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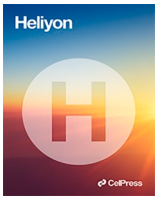

Research article

Exploring the Differential Effects of Transcranial Direct Current Stimulation: A Comparative Analysis of Motor Cortex and Cerebellar Stimulation

Qurat ul-ain [a,b,c], Saad Ilyas [d], Hamid Ali [e], Ijaz Ali [f], Riaz Ullah [g], Hafsah Arshad [h], Sana Khalid [i], Muhammad Ehab Azim [i], Tian Liu [a,b,c], Jue Wang [a,b,c,*]

[a] *The Key Laboratory of Biomedical Information Engineering of Ministry of Education, Institute of Health and Rehabilitation Science, School of Life Science and Technology, Xi'an Jiaotong University, Xi'an, PR China*
[b] *National Engineering Research Center for Healthcare Devices Guangzhou, Guangdong, PR China*
[c] *The Key Laboratory of Neuro-informatics & Rehabilitation Engineering of Ministry of Civil Affairs Xi'an, Shaanxi, PR China*
[d] *Faculty of Computing, Shifa Tameer-e-Millat University, Islamabad, Pakistan*
[e] *Department of Biosciences, COMSATS University Islamabad, Pakistan*
[f] *Centre for Applied Mathematics and Bioinformatics, Gulf University for Science and Technology, Hawally, Kuwait*
[g] *Department of Pharmacognosy, College of Pharmacy King Saud University, Riyadh, Saudi Arabia*
[h] *Department of Physiotherapy and Rehabilitation, Ibadat International University, Islamabad, Pakistan*
[i] *Department of Physiotherapy and Rehabilitation, Foundation University Islamabad, Pakistan*

A R T I C L E I N F O

Keywords:
Transcranial direct current stimulation
Cerebellar transcranial direct current stimulation (tDCS) motor cortex cerebellar-transcranial direct current stimulation

A B S T R A C T

Background: Transcranial Direct Current Stimulation (tDCS) is a non-invasive brain stimulation technique. Constant electric current is passed through the patient's scalp with the aim of modulating cortical excitability. Stroke is a cerebrovascular disease characterized by hemorrhage or cerebral ischemia. This systematic review and meta-analysis are aimed at comparing the efficacy of motor cortex stimulation with that of cerebellar stimulation by using transcranial direct current stimulation.

Method: Google Scholar, PubMed, EMBASE, Cochrane CENTRAL, and Physiotherapy Evidence Database (Pedro) databases were searched for studies. The extracted qualitative data was synthesized systematically. Cochrane RevMan software was used to conduct a meta-analysis of quantitative data. The fixed effects mean difference of the collected data was calculated at a 95% confidence interval (CI) for the changes in balance and side effects.

Results: This research included 10 articles with seven studies assessing changes in balance (outcome measured in CoP and FMA scores) and side effects (tingling and itching were the most prevalent). There was no significant difference between the efficacy levels of m1-tDCS versus ctDCS ($P = 0.18$), m1-tDCS versus sham ($P = 0.92$), and ctDCS versus sham ($P = 0.19$). Itching and tingling sensation were the most common and were significantly prevalent in sham interventions ($P < 0.00001$).

Conclusion: We found that motor cortex and cerebellar stimulations are both effective in improving motor function in stroke patients. There are no adverse effects to using the interventions besides mild itching and tingling experienced during the stimulation.

* Corresponding author. The Key Laboratory of Biomedical Information Engineering of Ministry of Education, Institute of Health and Rehabilitation Science, School of Life Science and Technology, Xi'an Jiaotong University, Xi'an, PR China.
E-mail address: juewang1@126.com (J. Wang).

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What is known?

The literature shows that transcranial direct current stimulation is likely effective in improving motor function in both cerebral motor cortex stimulation and cerebellar stimulation in stroke patients. Still, the evidence is greatly lacking when we compare the two stimulation sites.

What is new?

Current studies aim to investigate the efficacy of motor cortex stimulation compared to cerebellar stimulation using transcranial direct current stimulation. Although a previous study stated cerebellar stimulation to be more effective, we found no statistical difference between the effectiveness of the two modalities in improving motor function.

1. Introduction

Transcranial Direct Current Stimulation (tDCS) involves brain stimulation techniques where a constant electric current is applied to a patient's scalp. It is a non-invasive method that modulates cortical excitability [1]. Stroke is a cerebrovascular disease characterized by hemorrhage or cerebral ischemia. Stroke often leads to various health challenges, including impaired cognitive function, decreased muscle strength, proprioceptive abilities, and cognitive function impairment [2]. These sensorimotor deficits ultimately affect the postural and balance control abilities of stroke patients [3]. Statistically, around 80% of patients who have experienced stroke encounter difficulties in maintaining motor function [4]. Additionally, approximately 38% of them remain in a non-ambulatory state for more than 180 days after the stroke, whether it is chronic or mild [5]. Data from Błaszcz et al. non-ambulatory post-stroke patients revealed that with a proper rehabilitation regimen, physical activity can be restored after 6 weeks [6].

During the past decades, therapies based on modulating plasticity and motor learning have significantly improved and continued to evolve greatly. Transcranial direct current stimulation has been an innovative, favorable, and non-invasive stimulation where a weak direct current of approximately 1–2 mA is applied using electrodes over a patient's scalp. The impact of tDCS is specifically related to the polarity of the electrodes; cathodal stimulation reduces motor cortex excitability, while anodal stimulation can increase excitability [7]. Recent investigations by Takano et al. provide a clearer and updated understanding of the clinical application of tDCS by monitoring changes in corticospinal excitability and motor control during stimulation in healthy individuals [8]. Different tDCS montages induce diverse results on a patient's brain networks. Stimulation results directly correlate with the polarity and positioning of the electrodes. The polarity of electrode montages defines the specific implications of the stimulation [7]. This is a result of the effects of the medical procedure on the modulation of cortical excitability, especially when directed at the primary motor cortex [9].

Stroke is one of the most common medical conditions to which brain stimulation can be applied [10]. Considerable research has been conducted over the years to assess the efficacy and safety of tDCS for improving motor function in stroke patients. A number of studies have concluded that tDCS is safe and effective in improving cognitive and motor function in stroke patients [11–13]. Moreover, He et al. and Huang et al. emphasize the scarcity of data to completely inform the safety and efficacy of this modality [12,13]. Similar sentiments of data limitation have been echoed by the latest research on the subject that monitored changes in cognitive function after stimulation of schizophrenic patients [14].

The concept of modulation of the patient's neuronal activities prompted by tDCS has not been fully analyzed. However, according to numerous studies, the electric current generated through the stimulation significantly interferes with the resting membrane potential of neuronal cells, thereby modulating voluntary activities in brain circuits [15]. According to some researchers, tDCS may affect the strength of neuronal synapses, which, in turn, alters the activity of GABA and NMDA receptors. Ultimately, this process may activate the plasticity process, including long-term depression and potentiation [16]. When a stimulus is applied, it creates a time varying electrofield in the brain, which may trigger action potentials in cortical neurons [17]. Chen and Liu provide an overview of neuronal activity and the generated action potentials in neurons, highlighting the potential of tDCS in modulating the electrical potential of neuronal cells, thereby influencing their voluntary activities in brain circuits [18].

The long-term effects of the brain stimulation procedure are also believed to have a strong correlation with changes in gene expression and alterations in protein synthesis [19]. Furthermore, according to a previous neuroimaging study, changes in blood flow occur following stimulation, which may correlate with the effect of brain stimulation on blood flow, leading to an increase in oxygen supply in cortical areas followed by a boost in neuronal excitability [20]. No extreme side effects are documented in any clinical trials; some mild side effects include a burning sensation, low-intensity discomfort, itching, tingling under the electrode, and mild skin irritation. Apart from the aforementioned side effects, tDCS is relatively safe [21]. According to researchers, the procedure has the potential to impact deeper brain structures, and this possibility has supported broader investigations into brain stimulation procedures for different disorders, including stroke patients. Given the prevalence of the procedure in stroke treatment, it is necessary to conduct research to test alternative targets for tDCS to enhance motor recovery in stroke patients.

