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UPDATED SYSTEMATIC REVIEW

PM&R

The efficacy of transcranial direct current stimulation on upper extremity motor function after stroke: A systematic review and comparative meta-analysis of different stimulation polarities

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Abstract

Background: The efficacy of transcranial direct current stimulation (tDCS) has been studied extensively. The cathodic (c-tDCS), anodic (a-tDCS), and bihemispheric stimulation have demonstrated efficacy in the management of the paretic upper extremity (UE) after stroke, but it has not been determined which stimulation polarity has, so far, shown the best results.

Objective: To evaluate the available evidence to determine which tDCS polarity has the best results in improving UE motor function after stroke.

Methods: PubMed, PEDro, Web of Science, EMBASE, and SCOPUS databases were searched. Different Medical Subject Headings (MeSH) terms were combined for the search strategy, to cover all studies that performed a comparison between different tDCS configurations focused on UE motor rehabilitation in people with lived experience of stroke.

Results: Fifteen studies remained for qualitative analysis and 12 for quantitative analysis. Non-significant differences with a 95% confidence interval (CI) were obtained for c-tDCS versus a-tDCS ($g = 0.10$, 95% CI $= -0.13$; 0.33, $p = .39$, $N = 292$), for a-tDCS versus bihemispheric ($g = 0.02$, 95% CI $= -0.46$; 0.42, $p = .93$, $N = 81$), and for c-tDCS versus bihemispheric ($g = 0.09$, 95% CI $= -0.84$; .66, $p = .73$, $N = 100$). No significant differences between the subgroups of the meta-analysis were found.

Conclusions: The results of the present meta-analysis showed no evidence that a stimulation polarity is superior to the others in the rehabilitation of UE motor function after stroke. A non-significant improvement trend was observed toward c-tDCS compared to a-tDCS.

INTRODUCTION

Stroke is the leading cause of neurological disability worldwide. People with lived experience of stroke present chronic sequelae that affect their quality of life.[1] Medical advances and the increase in life expectancy of post-stroke patients indicate that in the future, the number of stroke cases will increase, increasing the number of people with neurological deficits that affect their autonomy.[2] One of the major repercussions for people after stroke is the limitation of the functionality of the upper extremities (UEs). These people can experience severe paresis in the arm and hand, achieving full motor recovery in only 5% to 20% of those affected,[3] which may be accompanied by possible loss of strength, sensation, or spasticity. This will especially affect manual dexterity, which is essential for activities of daily living.[4] Because of these deficits, it is necessary to seek approaches that enhance the brain's plasticity to promote recovery of UE functionality.[5]

Transcranial direct current stimulation (tDCS) has been shown to promote permanent plastic changes through long-term potentiation mechanisms, especially associated with rehabilitation.[6] There are two polarities of tDCS, which can modify cortical excitability, but in a different way. Anodic tDCS (a-tDCS) can increase the cortical excitability of the affected cerebral hemisphere, whereas cathodic tDCS (c-tDCS) has the capacity to reduce the cortical excitability of the contralesional hemisphere.[6] There is a third tDCS approach, which consists of stimulation in both hemispheres, combining a-tDCS of the affected hemisphere and c-tDCS of the unaffected hemisphere. Different systematic reviews have shown that the three assemblies have positive effects compared to sham in the motor rehabilitation of the UE in stroke.[7,8]

Although several studies have compared the effectiveness of various configurations of tDCS aimed at improving UE function in people with lived experience of stroke, to date no review has been conducted that brings together the evidence found in this regard. Given the large heterogeneity of protocols in the application of tDCS (current density, stimulation time, number of sessions, combination with online or offline therapy), and given the heterogeneity of people with stroke (with the severity of involvement and time since stroke being considered important parameters in the application of tDCS), and the time since stroke, it is necessary to establish which protocols may be more effective for each type of patient. One of the sources of heterogeneity is the polarity of tDCS used (a-tDCS, c-tDCS, bihemispheric); to date it is unknown which polarity is more effective in UE motor rehabilitation of stroke. Thus the aim of the present study is to determine which polarity of tDCS is more effective in the UE motor rehabilitation after stroke.

MATERIALS AND METHODS

The systematic review and meta-analysis were conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[9] (Supplementary Material 1). This systematic review and meta-analysis were registered in International Prospective Register of Systematic Review (PROSPERO) with the registration number: CRD42022303033.

Search strategy and database

The following databases were searched on January 2022 (including Jan-22 as search deadline): PubMed, PEDro, Web of Science, EMBASE, and SCOPUS. Different keywords in reference to the technique (tDCS) and pathology (stroke) were used for the systematic search. The different keywords were combined with the Boolean operators "AND" and "OR" (see Supplementary Material 2 for PubMed search strategy). The medical subheadings in each database were used when provided.

Eligibility criteria

We used the Population, Intervention, Comparison, Outcomes, Time, and Study design (PICOTS) as a framework to formulate eligibility criteria.

- **Population**: Persons with hemorrhagic or ischemic stroke (without limit of lesion location), >18 years of age and >7 days after stroke (subacute and chronic), with motor involvement of the UE.
- **Intervention**: tDCS applied online or offline, alone or with any motor rehabilitation intervention or motor training paradigm.
- **Comparison**: Comparison between different polarities of tDCS (c-tDCS vs. a-tDCS, c-tDCS vs dual, or a-tDCS vs. dual tDCS.
- **Outcomes**: Validated tests that measure UE motor function, activity, or participation on the UE, or change in a UE motor performance variable.
- **Time**: No temporal restrictions were applied to the duration of the intervention or outcome measures.
- **Studies**: Randomized controlled trials (RCTs) and pilot RCTs in English, Spanish, or Portuguese.

Studies applying a noninvasive brain stimulation (NIBS) technique other than tDCS, or combining an NIBS technique with tDCS, were excluded. Review articles, conference abstracts, and case reports were also excluded.

Selection of studies

Two authors independently reviewed the articles identified in different databases. First, duplicates were removed. Second, articles were screened by reading titles and abstracts to determine eligibility. Next, full-text articles were assessed against the eligibility criteria. The authors had to reach consensus on the inclusion of each article. In case of disagreement, a third author participated in the process to determine whether the study should be included.

Data extraction and quality assessment

The following information was extracted for each included study: sample size, patient characteristics, type of intervention (type of stimulation, electrode placement and size, number of sessions, application time, intensity, and duration of tDCS), and outcome measures. For the primary outcome, the effect of tDCS alone or combined with rehabilitation on UE function

was analyzed using functional scales and tests, including: Fugl-Meyer motor assessment of the UE (FMA-UE), Jebsen Taylor hand function test, Action Research Arm Test, Box and Block Test, Wolf Motor Function Test, Nine Hole Peg Test, Medical Research Council, or the hand grip strength. In the studies where it was necessary to obtain or clarify missing data, the corresponding authors were contacted for additional information.

Two investigators independently assessed the quality of the evidence using the Physiotherapy Evidence Database (PEDro).[10] The PEDro scale includes 11 items, the first of which is not used to calculate the PEDro score, but if the studies do not meet this item, should be excluded. Scores of 9 and 10 reflect studies of excellent quality, 6–8 of good quality, 4–5 of fair quality, and <4 of poor methodological quality. To assess the risk of bias for each study, we used the modified Cochrane library criteria,[11] giving a score regarding the risk of bias presented by the studies (such as "high," "low," or "some concerns"). Discrepancies were resolved by a third investigator.

