Anil S, Lu H, Rotter S, Vlachos A. Repetitive transcranial magnetic stimulation (rTMS) triggers dose-dependent homeostatic rewiring in recurrent neuronal networks. *PLOS Comput Biol* 2023;19:e1011027. doi: 10.1371/journal.pcbi.1011027.
43. Aydin-Abidin S, Trippe J, Funke K, Eysel UT, Benali A. High- and low-frequency repetitive transcranial magnetic stimulation differentially activates c-Fos and zif268 protein expression in the rat brain. *Exp Brain Res* 2008;188:249-61. doi: 10.1007/s00221-008-1356-2.
44. Voineskos D, Blumberger DM, Rogasch NC, *et al*. Neurophysiological effects of repetitive transcranial magnetic stimulation (rTMS) in treatment resistant depression. *Clin Neurophysiol* 2021;132:2306-16. doi.org/10.1016/j.clinph.2021.05.008.
45. Zhou J, Fogarty A, Pfeifer K, Seliger J, Fisher RS. EEG evoked potentials to repetitive transcranial magnetic stimulation in normal volunteers: inhibitory TMS EEG evoked potentials. *Sensors* 2022;22:1762. doi: 10.3390/s22051762.
46. Hamidi M, Slagter HA, Tononi G, Postle BR. Brain responses evoked by high-frequency repetitive transcranial magnetic stimulation: an event-related potential study. *Brain Stimul* 2010;3:2-14. doi: 10.1016/j.brs.2009.04.001.
47. Ameli M, Grefkes C, Kemper F, *et al*. Differential effects of high-frequency repetitive transcranial magnetic stimulation over ipsilesional primary motor cortex in cortical and subcortical middle cerebral artery stroke. *Ann Neurol* 2009;66:298-309. doi: 10.1002/ana.21725.
48. Helfrich C, Pierau SS, Freitag CM, *et al*. Monitoring cortical excitability during repetitive transcranial magnetic stimulation in children with ADHD: a single-blind, sham-controlled TMS-EEG study. *PLoS One* 2012;7:e50073. doi: 10.1371/journal.pone.0050073.
49. Roos D, Biermann L, Jarczok TA, Bender S. Local differences in cortical excitability - A systematic mapping study of the TMS-evoked N100 component. *Front Neurosci* 2021;25:15:623692. doi: 10.3389/fnins.2021.623692.
50. Hosono Y, Urushihara R, Harada M, *et al*. Comparison of monophasic versus biphasic stimulation in rTMS over premotor cortex: SEP and SPECT studies. *Clin Neurophysiol* 2008;119:2538-45. doi: 10.1016/j.clinph.2008.07.279.
51. Iglesias AH. Transcranial magnetic stimulation as treatment in multiple neurologic conditions. *Curr Neurol Neurosci Rep* 2020**;**20:1. doi: 10.1007/s11910-020-1021-0.
52. Boggio PS, Alonso-Alonso M, Mansur CG, *et al*. Hand function improvement with low-frequency repetitive transcranial magnetic stimulation of the unaffected hemisphere in a severe case of stroke. *Am J Phys Med Rehabil* 2006;85:927-30. doi: 10.1097/01.phm.0000242635.88129.38.
53. Sebastianelli L, Versace V, Martignago S, *et al*. Low-frequency rTMS of the unaffected hemisphere in stroke patients: A systematic review. *Acta Neurol Scand* 2017;36:585-605. doi: 10.1111/ane.12773.
54. Dionísio A. Duarte IC, Patrício M, Castelo-Branco M. The use of repetitive transcranial magnetic stimulation for stroke rehabilitation: a systematic review. *J Stroke Cerebrovasc Dis* 2018;27:1-31. doi: 10.1016/j.jstrokecerebrovasdis.2017.09.008.
55. Brunoni AR, Nitsche MA, Bolognini N, *et al*. Clinical research with transcranial direct current stimulation (tDCS): Challenges and future directions. *Brain Stimul* 2012;5:175-95. doi: 10.1016/j.brs.2011.03.002.
56. Gomez Palacio Schjetnan A, Faraji J, Metz GA, Tatsuno M, Luczak A. Transcranial direct current stimulation in stroke rehabilitation: a review of recent advancements. *Stroke Res Treat* 2013;2013:170256. doi: 10.1155/2013/170256.
57. Hummel F, Celnik P, Giraux P, *et al*. Effects of non-invasive cortical stimulation on skilled motor function in chronic stroke. *Brain* 2005;128:490-9. doi: 10.1093/brain/awh369.