The cerebellum is an additional subcortical region, besides cortical areas, associated with motor functions. It is vital in numerous aspects of motricity as well as balanced and fine motor functions. Besides the role of the cerebellum in motor functions, researchers suggest that the process may also have an effect on cognition, including motor learning [22]. Considering the role played by the cerebellum in aspects of motion, scientists have perceived the cerebellum as a likely focus of stimulation using tDCS to improve motor recovery after a stroke [23]. Stimulation through the cerebellum can be applied to improve a patient's motor, balance, and lower limb functioning. With the apparent divide between the efficacy of motor cortex and cerebellum tDCS, this study aims to compare the two.

The purpose of this systematic review and meta-analysis is to compare the efficacy and safety of motor cortex stimulation with cerebellar stimulation using tDCS.

2. Methodology

2.1. Study design

This is a systematic review and meta-analysis conducted in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

2.2. Literature search

An online database search was conducted on Google Scholar, PubMed, EMBASE, Cochrane CENTRAL, and Physiotherapy Evidence Database (Pedro) databases until October 2023. The search strategy employed keyword combinations and Boolean operators to prepare a search string. Primary keywords were "transcranial direct current stimulation" OR "cerebellar transcranial direct current stimulation" OR "ctDCS" OR "tDCS" AND "motor cortex cerebellar transcranial direct current stimulation" AND "m1-tDCS". A hand search through reference lists was also used to identify new articles for inclusion.

2.3. Inclusion and exclusion criteria

A limitation was given to scholars working together with articles from peer-reviewed publications from conventional channels; any unpublished randomized controlled trials were excluded. Also, all articles written in languages other than English, authored before 1999, or that were not relevant to the research topic were excluded. A PECOS criterion of study selection was used to formulate the inclusion and exclusion criteria for this systematic review and meta-analysis. Participants (P) for trials had to be stroke patients. The groups in these experiments had to have been exposed (E) to motor cortex tDCS, with the findings observed against cerebellar tDCS as the comparator (C). Sham comparisons were also allowed. To compare the effectiveness of each stimulation location, the trials had to have observed the following outcomes (O): changes in the outcome of balance, movement function, joint range of motion, sensation, and side effects such as tingling and itching on the stimulated area. Study designs (S) were exclusively randomized controlled trials or clinical trials. All reviews, cohort studies, or case reports were excluded from inclusion. All disagreements or variances were settled through concessions or consultations.

2.4. Data extraction

Excel was used to prepare standardized data tables for data extraction. The information recorded from the articles includes the study author(s) and publication's year, sample size, and intervention characteristics (type, frequencies, durations, and intensities). Patient attributes at baseline, such as mean age and randomization, were extracted. Key outcomes of the studies were extracted and sub-grouped in line with comparisons, type of outcome, and nature of stimulation. The author resolved any inconsistencies relating to the extraction of any data item before the data was synthesized.

2.5. Data synthesis

The core of this investigation is a quantitative approach to data analysis, which requires the conduction of a meta-analysis. The Cochrane RevMan program/software was used to conduct the meta-analysis. A fixed-effects model computed the mean difference at a 95% confidence interval (CI). The level of significance of the comparison was reported by the P-value (significant exists at $P \leq 0.05$). Heterogeneity was reported by the I^2 statistic and judged according to the value, which ranges from 0% (complete consistency), 50% (low consistency), 75% (high inconsistency), to 100% (complete inconsistency). Moreover, a systematic descriptive analysis of the collected data was also done. Results were reported using forest plots, and the publication bias among the analyzed studies was expressed on the funnel plot.

3. Results

3.1. Study selection

All the identified studies were assessed against the predetermined criteria of eligibility. Studies relevant to high-frequency external muscle stimulation for neuropathy were the first ones excluded from the review process. An online search identified 3139 studies (PubMed = 1440, Embase = 391, Cochrane CENTRAL = 668, and Pedro = 640). Following the removal of copies through automated filters, 1996 research/studies were left. The remaining copies were filtered against the eligibility criteria, leaving 953 studies. The abstracts and headlines of the 953 searches/studies were scanned, determining their significance for the present study. The process eliminated 899 studies and left 54 studies for full-text screening. Due to failure on several eligibility requirements, 40 studies were eliminated. Most of these failed the inclusion for not reporting our outcomes of interest. A further hand search through reference lists of

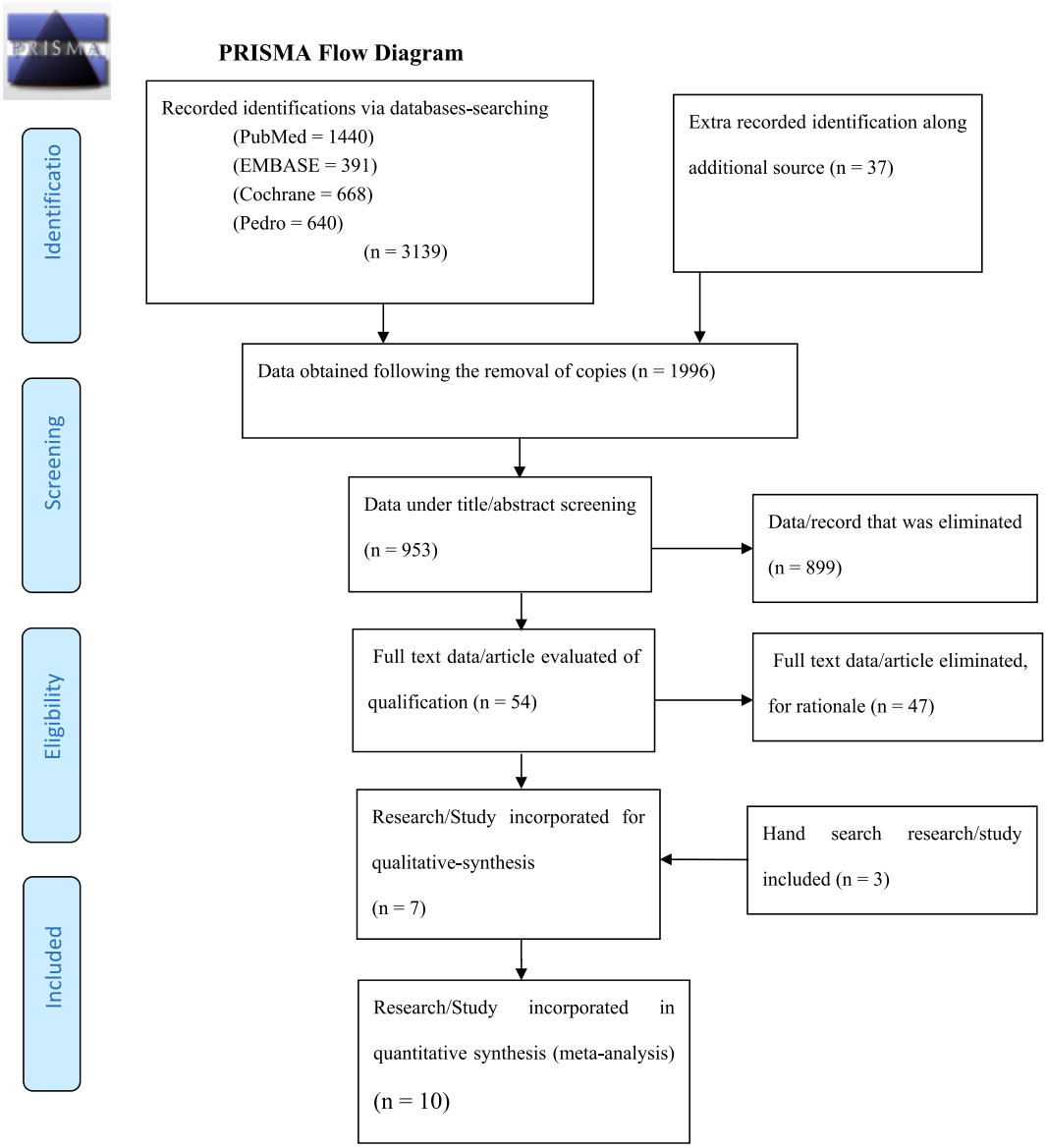

Fig. 1. P.R.I.S.M.A Flow-diagram outlining research/studies selecting procedure for present systematic-review and meta-analysis.

the 7 included studies identified three additional studies that were included. Finally, 10 studies were included in the study. Fig. 1 is a PRISMA flow diagram illustrating the selection process.