Data synthesis and analysis

The mean differences (MDs) between pre-intervention and post-intervention were used to detect the comparison values between the tDCS groups and control group. The MD between groups was converted to the standardized mean difference (SMD), with a 95% confidence interval (CI). The SMD was used to express the results for UE function. The value of the functionality assessed by motor performance time tests was multiplied by −1 to align the direction of the effect, since a lower score is equivalent to a higher motor functionality.

A random-effects model was used to determine the overall effect size. Regarding SMD, an effect size of 0.8 was considered large, 0.5–0.8 was considered medium, and 0.2–0.5 was considered small.[12] p values < .05 were considered statistically significant. The overall effect size and calculation of the effect size were presented as forest plots. The restricted maximum likelihood method estimated variance of heterogeneity between studies; the degree of heterogenicity among the studies was estimated by Cochran's Q statistical test (with p values < .05 considered to be significant)[13] and the inconsistency index (I^2). I^2 > 25% was considered to represent small, I^2 > 50% medium, and I^2 > 75% large heterogenicity.[14] The I^2 is a complement to the Q test, although it has the same power issues when the number of studies is small.[14] When the Q test was significant (p < .1) and/or the result of I^2 was >25%, indicating heterogenicity among the studies, the random-effects model was applied in the meta-analysis. When heterogeneity was >25% according to the I^2 statistic, outliers (studies of which the 95% CI bound was lower/higher than the pooled 95% CI upper/lower bound) and influential cases analysis were performed using the analysis according to the Baujat et al. plot (plot displaying each individual study's contribution to overall heterogeneity plotted against its contribution to the overall pooled result),[15] influence diagnostics performed with the leave-one-out method, according to Viechtbauer and Cheung,[16] the externally standardized residuals plot, the Cook's distance plot, and the covariance ratio plot. Identified studies were marked as outliers or influential cases and were removed.

Asymmetry was evaluated using a contour-enhanced funnel plot in those analyses formed by at least five studies, which indicates the possible risk of publication of small studies with negative results.[17] If no publication bias is present, the plot resembles a symmetrical funnel shape.

A subgroup analysis was performed according to the type of measurement tool used (measures of functionality vs. measures of motor performance speed), and according to the methodological quality of the studies (excellent, fair, or good). The subgroup analysis was performed if the included studies were >10. A post hoc meta-regression analysis was performed to investigate potential moderators: stage of stroke, current density, and sessions. Studies were analyzed using R software,[18] using the metafor package according to the Harrer et al.[19] guide.

Quality of evidence

To assess the quality of the evidence, the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was used. It was performed independently by two authors, and in case of discrepancies, a third author intervened. The quality of the evidence was classified as high, moderate, low, or very low based on the presence of study limitations (RoB), inconsistency of the results, unexplained heterogeneity, imprecision of the results, high probability of publication bias, or lack of directionality of the evidence.[20] The quality of the evidence was classified as very low when all items had a serious risk or more than two items had a very serious risk; low when two or three items had a serious risk or one or two items had a very serious risk; moderate when one item included a serious risk; and high when all items were negative.

Inter-rater reliability

Inter-rater reliability for screening, risk of bias assessment, and quality of the evidence rating were assessed using percentage agreement and Cohen's kappa coefficient. There was strong agreement between reviewers for the screening records and full texts (90.5%

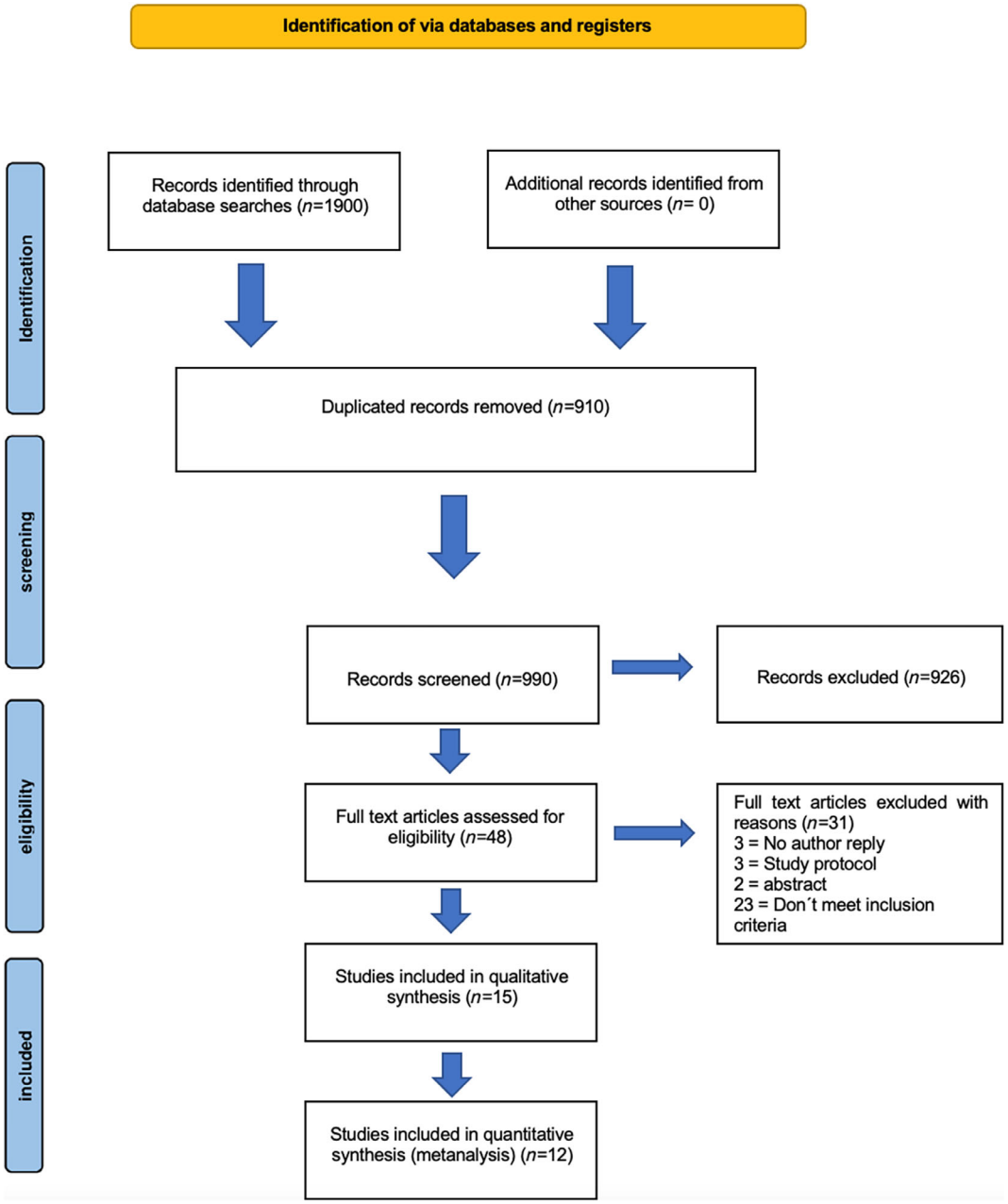

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

agreement rate and $k = 0.91$), the risk of bias assessment (92% agreement rate and $k = 0.83$), and the quality and strength of the evidence assessment (91.8% rate and $k = 0.83$).