58. Hassanzahraee M, Nitsche MA, Zoghi M, Jaberzadeh S. Determination of anodal tDCS intensity threshold for reversal of corticospinal excitability: an investigation for induction of counter-regulatory mechanisms. *Sci Rep* 2020;10:16108. doi: 10.1038/s41598-020-72909-4.
59. Brunoni AR, Amadera J, Berbel B, *et al*. A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. *Int J Neuropsychopharmacol* 2011;14:1133-45. doi: 10.1017/S1461145710001690.
60. Langhorne P, Coupar F, Pollock A. Motor recovery after stroke: a systematic review. *Lancet Neurol* 2009;8:741-54. doi: 10.1016/S1474-4422(09)70150-4.
61. Bradnam LV, Stinear CM, Barber PA, *et al*. Contralesional hemisphere control of the proximal paretic upper limb following stroke. *Cereb Cortex* 2012;22:2662-71. doi: 10.1093/cercor/bhr344.
62. Li C, Tu S, Xu S, *et al*. Research hotspots and frontiers of transcranial direct current stimulation in stroke:

a bibliometric analysis. *Brain Sci* 2022;13:15. doi: 10.3390/brainsci13010015.
63. Badoiu A, Mitran SI, Catalin B, *et al*. From molecule to patient rehabilitation: the impact of transcranial direct current stimulation and magnetic stimulation on stroke-a narrative review. *Neural Plast* 2023;2023:5044065. doi: 10.1155/2023/5044065.
64. Nowak DA, Grefkes C, Ameli M, Fink GR. Interhemispheric competition after stroke: brain stimulation to enhance recovery of function of the affected hand. *Neurorehabil Neural Repair* 2009;23:641-56. doi: 10.1177/1545968309336661.
65. Lefebvre S, Thonnard JL, Laloux P, *et al*. Single session of dual-tDCS transiently improves precision grip and dexterity of the paretic hand after stroke. *Neurorehabil Neural Repair* 2014;28:100-10. doi: 10.1177/1545968313478485.
66. Barlow SJ. Identifying the brain regions associated with acute spasticity in patients diagnosed with an ischemic stroke. *Somatosens Mot Res* 2016;33:104-11. doi: 10.1080/08990220.2016.1197114.
67. Lee KB, Hong BY, Kim JS, *et al.* Which brain lesions produce spasticity? An observational study on 45 stroke patients. *PLoS One* 2019;14:e0210038. doi: 10.1371/journal.pone.0210038.
68. Ri S, Glaess-Leistner S, Wissel J. Early brain imaging predictors of post-stroke spasticity. *J Rehabil Med* 2021;53:1-6. doi: 10.2340/16501977-2803.
69. Clark BC, Taylor JL. Age-related changes in motor cortical properties and voluntary activation of skeletal muscle. *Curr Aging Sci* 2011;4:192-9. doi: 10.2174/1874609811104030192.
70. Haug H, Eggers R. Morphometry of the human cortex cerebri and corpus striatum during aging. *Neurobiol Aging* 1991;12:336-8. doi: 10.1016/0197-4580(91)90013-a.
71. Salat DH, Buckner RL, Snyder AZ, *et al*. Thinning of the cerebral cortex in aging. *Cereb Cortex* 2004;14:721-30. doi: 10.1093/cercor/bhh032.
72. McGinley M, Hoffman RL, Russ DR, *et al*. Older adults exhibit more intracortical inhibition and less intracortical facilitation than young adults. *Exp Gerontol* 2010;45:671-8. doi: 10.1016/j.exger.2010.04.005.
73. Rocha S, Silva E, Foerster A, *et al.* The impact of transcranial direct current stimulation (tDCS) combined with modified constraint-induced movement therapy (mCIMT) on upper limb function in chronic stroke: a double-blind randomized controlled trial. *Disabil Rehabil* 2016;38:653-60. doi: 10.3109/09638288.2015.1055382.
74. Plow EB, Cunningham DA, Beall E, *et al.* Effectiveness and neural mechanisms associated with tDCS delivered to premotor cortex in stroke rehabilitation: study protocol for a randomized controlled trial. *Trials.* 2013:14,331. doi: 10.1186/1745-6215-14-331.
75. Andressa de Souza J, Ferrari Corrêa JC, Marduy A, *et al.* To combine or not to combine physical therapy with tDCS for stroke with shoulder pain? analysis from a combination randomized clinical trial for rehabilitation of painful shoulder in stroke. *Front Pain Res* 2021;2:696547. doi: 10.3389/fpain.2021.696547.
76. Zhang X, Huai Y, Wei Z, Yang W, Xie Q, Yi L. Non-invasive brain stimulation therapy on neurological symptoms in patients with multiple sclerosis: A network meta-analysis. *Front Neurol* 2022;13:1007702. doi: 10.3389/fneur.2022.1007702.