3.2. Study characteristics

Ten studies were selected for this meta-analysis, all including 347 participants randomized between m1-tDCS, ctDCS, or sham stimulations. Table 1, Table 2, and Table 3 represent data extracted from the selected studies grouped according to the outcome measures of center of pressure (CoP), Fugl-Meyer Assessment (FMA) scores, and the side effects of itching and tingling sensations.

1. Extracted Data on Changes in CoP Values
2. Extracted Data on Fugl-Meyer Assessment (FMA) Scores
3. Extracted Data on the Side Effects of Stimulation

Table 1
Study characteristics for the studies reporting the outcome Center of Pressure (CoP).

Author	Intervention Characteristics	Current Placement	Outcome Measure	Study design	Patient Characteristics	Sample size	Trial Duration	Randomization	Changes in CoP Values
Motor cortex VS. Cerebellum Stimulation									
Baharlouei et al. (2020) [24]	1). Bilateral cerebellar a-tDCS with postural training. 2). a-tDCS of the left (dominant) M1 with postural training. 3). Sham a-tDCS with postural training. 4). Postural training alone (control group 1). 5). Bilateral cerebellar a-tDCS alone (control group 2).	Anodal	Center of Pressure (CoP)	RCT	Ages between 60 and 85 (66.07 ± 4.37)	65 participants	20 minutes	**M1:** 16. **CB:** 16	**M1:** 20.06 (8.07). **CB:** 15.71 (8.77)
Galea et al. (2010) [25]	Eperiment 1: Subjects were instructed to move a digitizing pen with their right hand over a horizontal digitizing tablet located at waist height to reach eight different targets projected over a computer screen. The position of the pen was sampled at 75 Hz through a custom Matlab program.	Cathodal	Center of Pressure (CoP)	RCT	mean age 25 ± 5 years	30 participants	15 minutes	**M1:** 10. **CB:** 10	**M1:** 65 ± 3. **CB:** 65 ± 3
Cerebellum VS. Sham Stimulation									
Poortvliet et al. (2017) [26]	Sham-ctDCS controlled study. Standing blindfolded on a force platform, four trials were completed: 60 s quiet standing followed by 20 min active (anodal-tDCS, 1 mA, 20 min, N = 14) or sham-ctDCS (40 s, N = 14) tDCS; three quiet standing trials with 15 s of Achilles tendon vibration and 25 s of postural recovery.	Anodal	Center of Pressure (CoP)	CT	25.14 ± 4.44 vs. 25.64 ± 3.82 years	28 participants	20 minutes	**CB:** 14. **Sham:** 14	**CB:** 43.85 ± 29.62. **Sham:** 41.14 ± 25.67
Jackson et al. (2019) [27]	A practice session and a retention session. The practice session involved an overhand throwing task to a small target (6 m away) in a pre-test block, 6 practice blocks, a post-test block, and a retention-test block (24 h later)	Anodal	Center of Pressure (CoP)	RCT	Mean age 25 ± 3.9 years	42 participants	25 minutes	**CB:** 21. **Sham:** 21	**CB:** 23.20 (9.16). **Sham:** 27.86 (8.96).
Baharlouei et al. (2020)* [24]	1). Bilateral cerebellar a-tDCS with postural training. 2). a-tDCS of the left (dominant) M1 with postural training. 3). Sham a-tDCS with postural training. 4). Postural training alone (control group 1). 5). Bilateral cerebellar a-tDCS alone (control group 2).	Anodal	Center of Pressure (CoP)	RCT	Ages between 60 and 85 (66.07 ± 4.37)	65 participants	20 minutes	**CB:** 16. **Sham**: 16	**CB:** 15.71 (8.77). **Sham**: 23.23 (12.44).
Galea et al. (2010)* [25]	Eperiment 1: Subjects were instructed to move a digitizing pen with their right hand over a horizontal digitizing tablet located at waist height to reach eight different targets projected over a computer screen. The position of the pen was sampled at 75 Hz through a custom Matlab program.	Cathodal	Center of Pressure (CoP)	RCT	mean age 25 ± 5 years	30 participants	15 minutes	**CB:** 10. **Sham:** 10	**CB:** 65 ± 3. **Sham:** 65 ± 4
Motor Cortex VS. Sham Stimulation									
Baharlouei et al. (2020)** [24]	1). Bilateral cerebellar a-tDCS with postural training. 2). a-tDCS of the left (dominant) M1 with postural training. 3). Sham a-tDCS with postural training. 4). Postural training alone (control group 1). 5). Bilateral cerebellar a-tDCS alone (control group 2).	Anodal	Center of Pressure (CoP)	RCT	Ages between 60 and 85 (66.07 ± 4.37)	65 participants	20 minutes	**M1:** 16. **Sham:** 16	**M1:** 20.06 (8.07). **Sham:** 27.36 (24.18)
Galea et al. (2010)** [25]	Eperiment 1: Subjects were instructed to move a digitizing pen with their right hand over a horizontal digitizing tablet located at waist height to reach eight different targets projected over a computer screen. The position of the pen was sampled at 75 Hz through a custom Matlab program.	Cathodal	Center of Pressure (CoP)	RCT	mean age 25 ± 5 years	30 participants	15 minutes	**M1:** 10. **Sham:** 10	**M1:** 65 ± 3. **Sham:** 65 ± 4

3.3. Statistical analysis

Three comparisons were adopted for this meta-analysis: motor cortex tDCS versus cerebellar tDCS, motor cortex tDCS versus sham stimulation, and cerebellar tDCS versus sham stimulation. The first comparison looked into the outcome of balance measured by the center of pressure (CoP); the second comparison investigated the outcome of balance measured by CoP and Fugl-Meyer Assessment (FMA) scores. Additionally, there was a look into the side effects of the stimulation, with data on tingling sensation and itching analyzed. The latter comparison (ctDCS vs. Sham) investigated the same outcomes without a subgroup of FMA scores.

1. Changes in Balance Post-Stimulation

A total of seven studies were assessed for this outcome. In the first comparison (m1-tDCS vs. ctDCS), two studies [24,25] investigating 52 participants (equally randomized) were used to calculate the fixed effects mean difference (MD) of changes in CoP. The MD was 0.73 [−1.66, 3.13] at the 95% confidence interval (CI), and the overall effect was Z = 0.60 (P = 0.55). Fig. 2 below is the forest plot of the meta-analysis, and Fig. 3 is a funnel plot of two studies.

Table 2
Study characteristics from the studies reporting Fugl-Meyer Assessment (FMA) scores.

Author	Intervention Characteristics	Current Placement	Outcome Measure	Study design	Patient Characteristics	Sample size	Trial Duration	Randomization	Fugl-Meyer Assessment (FMA)
Motor Cortex VS. Sham Stimulation									
Lindenberg et al. (2010) [28]	1). Bihemispheric transcranial direct current stimulation (tDCS): Anodal tDCS to upregulate excitability of ipsilesional motor cortex and cathodal tDCS to downregulate excitability of contralesional motor cortex. With simultaneous physical/occupational therapy. 2). Sham stimulation	Anodal & Cathodal	Fugl-Meyer score (FMS)	RCT	Average age 58.75 ± 13.8 years	20 participants	30 minutes	**M1:** 10. **Sham:** 10	**M1**: 44.3 ± 11.5. **Sham**: 40.9 ± 11.7
Ang et al. (2015) [29]	1). Motor cortex transcranial direct current stimulation (M1-tDCS): Current was applied using a saline-soaked pair of surface sponge electrodes from a battery-operated constant current stimulator at an intensity of 1mA with the anode placed over the M1 motor cortex. 2). Sham: The current was applied to give the sensation of the stimulation.	Anodal & Cathodal	Upper extremity Fugl-Meyer Motor Assessment (FMMA) scores	RCT	Average age 54.1 ± 10.6 years	19 participants	20 minutes	**M1:** 10. **Sham:** 9	**M1**: 40.3 ± 12.2. **Sham**: 38.0 ± 13.8
Rocha et al. (2015) [30]	1). Motor cortex transcranial direct current stimulation (M1-tDCS): The anode electrode placed over the primary motor cortex of the affected hemisphere and the cathode was placed above supra-orbital region. 2). Sham: Current flow for 30 s to achieve a good level of blinding.	Anodal Cathodal	Fugl–Meyer assessment (FMA),	RCT	Average age 58.43 (56-58) years	21 participants	_	**M1**: 7. **Sham:** 7	**M1**: 124.6 ± 6.1. **Sham:** 123.7 ± 8.9

Table 3
Study characteristics reporting the side effects of stimulation.