RESULTS

Study Selection

The electronic search identified 1900 studies for review. After duplicates were eliminated, 990 studies remained. After review of the titles and abstracts, 942 studies were eliminated because they did not meet the inclusion criteria, leaving 48 articles for full-text analysis. Thirty-one studies were excluded for the following reasons: 10 studies were abstracts or protocols of studies, 8 did not evaluate variables of interest, 5 studies were requested but no response was obtained, 4 were in Chinese, 2 applied tDCS combined with other types of brain stimulation, 1 was a case study, 1 did not compare tDCS setups, 1 was applied in pathology other than stroke, 1 included healthy participants, and 1 was a review. Finally, 15 studies were included in the systematic review, and 12 were used for quantitative analysis. The search flowchart is shown in Figure 1.

TABLE 1 Characteristics of included studies.

Study	*n*	Mean age (SD) (y), % Male	Time since stroke and type	Design	Current density (mA/cm^2)	Number and time of sessions	Stimulation site	Outcome measure	Therapy (patients per group)	Baseline functionality
Adeagbo et al. 2021[21]	78	56.8 ± 10.2; 59%	Subacute/chronic, Cortical/subcortical	Single-blind RCT	1.6 mA/25 cm^2–0.064 mA/cm^2	12; 20 min	M1	FMA-UE, BBT	Group 1: A tDCS RFT Group 2: C tDCS RFT Group 3: RFT	FMA-UE Group 1: 25.96 ± 8.57 Group 2: 27.85 ± 9.11 Group 3: 29 ± 8.89
Boggio et al. 2009[22]	4	57.4 ± 12.9; 100%	Chronic (40.9 months). Subcortical	Double blinded, crossover sham-controlled crossover study	1 mA/35 cm^2–0.029 mA/cm^2	1; 20 min	M1	JTT	Group 1: A tDCS (4) Group 2: C tDCS (4) Group 3: sham tDCS (4)	JTT 54 ± 16.2
Chelette et al. 2014[23]	26	58.8 ± 4.7; 61.5%	Chronic, cortical/subcortical	Double-blind, RCT	1.4 mA/35 cm^2–0.04 mA/cm^2	10, 20 min	M1	FMA-UE, ARAT	Group 1: A tDCS + 3 h RFT (7) Group 2: C tDCS + 3 h RFT (6) Group 3: B tDCS + 3 h RFT (7) Group 4: sham tDCS + 3 h RFT (6)	FMA-UE Group 1: 26.14 ± 4.68 Group 2: 22.83 ± 0.95 Group 3: 26.14 ± 2.8 Group 4: 23.67 ± 3.46
Del Felice et al. 2016[24]	10	62 (44–80); 70%	Chronic (2.3 years; 9 mo-9 years), cortical/subcortical	Cross-over, double-blinded.	1 mA/25 cm^2–0.04 mA/cm^2	5, 20 min	M1	ARAT, MRC	Group 1: C tDCS (10) Group 2: B tDCS (10)	ARAT Group 1: 6.5 ± 5 Group 2: 5.4 ± 4.8
Fleming et al. 2017[25]	24	59.8 ± 13.1	Chronic/subacute (19.7 ± 27.4 months), cortical/subcortical	Single-blinded crossover study.	1 mA/25 cm^2–0.04 mA/cm^2	1, 20 min	M1	JTT	Group 1: A tDCS Group 2: C tDCS Group 3: B tDCS Group 4: sham tDCS	JTT 77.4 ± 72.2
Fregni et al. 2005[26]	6	53.7 ± 16.6; 33.3%	Chronic (27.1 ± 24.3 months), cortical/subcortical	Double- blinded, sham- controlled crossover study	1 mA/35 cm^2–0.029 mA/cm^2	1, 20 min	M1	JTT	Group 1: A tDCS (6) Group 2: C tDCS (6) Group 3: sham tDCS (6)	JTT Group 1: 63.80 ± 18.22 Group 2: 63.63 ± 17.29 Group 3: 63.06 ± 17.95
Fusco et al. 2014[27]	9	53.5 ± 20.7; 55.6%	Chronic (28.3 ± 10.4); cortical	Single-blind, crossover, sham-controlled study	1.5 mA/35 cm^2–0.043 mA/cm^2	1, 15 min	M1	9HPT	Group 1: A tDCS (3) Group 2: C tDCS (3) Group 3: B tDCS (3) Group 4: sham tDCS (9)	9HPT% Group 1: 23.97 ± 3–82 Group 2: 71.57 ± 23.59 Group 3: 74.43 ± 16.09 Group 4: 47.47 ± 34.11
Hesse et al. 2011[28]	96	65.0 ± 9.8; 61.5%	Subacute (3.6 ± 1.5 weeks), cortical	Double-blind, RCT.	2 mA/35 cm^2–0.057 mA/cm^2	30, 20 min	M1	FMA-UE, BBT, MRC	Group 1: A tDCS + RAT (29) Group 2: C tDCS + RAT (28) Group 3: sham tDCS + RAT (28)	FMA-UE Group 1: 7.8 ± 3.8 Group 2: 7.9 ± 3.4 Group 3: 8.2 ± 4.4
Kim et al. 2010[29]	18	57.3 ± 13.5; 72%	Subacute (25.4 ± 14.6 days), cortical/subcortical	Prospective, RCT.	2 mA/25 cm^2–0.08 mA/cm^2	10, 20 min	M1	FMA-UE	Group 1: A tDCS + OT (6) Group 2: C tDCS + OT (5) Group 3: sham tDCS + OT (7)	FMA-UE Group 1: 39.2 ± 19 Group 2: 31 ± 11.2 Group 3: 41 ± 13

(Continues)

TABLE 1 (Continued)