Author	Intervention Characteristics	Current Placement	Outcome Measure	Study design	Patient Characteristics	Sample size	Trial Duration	Randomization	Side effects (Tingling)		Side effects (Itching)	
Motor cortex VS. Cerebellum Stimulation												
									Cathodal	*Anodal*	*Cathodal*	*Anodal*
Ehsani et al. (2016) [31]	1). Transcranial Direct Current Stimulation 2 mA and 20 minutes. 2). Cerebellum. Transcranial Direct Current Stimulation.	Anodal Cathodal	Center of Pressure (CoP)	RCT	Age above 60 years	60 participants	20 minutes	**M1:** 20. **CB:** 20	**M1:** 1.2 ± 0.13. **CB:** 0.6 ± 0.13.	**M1:** 1.6 ± 0.22. **CB:** 1.9 ± 0.17.	**M1:** 1.6 ± 0.22. **CB:** 1.9 ± 0.17.	**M1:** 1.2 ± 0.18. **CB:** 1.7 ± 0.19.
Cerebellum VS. Sham Stimulation												
Samaei et al. (2017) [32]	Experimental group received 2 mA cerebellar a-tDCS for 20 min. However, the tDCS was turned off after 30 seconds in sham group.	Anadal Cathodal	Center of Pressure (CoP)	RCT	Mean age 69.40± 5.08 years vs. 68± 5.55 years	30 participants	30 minutes	**CB:** 15. **Sham:** 15	**CB:** 0.65±0.15. **Sham:** 0.54±0.21.	**CB:** 2.2±0.27. **Sham:** 0.7±0.19.	**CB:** 0.81±0.21. **Sham:** 0.27±0.08.	**CB:** 1.9±0.19. **Sham:** 0.3±0.04.
Ehsani et al. (2016) * [31]	1). Transcranial Direct Current Stimulation 2 mA and 20 minutes. 2). Cerebellum. Transcranial Direct Current Stimulation.	Anodal Cathodal	Center of Pressure (CoP)	RCT	Age above 60 years	60 participants	20 minutes	**M1:** 20. **CB:** 20	**CB:** 0.6 ± 0.13. **Sham:** 0.7 ± 0.08	**CB:** 1.9 ± 0.17. **Sham:** 0.6 ± 0.15	**CB:** 0.8 ± 0.11. **Sham:** 0.2 ± 0.07	**CB:** 1.7 ± 0.19. **Sham:** 0.2 ± 0.04
Motor Cortex VS. Sham Stimulation												
Halakoo et al. (2020) [33]	There are three groups (intervention, sham, and control). All participants in the first two groups received 20-min concurrent M1 a-tDCS or sham tDCS and functional electrical stimulation (FES) for 10 sessions (5 sessions per week), while participants in control group were given only 20-min FES for 10 sessions.	Anodal Cathodal	Center of Pressure (CoP)	RCT	Mean ages 61.83 ± 7.60 yeas vs. 67.20 ± 4.96 years vs. 58.80 ± 5.23 years	32 participants	20 minutes	**M1:** 11. **Sham:** 11	**M1:** 0.66 ± 0.13. **Sham:** 0.52 ± 0.08	**M1:** 2.29 ± 0.24. **Sham:** 0.76 ± 0.16	**M1:** 0.72 ± 0.13. **Sham:** 0.22 ± 0.04	**M1:** 1.72 ± 0.42. **Sham:** 0.73 ± 0.07
Ehsani et al. (2016)** [31]	1). Transcranial Direct Current Stimulation 2 mA and 20 minutes. 2). Cerebellum. Transcranial Direct Current Stimulation.	Anodal Cathodal	Center of Pressure (CoP)	RCT	Age above 60 years	60 participants	20 minutes	**M1:** 20. **CB:** 20	**M1:** 1.2 ± 0.13. **Sham:** 0.7 ± 0.08	**M1:** 1.6 ± 0.22. **Sham:** 0.6 ± 0.15	**M1:** 1.4 ± 0.16. **Sham:** 0.2 ± 0.07	**M1:** 1.2 ± 0.18. **Sham:** 0.2 ± 0.04

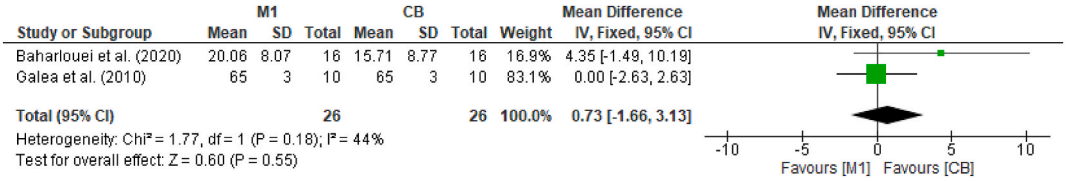

Fig. 2. Forest plot of the CoP changes comparing m1-tDCS vs. ctDCS.

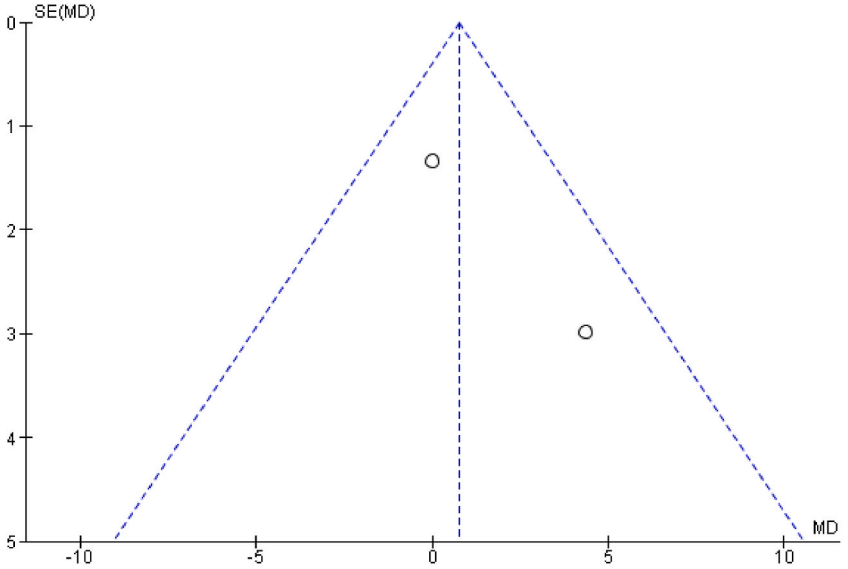

Fig. 3. Funnel plot of the CoP changes meta-analysis comparing m1-tDCs vs. ctDCS.

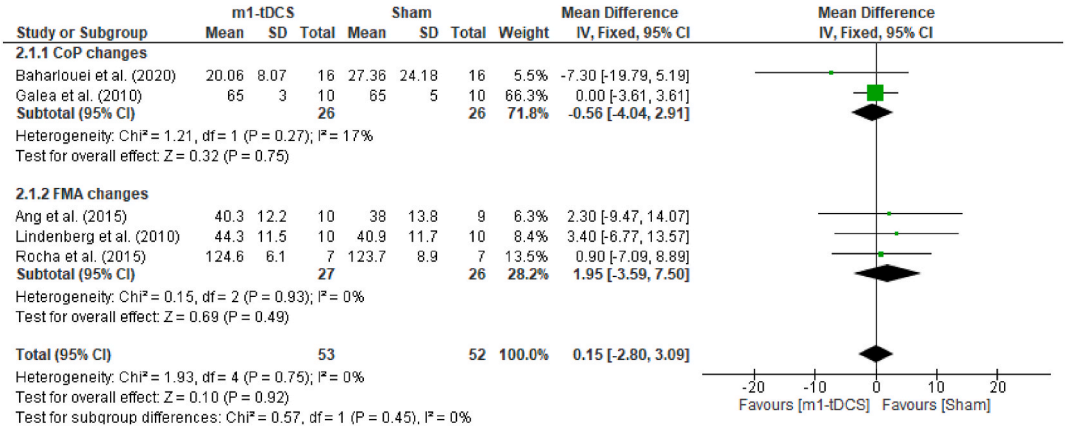

Fig. 4. Forest plot of the CoP and FMA scores changes comparing m1-tDCS vs. sham stimulation.

To look at changes in balance between m1-tDCS stimulation and sham stimulation in a subgroup, five studies used CoP data [24,25] and FMA scores [28–30] from their studies. The overall fixed effects MD was 0.15 [−2.80, 3.09] at 95% CI. With a test or overall effect being Z = 0.10 (P = 0.92). Fig. 3 shows the results of this subgroup analysis, and Fig. 5 is a funnel plot of five studies (see Fig. 7) (see Fig. 6).

The last comparison showing changes in the balance was ctDCS vs. sham stimulation. Four studies [24–27] investigating 122 participants (equally randomized) were included. The fixed effects MD was −1.80 [−4.32, 0.72] at 95% CI with Z = 1.40 (P = 0.16) as the test for overall effect. The results of this meta-analysis are shown in Fig. 4 below.

The p-values of each of the three comparisons were P = 0.55, P = 0.92, and P = 0.16. This signifies the lack of a significant difference between balance changes after m1-tDCS, ctDCS, and sham stimulations.

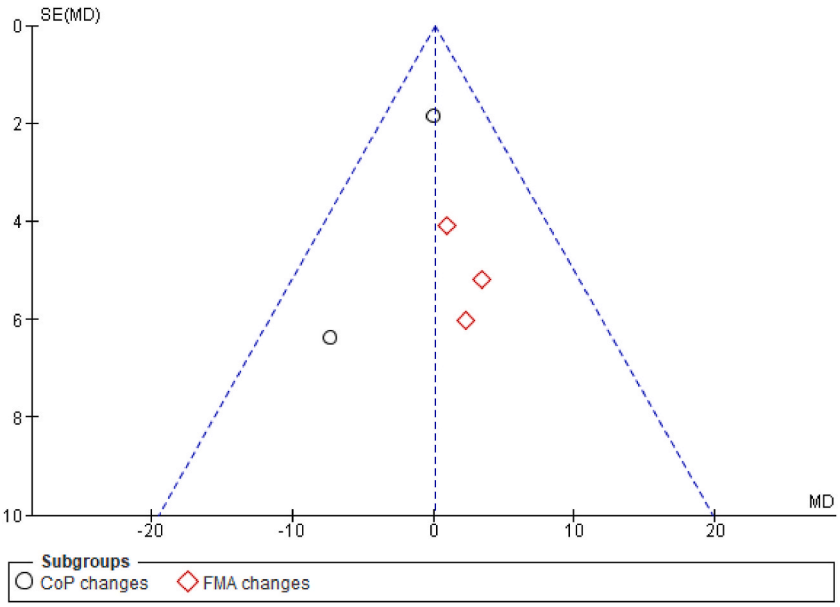

Fig. 5. Funnel plot of the CoP changes and FMA scores meta-analysis comparing m1-tDCS vs. sham stimulation.

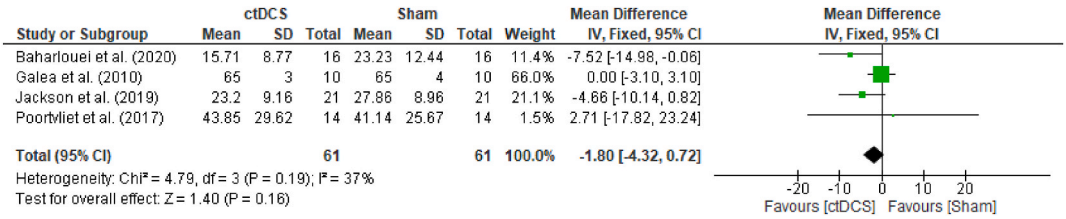

Fig. 6. Forest plot of the CoP changes comparing ctDCS vs. sham stimulation.

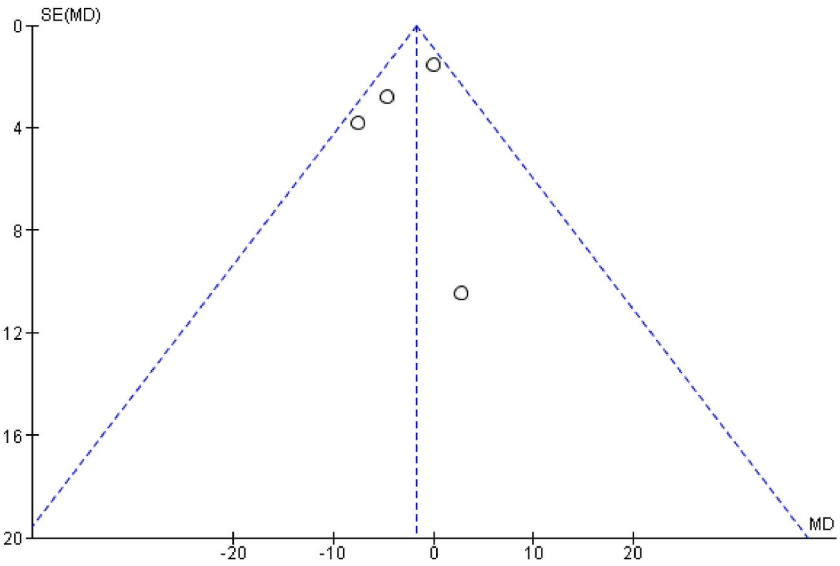

Fig. 7. Funnel plot of the CoP changes meta-analysis comparing ctDCS vs. sham stimulation.

2. Side Effects of the Stimulation Intervention

Two common side effects were identified from 3 studies and sub-grouped with respect to the current placement. The outcomes of tingling sensation and itching after tDCS were only reported in three studies [31–33], which reported different results when stimulation was cathodal or anodal.

3.3.1. Tingling sensation

The meta-analysis results report an overall fixed effects MD of 0.62 [0.55, 0.68] at 95% CI ($P < 0.00001$) when comparing m1-tDCS vs. sham stimulation. On the other hand, a fixed effects MD of 0.40 [0.36, 0.45] at 95% CI ($P < 0.00001$) when comparing ctDCS vs. sham stimulation. Figs. 8 and 10 (forest plots) show a clear and significant difference in edged towards sham stimulation (see Fig. 11) (see Fig. 9).

3.3.2. Itching

The meta-analysis results report a fixed effects MD of 0.91 [0.87, 0.96] at 95% CI ($P < 0.00001$) when comparing m1-tDCS with sham stimulation. In the case of ctDCS vs. sham stimulation, the fixed effects MF for itching were 0.96 [0.92, 1.00] at 95% CI ($P < 0.0001$). Figs. 12 and 14 (forest plots) show a clear significant difference in edged towards sham stimulation (see Fig. 15) (see Fig. 13).

3.4. Risks of Biases

We used the Cochrane Risk of bias tool (RoB2) to appraise the quality of the selected studies. The tool assesses seven elements bias as per the Cochrane-handbook of Systematic-reviews for intervention (5.4). There was a moderately low bias, as indicated in the risk of bias graph (Fig. 16). Bias was lowest in selection, performance, and detection, while it remained moderately high in attrition and reporting. Figs. 16 and 17 are the RoB graph and RoB summary, which represent the results of the assessment.