Study	*n*	Mean age (SD) (y), % Male	Time since stroke and type	Design	Current density (mA/cm^2)	Number and time of sessions	Stimulation site	Outcome measure	Therapy (patients per group)	Baseline functionality
Mahamoudi et al. 2011[30]	10	60.8 ± 14.1; 70%	Chronic (8.3 ± 5.4 months); cortical/subcortical	Double-blinded, crossover study	1 mA/35 cm^2–0.029 mA/cm^2	1, 20 min	M1	JTT	Group 1: A tDCS (10) Group 2: C tDCS (10) Group 3: B tDCS (10) Group 4: sham tDCS (10)	JTT Group 1: 10.6 ± 7.43 Group 2: 9.68 ± 4.46 Group 3: 10.16 ± 5.61 Group 4: 10.13 ± 4.27
Ochi et al. 2013[31]	18	61.1 ± 10; 78%	Chronic (2.2 ± 3.4 years)	Double-blinded, crossover study	1 mA/35 cm^2–0.029 mA/cm^2	5, 10 min	M1	FMA-UE, MAL	Group 1: A tDCS + RAT (18) Group 2: C tDCS + RAT (18)	FMA-UE Group 1: 23.2 ± 16.6 Group 2: 23.6 ± 16.7
Rocha et al. 2015[32]	21	58.4 (41–71); 72.4%	Chronic (29.4 [6–67] months)	Double-blind, RCT	1 mA/35 cm^2–0.029 mA/cm^2	12, 13 min a-tDCS, 9 min c-tDCS	M1	FMA-UE, MAL, HG	Group 1: A tDCS + mCIMT (7) Group 2: C tDCS + mCIMT (7) Group 3: sham tDCS + mCIMT (7)	FMA-UE Group 1: 44.6 ± 4.1 Group 2: 51.6 ± 4.2 Group 3: 51 ± 8.9
[a]Sik et al. 2015[33]	36	60 (55–67); 56%	Chronic (22 [10–36] months)	Prospective, RCT	2 mA/16 cm^2–0.125 mA/cm^2	15, 20 min	M1	WMFT, JTT	Group 1: A tDCS + 2 h PT (12) Group 2: B tDCS + 2 h PT (12) Group 3: sham tDCS + 2 h PT (12)	NR
Taud et al. 2021[34]	40	59.6 ± 12; 77.5%	Chronic (26.2 ± 25.9 months)	Double-blind, RCT	1 mA/35 cm^2–0.029 mA/cm^2	5, 23 min	M1	FMA-UE, WMFC	Group 1: A tDCS + PT Group 2: B tDCS + PT Group 3: sham tDCS + PT	FMA-UE Group 1: 47.1 ± 17.9 Group 2: 46.9 ± 15 Group 3: 43.6 ± 20.7
Yeung et al. 2014[35]	10	62.6 ± 5.7; 100%	Chronic (8.3 ± 3.2 years)	Double-blind, three-arm crossover, RCT	1 mA/35 cm^2–0.029 mA/cm^2	3, 20 min	M1	Purdue peg test	Group 1: A tDCS (10) Group 2: C tDCS (10) Group 3: sham tDCS (10)	Purdue Group 1: 5.1 ± 4 Group 2: 4.7 ± 4.2 Group 3: 5.4 ± 4.1

Abbreviations: A, a-tDCS; ARAT, Action Research Arm Test; B, bihemispheric; BBT, Box and Block Test; C, c-tDCS; FMA-UE, Fugl-Meyer Assessment Scale Upper Limb section; HG, hand grip strength; JTT, Jebsen Taylor hand function Test; M1, motor primary cortex; mA: milliampere; MAL, Motor Activity Log; mCIMT, modified Constraint-Induced Movement Therapy; MRC, Medical Research Council; NR, not-reflected; OT, occupational therapy; PT, physical therapy; RCT, randomized controlled trial; RAT, robotic arm training; RFT, repetitive functional task; SD, standard deviation; tDCS, transcranial direct current stimulation; WMFC, Wolf Motor Function Test; 9HPT: Nine Hole Peg Test.

[a]Values are expressed as median and interquartile range.

Qualitative summary of the included studies

All included studies were, at least, single-blinded and sham-controlled. A description of the included studies is provided in Table 1. The studies that met the inclusion criteria were conducted between 2005 and 2021, including a total of 406 people with lived experience of stroke. The mean age of the patients included in the studies in this review was 55 years, including men and women, with hemorrhagic and ischemic, cortical and subcortical strokes, in all stages of the disease (acute/subacute[21,25,28,29] and chronic[21–27,30–35]). Regarding stimulation polarity, four studies compared the effectiveness of a-tDCS, c-tDCS, and bihemispheric tDCS, as well as sham stimulation,[23,25,27,30] nine studies compared a-tDCS versus c-tDCS (of which seven included sham stimulation,[22,26,28,29,32,33,35] and two did not include sham stimulation[21,31]), one study compared c-tDCS versus bihemispheric stimulation,[24] and one compared a-tDCS versus bihemispheric stimulation, including sham stimulation.[34] Among the included studies, eight performed UE motor training in addition to stimulation,[21,23,28,29,31–34] whereas seven performed only tDCS stimulation.[22,24–27,30,35] Sessions ranged from a single session[22,25–27,30] to 3,[5,24,31,34,35] 10,[23,29] 12,[21,32] 15,[33] and 30 sessions.[28] The duration of tDCS application was 10 minutes in one study,[31] 15 minutes in one study,[27] 20 minutes in 11 studies,[21–26,28–30,33,35] and 23 minutes in one study.[34] Rocha et al.[32] applied 13 minutes in the case of a-tDCS and 9 minutes in the case of c-tDCS. The current density ranged from 0.029 mA/cm^2[21,26,30–32,34,35] to 0.04[23–25] 0.043,[27] 0.057[28] 0.064,[21] 0.08,[29] and 0.125 mA/cm^2.[33] The stimulation site was over the primary motor cortex (M1) in all studies.[29–35] The change in UE function was measured with the FMA-UE scale in seven studies,[21,23,28,29,31,32,34] the Jebsen Taylor hand function Test in four studies,[22,25,26,30] the Action Research Arm Test in one study,[24] the Wolf Motor Function Test in one study,[33] and the nine Hole Peg Test in one study.[27]

Quality assessment

The methodological quality score ranged from 5 to 10 out of a maximum of 10 points, so that the included studies are considered studies of moderate and high methodological quality. The most frequent biases were the lack of information on how randomization to intervention groups was performed (high risk of bias in 66% of the studies) and the lack of blinding of the therapist (high risk of bias in 60% of the studies). The blinding of outcome assessment also showed considerable risk of bias (high risk of bias in 20% of the studies). Table 2 shows the details of the PEDro scale items and Figure 2 the risk of bias analysis.

a-tDCS versus c-tDCS stimulation

Twelve studies[21–23,25–32,35] evaluated a-tDCS versus c-tDCS in motor recovery of the UE after stroke. Among these 12 studies, 2 studies[21,32] found better results in favor of a-tDCS, 2 studies[29,35] found better results

TABLE 2 PEDro characteristics of included studies.

Study	1	2	3	4	5	6	7	8	9	10	11	Total
Adeagbo et al. 2021[21]	1	1	0	1	0	0	0	0	0	1	1	5
Boggio et al. 2007[22]	0	1	0	1	1	0	1	1	1	1	1	8
Chelette et al. 2014[23]	1	1	0	1	1	1	1	1	1	1	1	9
Del Felice et al. 2016[24]	1	1	0	1	1	1	1	1	1	1	1	9
Fleming et al. 2017[25]	1	1	0	0	1	0	0	1	0	1	1	5
Fregni et al. 2005[26]	0	1	0	1	1	0	1	1	1	1	1	8
Fusco et al. 2014[27]	1	1	0	1	1	0	0	1	1	1	1	7
Hesse et al. 2011[28]	1	1	1	1	1	1	1	1	1	1	1	10
Kim et al. 2010[29]	1	1	1	1	1	1	1	1	0	1	1	9
Mahamoudi et al. 2011[30]	1	1	0	1	1	0	1	1	1	1	1	8
Ochi et al. 2013[31]	1	1	1	1	1	1	1	1	1	1	1	10
Rocha et al. 2015[32]	1	1	1	1	1	0	1	1	1	1	1	9
Sik et al. 2015[33]	1	1	0	1	1	0	1	1	0	1	1	7
Taud et al. 2021[34]	1	1	0	0	1	1	1	1	0	1	1	7
Yeung et al. 2014[35]	1	1	1	1	1	0	1	1	1	1	1	9

Note: 1, Specified study eligibility; 2, Random allocation of participants; 3, Concealed allocation; 4, Similarity between groups at baseline; 5, Participant blinding; 6, Therapist blinding; 7, Assessor blinding; 8, <15% Dropouts; 9, Intention-to-treat analysis; 10, Between-group statistical comparisons; 11, Point measures and variability data.

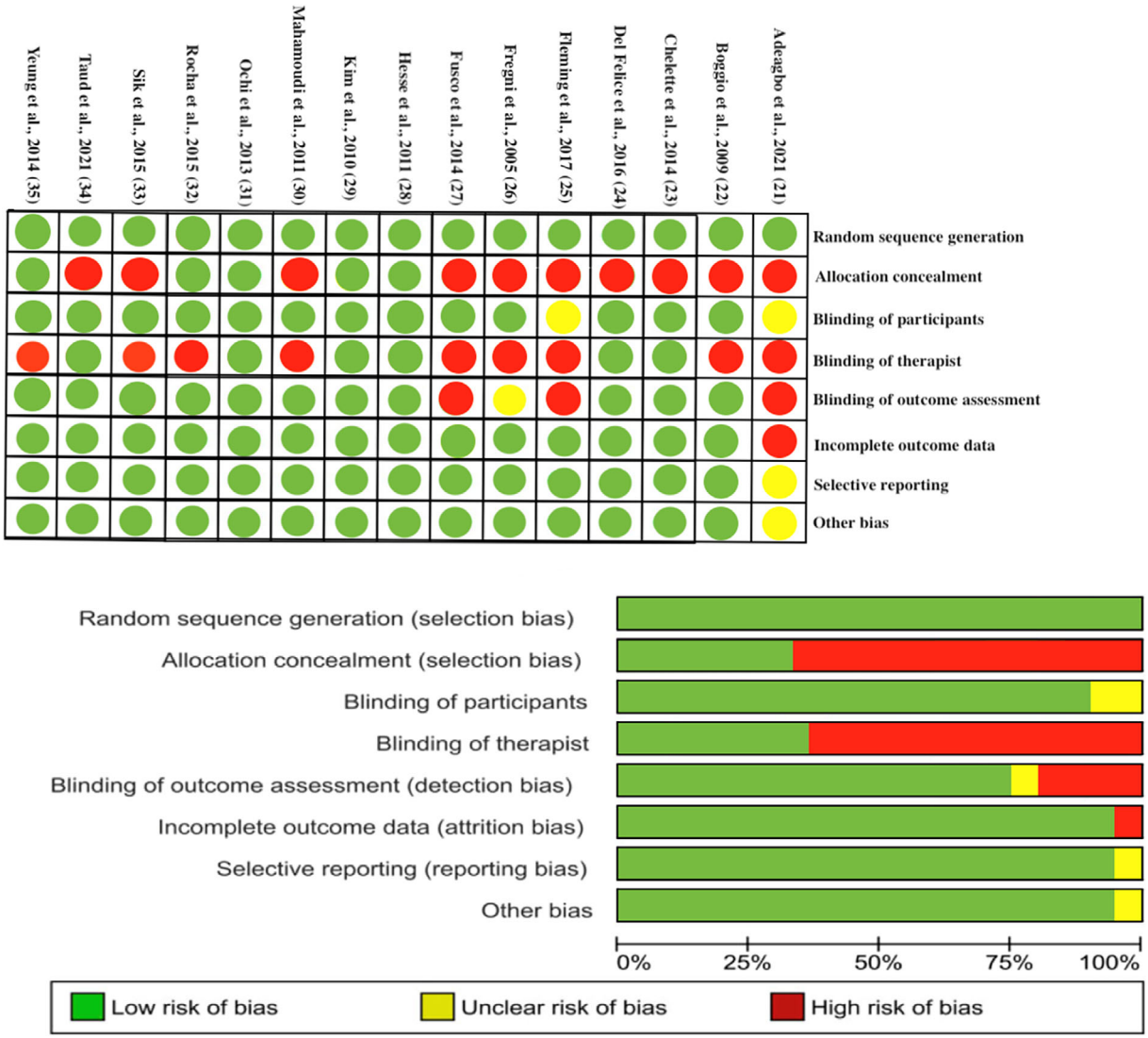

FIGURE 2 Risk of bias assessment.

in favor of c-tDCS, and 8 studies[22,23,25–28,30,31] showed equality between both types of stimulation.

Eleven studies were included in the quantitative analysis on the effect of c-tDCS compared to a-tDCS. The meta-analysis showed that c-tDCS had a small nonsignificant effect ($g = 0.10$, 95% CI $= -0.13$; .33, $p = .39$, $N = 292$) over anodal stimulation (prediction interval: 95% CI: −0.11; 0.36) (Figure 3A). The restricted maximum likelihood method estimated a between-study heterogeneity variance of $\tau^2 = 0$ (95% CI: 0.000; 0.2), with an I^2 value of 0% (95% CI: 0%–71%), indicating that no heterogeneity was observed ($p = .19$). The funnel plot presents asymmetry, indicating the risk of publication bias (Figure 4). A subgroup analysis was performed according to the measurement tool (motor score versus execution speed). Subgroup analysis showed no significant differences between groups (p: .08): FMA ($g = 0.12$, 95% CI $= -0.15$; 0.39, $I^2 = 0\%$) (Figure 3B) and Jebsen Taylor hand function Test ($g = 0.05$, 95% CI $= -0.37$; 0.47, $I^2 = 0\%$) (Figure 3C). A subgroup analysis was performed according to methodological quality (excellent, fair, good), which showed no significant differences between groups (p: .98): excellent ($g = 0.11$, 95% CI $= -0.2$; 0.44, $I^2 = 0\%$); fair ($g = 0.07$, 95% CI $= -0.32$; 0.46, $I^2 = 0\%$); and good ($g = 0.12$, 95% CI $= -0.5$; 0.74, $I^2 = 0\%$). Meta-regression analysis showed that density ($p = .69$), chronicity ($p = .92$), or number of sessions ($p = .77$) did not influence the effect size of the included studies.