4. Discussion

Current stimulation has been used clinically to treat stroke patients. The idea is to improve motor function as well as other secondary effects of stroke. Electrical stimulations provide input to the neural pathways in the stroke-damaged portion of the brain. Such stimulations engage brain neuroplasticity, a process of self-rewiring which the brain uses to heal stroke injuries [34]. As we shall see in this discussion, stroke improves mobility, sensation, cognition, and several other outcomes. Every study included in this meta-analysis treated patients with at least two non-invasive brain stimulation techniques: tDCS and bi-hemispheric tDCS. Transcranial direct current is applied bilaterally through the scalp over the primary motor cortex or cerebellar region to modulate cortical excitability [35,36]. The effectiveness of tDCS can be improved by secondary therapies such as moto imagery and upper limb functional training. Bi-hemispheric tDCS is a more specialized form of tDCS that targets a single hemisphere of the brain rather than bilateral [35,36].

The majority of the current literature that conducts statistical pooling on the efficacy of tDCS on the after-effects of stroke focuses primarily on stimulating motor networks to improve other impaired functions. The present meta-analysis seems to be the first pooling of statistics to assess improvements in motor function after stimulation. tDCS has demonstrated positive results in aphasia recovery [37,38]. Ehsani et al. provide a more generalized perspective on the improvement in activities of daily living (ADLs) after tDCS treatments [31]. The majority of the evidence presented points to significant improvement in ADL performance, which includes function, muscle strength, cognitive abilities, and spatial neglect [31]. This study opens up the possible applications of tDCS, with more research focusing on specific outcomes. More recently, tDCS has been found to improve a lot of physiologic functions in stroke patients. Our focus sought to look at the efficacy of tDCS in improving motor functions in stroke patients. However, besides stroke patients, tDCS has been found to significantly improvecortical functions in patients with various neurological disorders. A 13-study meta-analysis found that anodal tDCS resulted in improved general cognitive performance in stroke patients [39]. Patients with cognitive impairment after stroke are more likely to show a significant change in general cognition after stimulation. Other impairments reported to improve significantly after stimulation include attention and concentration, figural memory, logical reasoning, reaction behavior, and functional independence measure (FIM) [40].

4.1. Efficacy of motor cortex and cerebellar tDCS

In our study, seven of the 10 studies included in the meta-analysis report on the changes in balance were observed through changes in CoP and FMA scores. Statistical analysis shows that there is no significant difference (0.73 [95% CI (−1.66-3.13)] ($P = 0.18$)) in the improvement of motor function when comparing m1-tDCS versus ctDCS. Similar findings have been replicated in the next two comparisons: m1-tDCS versus sham stimulation (0.15 [95% CI (−2.80-3.09)] ($P = 0.92$)) and ctDCS versus sham stimulation (−1.80 [95% CI (−4.32-0.72)] ($P = 0.19$)). While looking at static balance, Baharlouei et al. concluded that the effects exerted by each form of stimulation on the participants' postural balance were relatively the same [24]. These results do not necessarily provide evidence of which intervention gives superior results. Our meta-analysis findings indicate that, despite a lack of significant difference, the direction of the mean difference leans towards ctDCS and m1-tDCS when ether modalities are compared to a sham stimulation. Still, this point remains heavily suggestive rather than conclusive. This outcome is perfectly summed up by Galea et al., who state that the cerebellar and motor cortex have distinct functional roles. While anodal cerebellar tDCS enhances acquisition or motor function, anodal motor cortex tDCS influences an increase in retention of the visuomotor transformation. These findings have been reiterated in other studies

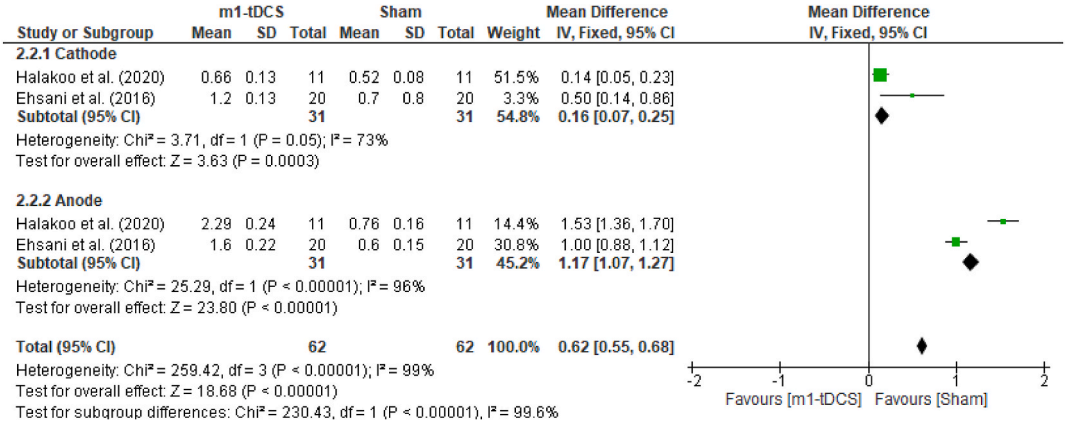

Fig. 8. Forest plot of the tingling sensation side effect comparing m1-tDCS vs. sham stimulation.

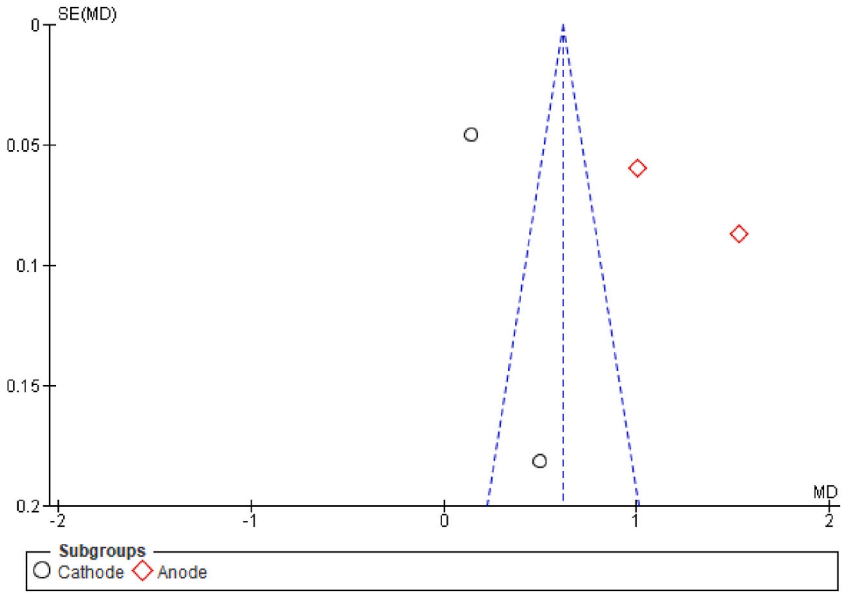

Fig. 9. Funnel plot of the side effects meta-analysis comparing tingling sensation in m1-tDCS vs. sham stimulation.

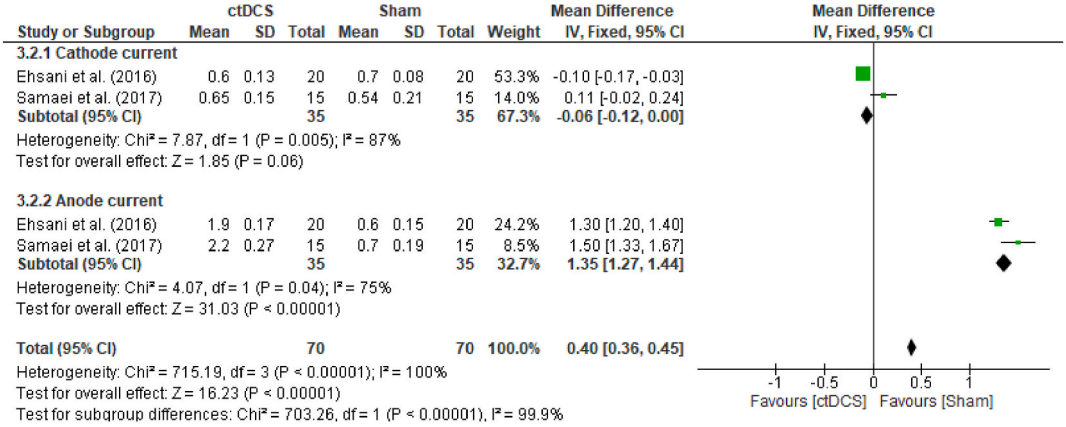

Fig. 10. Forest plot of the tingling sensation side effect comparing ctDCS vs. sham stimulation.