Bihemispheric versus a-tDCS stimulation

Six studies[23,25,27,30,33,34] evaluated a-tDCS versus bihemispheric stimulation in motor recovery of the UE after stroke. Among these six studies, four studies[23,25,27,34] found better results in favor of a-tDCS

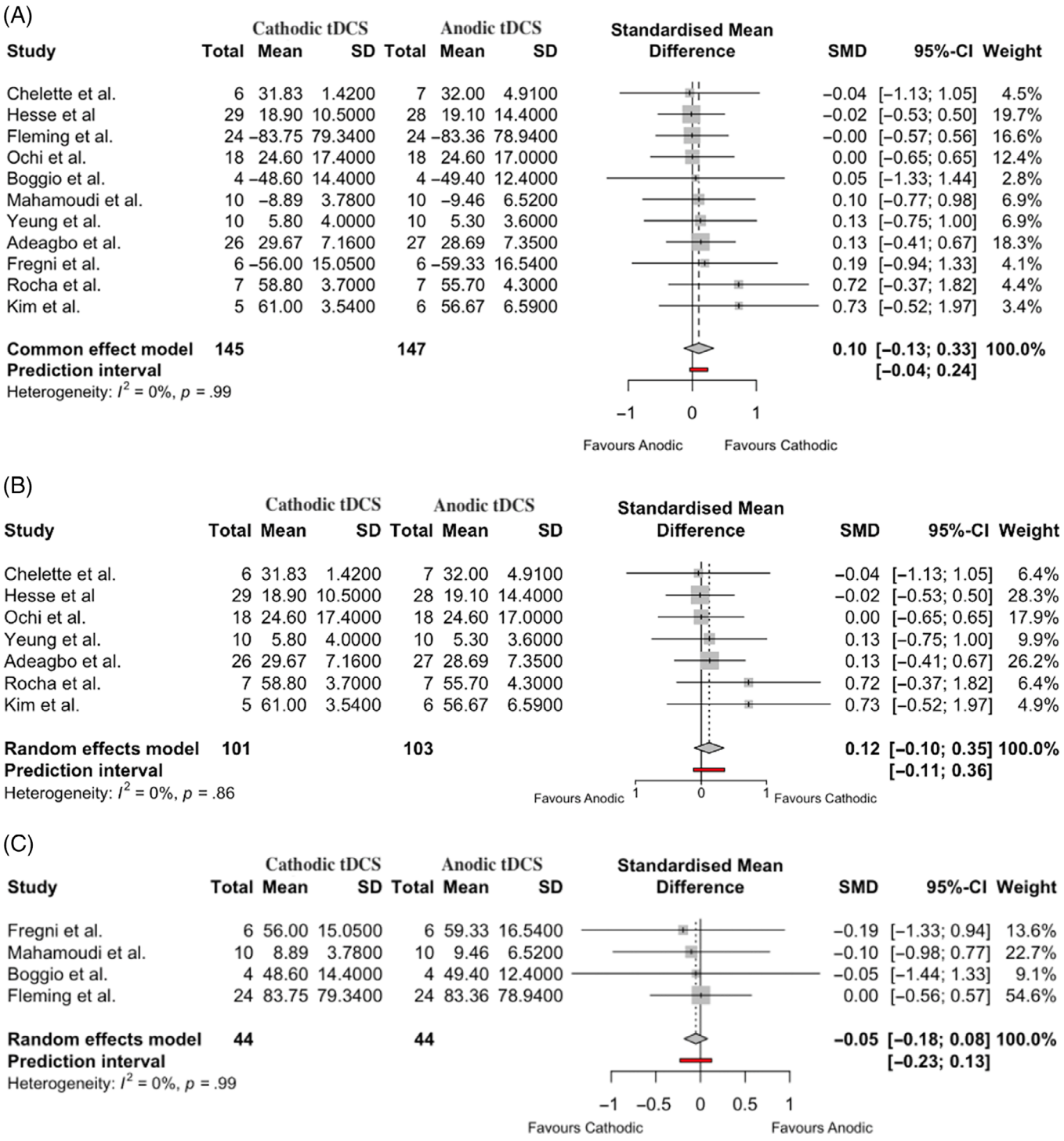

FIGURE 3 Forest plot of the results of a random-effects meta-analysis on upper limb function, shown as standardized mean differences (SMDs) with 95% confidence interval (CI) for (A) cathodic transcranial direct current stimulation (c-tDCS) versus anodic transcranial direct current stimulation (a-tDCS), (B) c-tDCS versus a-tDCS Fugl-Meyer Upper Extremity subgroup, and (C) c-tDCS versus a-tDCS Jebsen Taylor hand function Test subgroup. The shaded square represents the point estimate for each individual study and the weight of the study in the meta-analysis. The diamond represents the overall mean difference of the studies.

stimulation and two studies[30,33] found equality between both types of stimulation.

Three studies were included in the quantitative analysis on the effect of bihemispheric tDCS compared to a-tDCS. The meta-analysis showed that there is no clear effect toward any type of stimulation ($g = 0.02$, 95% CI $= -0.46$; 0.42, $p = .93$, $N = 81$; prediction interval: 95% CI: −2.92; 2.88) (Figure 5A). The restricted maximum likelihood method estimated a between-study heterogeneity variance of $\tau^2 =$ <0.001 (95% CI: 0.000;

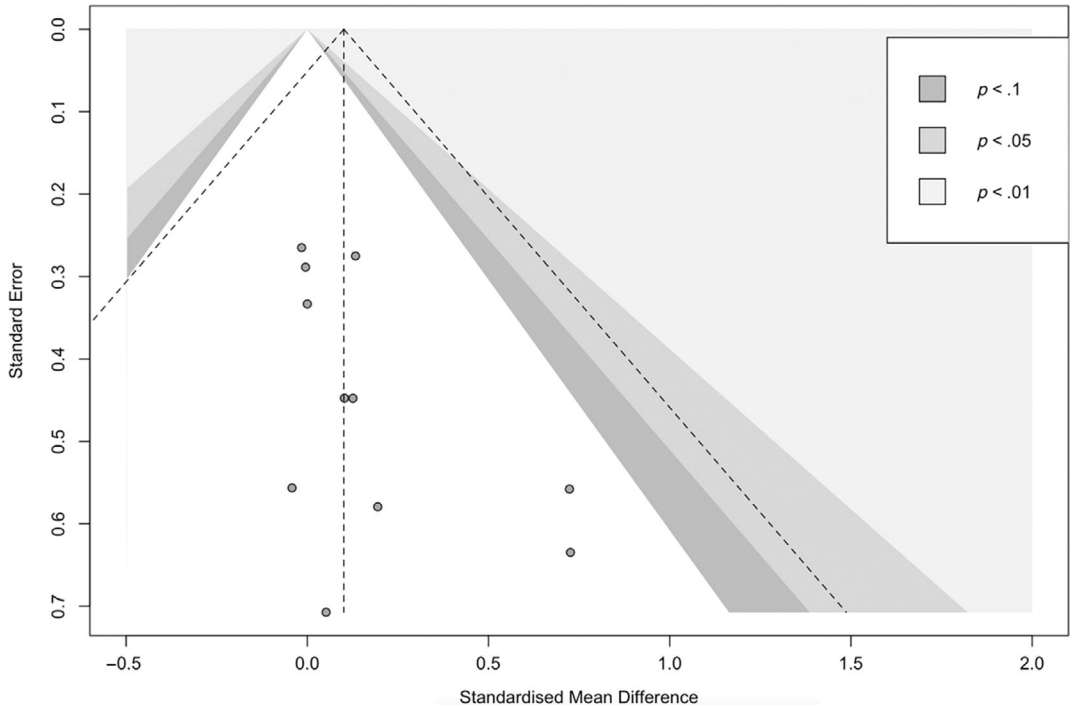

FIGURE 4 Cathodic transcranial direct current stimulation (c-tDCS) versus anodic transcranial direct current stimulation (a-tDCS) Contour-enhanced funnel plot. Dispersion of effect sizes. X-axis: observed effect sizes. Y-axis: inversed standard error (higher values on the Y-axis represent lower standard errors). Slight asymmetry, meaning possible publication bias. Inside to outside (0–2). White region $p > .05$; dark gray region $p < .1$; intermediate gray region $p < .05$; outer gray region $p < .001$.

10.93), with an I^2 value of 3.3% (95% CI: 0%–89.9%), and a minimum non-significative heterogeneity ($p = .35$).

Bihemispheric versus c-tDCS

Seven studies[23–25,27,30,33,34] evaluated cathodal versus bihemispheric stimulation in motor recovery of the UE after stroke. Among these seven studies, five studies[23–25,27,34] found better results in favor of cathodal stimulation and two studies[30,33] found equality between both types of stimulation.

Four studies were included in the quantitative analysis on the effect of bihemispheric tDCS compared to c-tDCS. The meta-analysis showed that there is no clear effect toward any type of stimulation ($g = 0.09$, 95% CI $= -0.84$; 0.66, $p = .73$, $N = 100$; prediction interval: 95% CI: −1.1; 0.93) (Figure 5B). The restricted maximum likelihood method estimated a between-study heterogeneity variance of $\tau^2 = <0.001$ (95% CI: 0.000; 6.01), with an I^2 value of 26% (95% CI: 0%–71.8%), and a small non-significant heterogeneity ($p = .26$). Supplementary Material 3 No outliers (random-effects model) were detected. Two influential cases (Fleming et al.[25] and Mahamoudi et al.[30]) were detected, because they showed an excessive weight on the pooled effect size. A new meta-analysis was performed without these data, which did not significantly affect the effect size but decreased heterogeneity (I^2: 0%) (Table 3).

Quality of evidence (GRADE)

Table 4 collects the details of the GRADE assessment, showing risk of bias, inconsistency of results, indirect evidence, imprecision of results, and high probability of publication bias. The risk of bias, the small number of studies, and the small effect size of the results lowered the level of evidence for the overall effect, resulting in a very small to small level of evidence.

DISCUSSION

This systematic review and meta-analysis aimed to determine which tDCS polarity (a-tDCS, c-tDCS, or bihemispheric) has the greatest benefit in the UE motor rehabilitation after stroke. The results of the present meta-analysis showed no evidence that one montage is superior to the others, with no significant differences between the pooled effect sizes of the included studies. Although not significantly so, c-tDCS (inhibitory over the healthy cerebral hemisphere) seems to be superior to anodal and bihemispheric stimulation in the UE motor rehabilitation after stroke.

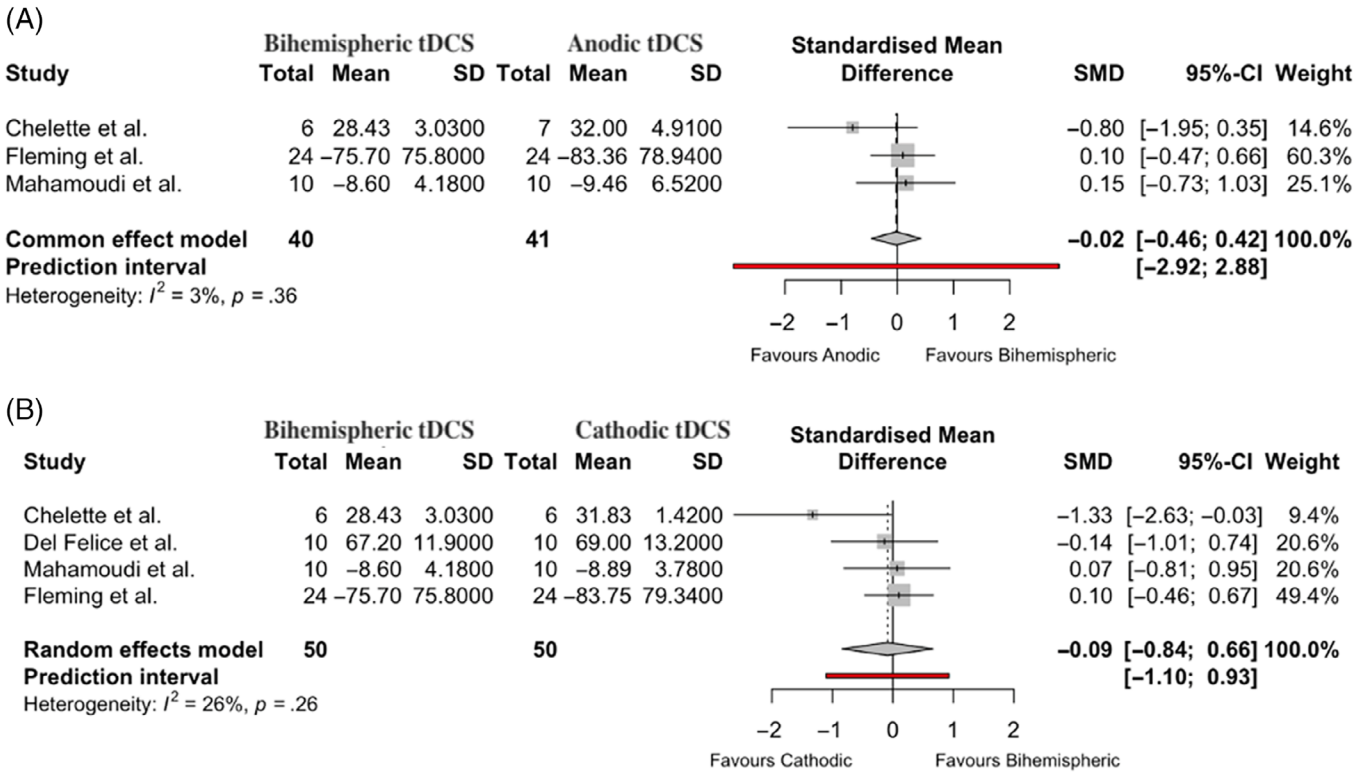

FIGURE 5 Forest plot of the results of a random-effects meta-analysis on upper limb function, shown as standardized mean differences (SMDs) with 95% confidence interval (CI) for (A) bihemispheric versus anodic transcranial direct current stimulation (a-tDCS), and (B) bihemispheric versus cathodic transcranial direct current stimulation (c-tDCS). The shaded square represents the point estimate for each individual study and the weight of the study in the meta-analysis. The diamond represents the overall mean difference of the studies.

tDCS modality

In our meta-analysis, no differences were observed in the pooled effect size of the included studies between the different types of stimulation.

a-tDCS versus c-tDCS stimulation

It was observed that c-tDCS showed a tendency to significance over a-tDCS; however, no significant differences were found in favor of any polarity ($g = 0.10$, 95% CI = −0.13; 0.33, $p = .39$, $N = 292$) (Figure 3A). The included studies that showed improvements in favor of a-tDCS performed stimulation combined with functional tasks.[21,32] Adeagbo et al.[21] applied 12 tDCS sessions with an intensity of 1.6 mA and 35 cm^2 electrodes in people with stroke of more than 3 months' duration. For their part, Rocha et al.[32] performed 12 tDCS sessions in people with chronic stroke (35 cm^2, 1 mA), but applied a-tDCS for 13 minutes and c-tDCS for 9 minutes, which may explain the differences in favor of a-tDCS due to the different application times.