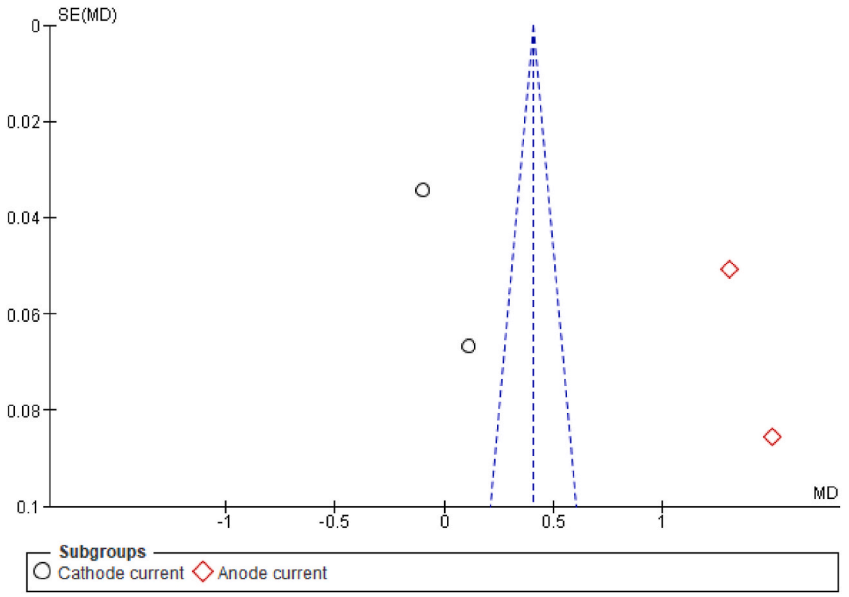

Fig. 11. Funnel plot of the side effects meta-analysis comparing tingling sensation in ctDCS vs. sham stimulation.

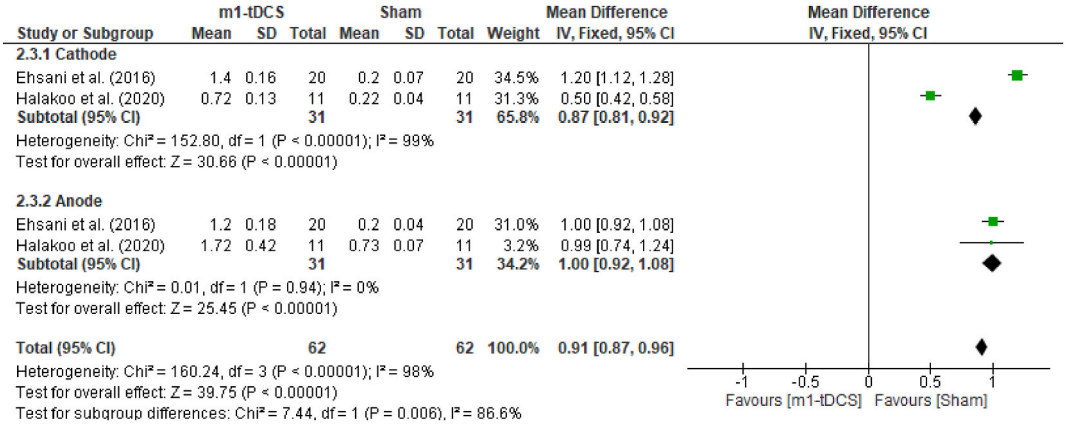

Fig. 12. Forest plot of the itching sensation side effect comparing m1-tDCS vs. sham stimulation.

that suggest that multi-session cerebellar and motor cortex tDCS positively impacts various aspects of motor function, especially static and dynamic postural [31]. Direct comparisons to sham stimulations have not demonstrated any conclusive results to indicate the superiority of each intervention over another.

On the contrary, findings by Poortvliet et al. and Jackson et al. have all positively concluded the utility of cerebellar tDCS in the short-term improvement of motor skills compared to sham stimulation [26,27]. Poortvliet et al. state that active tDCS significantly improved postural steadiness during vibration and reduced forward displacement and variability in COP derivatives during recovery [26]. Such immediate improvement in postural steadiness indicates rapid acquisition of adaptive motor skills. Similarly, ctDCS applied over three days significantly improves the force of accuracy during a visuo-motor isometric pinch grip task [27]. Other studies have reported a similar outcome, indicating significant improvements in motor function. When comparing bi-hemispheric tDCS with sham stimulation, Lindenberg et al. observed that effects persist after the intervention for at least a week [28]. Functional changes in the activation of the motor cortex were present along with these effects.

Same results where m1-tDCS and ctDCS induce significantly better outcomes have been reported by Ang et al. and Rocha et al. [29,30]. This consistency is an intriguing element when attempting to understand the underlying reasons why intervention stimulations are significantly better than sham stimulations. Applying weak direct current through the scalp has been observed to modulate excitability in the motor cortex. Cathodal direct current stimulations upregulate contra-lesional cortical excitability. On the other hand, anodal direct current stimulation may upregulate ipsi-lesional cortical excitability. Lindenberg et al. make the same point, demonstrating improvements in activation of the ipsi-lesional motor cortex following bi-hemispheric ctDCS [28]. Other findings

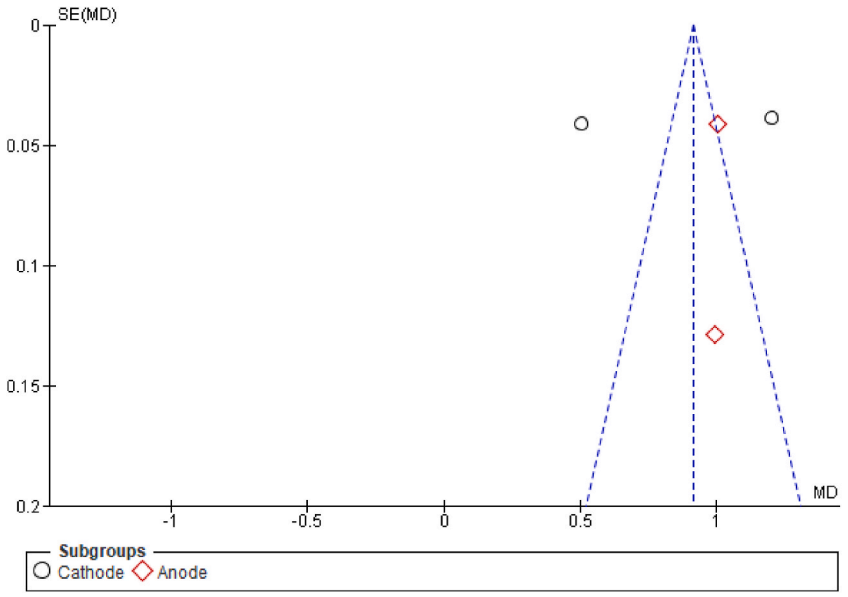

Fig. 13. Funnel plot of the side effects meta-analysis comparing itching in m1-tDCS vs. sham stimulation.