The included studies that showed improvements in favor of c-tDCS performed stimulation with or without UE motor rehabilitation. Yeung et al.[35] applied three tDCS sessions with an intensity of 1 mA and 35 cm^2 electrodes in people with chronic stroke and did not perform associated UE motor rehabilitation. On the other hand, Kim et al.[29] performed 10 tDCS sessions in people with subacute stroke (25 cm^2, 2 mA), associated with rehabilitation. It seems that a-tDCS (stimulation of the affected hemisphere) could have greater effects when associated with rehabilitation.

Elsner et al.[36] conducted a Cochrane review and found evidence of a moderately significant effect in favor of c-tDCS compared with placebo, whereas no significant effects were found for the other active tDCS interventions (a-tDCS and dual tDCS). In this regard, the evidence shows that tDCS compared to no intervention could have a significant effect on UE improvement, but when applied

TABLE 3 Influence analysis bihemispheric versus c-tDCS.

Analysis	g	95% CI	p	I^2
Main analysis	−0.09	−0.84; 0.66	.73	26%
Infl. cases removed[a]	−0.23	−0.67; 0.21	.15	0%

Abbreviation: CI, confidence interval.
[a]Removed as influential study: Fleming et al.[25] and Mahamoudi et al.[30]

TABLE 4 GRADE evidence for different polarities of tDCS in stroke motor rehabilitation.

Number of studies	Risk of bias[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Publication bias[e]	SMD (95% CI)	Quality of evidence
a-tDCS versus c-tDCS							
11	Very Serious (mainly by blinding the therapist and allocation concealment)	No serious ($I^2 = 0\%$)	No serious	No serious	Serious	SMD = 0.10 (−0.13; 0.33) SMD = 0.12 (−0.10; 0.36) SMD = −0.05 (−0.18; 0.08)	Small
a-tDCS versus bihemispheric							
3	Very Serious (mainly by blinding the therapist and allocation concealment)	No serious ($I^2 = 3\%$)	No serious	No serious	No serious	SMD = −0.02 (−0.46; 0.42)	Very small
c-tDCS versus bihemispheric							
4	Very Serious (mainly by blinding the therapist and allocation concealment)	No serious ($I^2 = 26\%$)	No serious	No serious	No serious	SMD = −0.09 (−0.84; 0.66)	Very small

Abbreviations: a-tDCS, anodic transcranial direct current stimulation; c-tDCS, cathodic transcranial direct current stimulation; CI, confidence interval; GRADE, grading of recommendations assessment, development, and evaluation; MD, mean difference; SMD, standardized mean difference.

[a]"No," most information is from results at low risk of bias; "serious," crucial limitation for one criterion or some limitations for multiple criteria sufficient to lower confidence in the estimate of effect; "very serious," crucial limitation for one or more criteria sufficient to substantially lower confidence in the estimate of effect.

[b]"Serious," $I^2 > 40\%$; "very serious," $I^2 > 80\%$.

[c]No indirectness of evidence was found in any study.

[d]Based on sample size. "Serious," $n < 250$ subjects; "very serious," $n < 250$ and the estimated effect is little or absent.

[e]Based on funnel plots. No publication bias was found. Funnel plots are not shown because the number of trials was less than 10.

in conjunction with rehabilitation compared to an active intervention, it does not appear to be significantly superior to the control group.

Our findings are consistent with other studies, showing a greater benefit of the c-tDCS versus the a-tDCS.[29,35,37] Current evidence suggests the potential benefits of c-tDCS in the motor rehabilitation of patients with chronic stroke.[38,39] These results highlight the interhemispheric inhibition model, which postulates that the unaffected hyperactive hemisphere exerts an inhibitory influence on the underactive affected hemisphere.[40,41] c-tDCS could have a potential effect,[5] decreasing the excitability of the healthy cerebral hemisphere and increasing the excitability of the damaged cerebral hemisphere. In the present meta-analysis, there was no evidence that the chronicity of the stroke has an influence on the results; however, current evidence suggests that chronic patients have a greater benefit than acute/subacute patients, both with a-tDCS and c-tDCS, with less than 10 session protocols and a current density greater than 0.029 mA/cm^2. Based on current evidence, a-tDCS may have greater benefits when applied to acute and subacute stroke, as it may enhance the neuronal reorganization that takes place, especially in these stages of stroke. On the other hand, c-tDCS could have greater benefits when applied to chronic strokes, since it could reverse maladaptive plasticity by decreasing the excitability of the contralesional cerebral hemisphere.[7,42] According to these findings, there are several studies that tested the efficacy of the tDCS according to stroke chronicity. Regarding the early phase after stroke (acute and sub-acute), Boasquevisque et al.[43] conducted a pilot randomized clinical trial in which they did not find significant beneficial effects of treatment in terms of motor impairment, disability, or quality of life immediately after treatment or 3 months later. Kim et al.[29] conducted an RCT in which they observed a potentially beneficial effect of tDCS during motor rehabilitation training of subacute stroke patients, but Nicolo et al.[44] by means of a double-blind RCT did not observe useful clinical changes in the subacute group, suggesting the need for further studies in the very early phase. In the chronic phase, tDCS has been found to improve UE function after stroke, being especially effective in this phase.[45,46]

Bihemispheric versus a-tDCS

Bihemispheric stimulation appears to produce significant improvements in motor rehabilitation of UE compared to sham,[47] but few studies have compared this stimulation to other electrode assemblies. The included studies in the meta-analysis showed that the

improvements of anodal and cathodal stimulation versus bihemispheric stimulation on UE motor function after stroke seem greater,[23–25,27,34] despite no significant differences being found between them in the meta-analysis. This may be due to the smaller number of studies; a larger number of studies could help to better understand the true impact of tDCS current polarity on UE motor rehabilitation in people after stroke.

Limitations

The present review was performed with a homogeneous assessment in most of the included studies (FMA-EU and Jebsen Taylor hand function Test), with a rigorous methodology, establishing a priori the subanalyses and measures of heterogeneity assessment. Even so, the present meta-analysis presented several limitations. In reference to the number of included studies, no clear statements toward the direction of the effect size could be established, so a larger number of comparative studies between the different types of electrode assessment will be necessary. In particular, the number of included studies was very limited in comparisons with bihemispheric stimulation. Subgroup analyses and meta-regressions were performed between groups of three to four studies, which did not allow correlations to be established between the effect size found and current density, number of sessions, or chronicity of stroke.

The selection criteria attempted to obtain homogeneous studies, as demonstrated by the I^2 index, but there was heterogeneity between each study, not explained by the differences in effect size between studies; the included studies applied different treatment protocols: different current densities (0.029–0.125 mA/cm^2), different numbers of sessions (1–30), as well as a heterogeneous population according to pathology (chronic, subacute, and acute individuals; cortical, sub-cortical, hemorrhagic, and ischemic strokes).

CONCLUSIONS

Our results showed that a-tDCS, c-tDCS, and bihemispheric stimulation have similar effectiveness in the rehabilitation of UE motor function after stroke. A non-significant improvement trend was observed toward c-tDCS compared to a-tDCS stimulation. More studies are needed to discern which type of stimulation is more effective in the UE motor function rehabilitation after stroke.

DISCLOSURES

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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