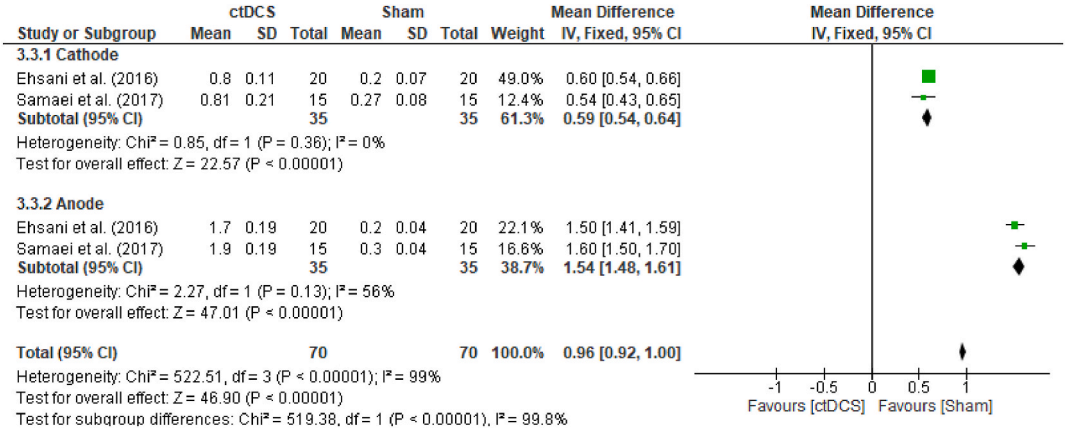

Fig. 14. Forest plot of itching side effect comparing ctDCS vs. sham stimulation.

suggest that interventional stimulations may have a pronounced influence on the activity of intracortical inhibitory neurons [41]. Therefore, such influence could exert a neuromodulatory effect on the ipsi-lesional motor cortex through transcallosal pathways.

Variations of current stimulation have been employed clinically to test for subtle differences in results when treating neurodegenerative disorders. Transcranial alternating current stimulation (tACS) has been compared to tDCS for memory enhancement in Alzheimer's patients [42]. Patients receiving tACS recalled significantly fewer words and made more memory errors compared to tDCS. Other variations, such as delayed current stimulation, have received almost no attention to compare the differences in recovery outcomes. The bulk of the research primarily explores the motor cortex and cerebellar stimulations. The choice of stimulation has largely been based on specific motor deficits and the stage of stroke. On one hand, anodal cerebellar is compared to anodal cerebral tDCS to assess improved gait, balance, and risk of fall in stroke patients [43]. On the other hand, cerebellar tDCS is used as an effective and safe treatment to promote recovery of upper limb motor function [44] or functional balance in chronic stroke patients [45]. Optimal stimulation parameters remain a point of contention to determine the long-term effects of tDCS on motor function. A general consensus from the literature is that either m1-tDCS or ctDCS should be applied when improving functional recovery in stroke patients. Different contexts have described functional recovery from a motor perspective or a psychological or cortical perspective.

4.2. Safety and side effects of tDCS

The general impression of both intervention modalities is that they are safe, with mild and meagerly reported adverse effects and various side effects. In our assessment, there is a significant difference in the amount of tingling sensation caused by sham stimulation

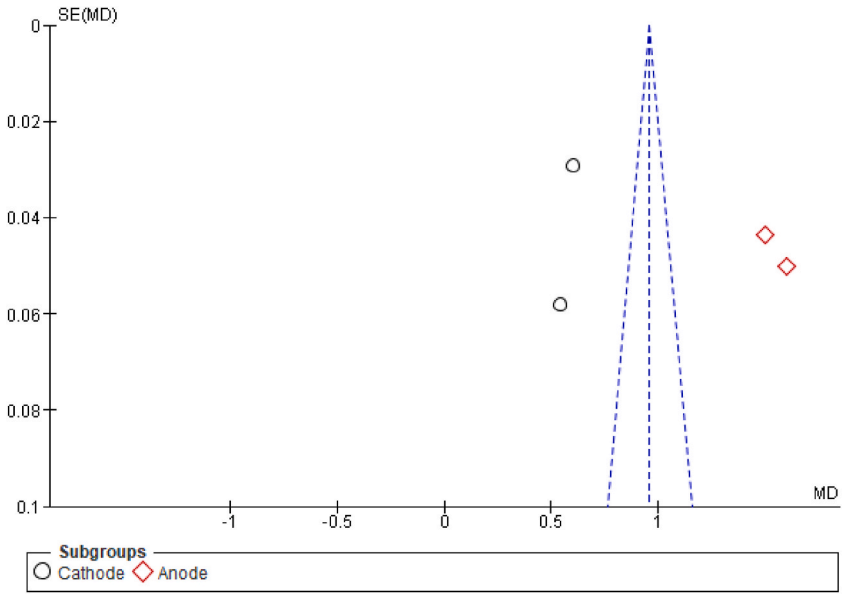

Fig. 15. Funnel plot of the side effects meta-analysis comparing itching in ctDCS vs. sham stimulation.

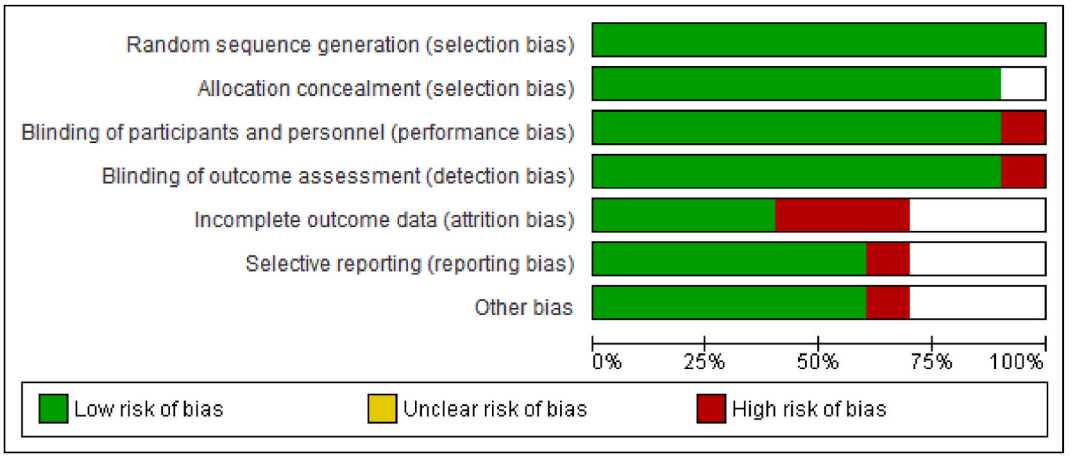

Fig. 16. Risk of bias graph from the quality appraisal in RoB2.

compared to m1-tDCS or ctDCS. Comparison with m1-tDCS has a mean difference of 0.91 [95% CI (0.87–0.96)] ($P < 0.00001$) and there is a fixed effect MD of 0.96 [95% CI (0.92–1.00)] ($P < 0.00001$) in the ctDCS comparison. Similarly, patients experienced more itching with sham stimulation than m1-tDCS (MD 0.62 [95% CI (0.55–0.68)] ($P < 0.00001$)) and ctDCS (MD 0.40 [95% CI (0.36–0.45) ($P < 0.00001$)). Ehsani et al. report itching and tingling sensation as a general discomfort experienced over the area of stimulation [31]. The tolerance of participants was high in both study groups, with no adverse effects reports recorded. According to Samaei et al., itching was the most common side effect recorded during the study [32]. In this case, there were no side effects identified at the end of the study. Without any burning sensation or pain under the electrodes, our assessment concludes that using tDCS on the motor cortex or cerebellar area is a safe intervention with minimum side effects for the stroke patients [33]. Beyond slight irritation and tingling during the current application, there seem to be no adverse effects during treatment.

Electric stimulation, like any other element of science, is under constant development. Medical advancements will constantly morph it into different mechanisms, optimally maximizing efficacy and minimizing side effects. Some studies have suggested that a single session of tDCS, either cerebellar or motor cortex stimulation, may fail to impact motor function in stroke patients [46]. Therefore, a multi-session cerebellar or motor cortex tDCS may have some accumulative impacts [47]. Numerous sections of the cerebellar, principally the vermis, have major impacts on postural control by processing and receiving inputs from the auditory, vestibular, visual, and somatosensory systems and by having control over the muscles that have been affected [48]. We have discussed other potential mechanisms of motor cortex and cerebellar tDCS in improving motor function, such as enhancing regional cerebral

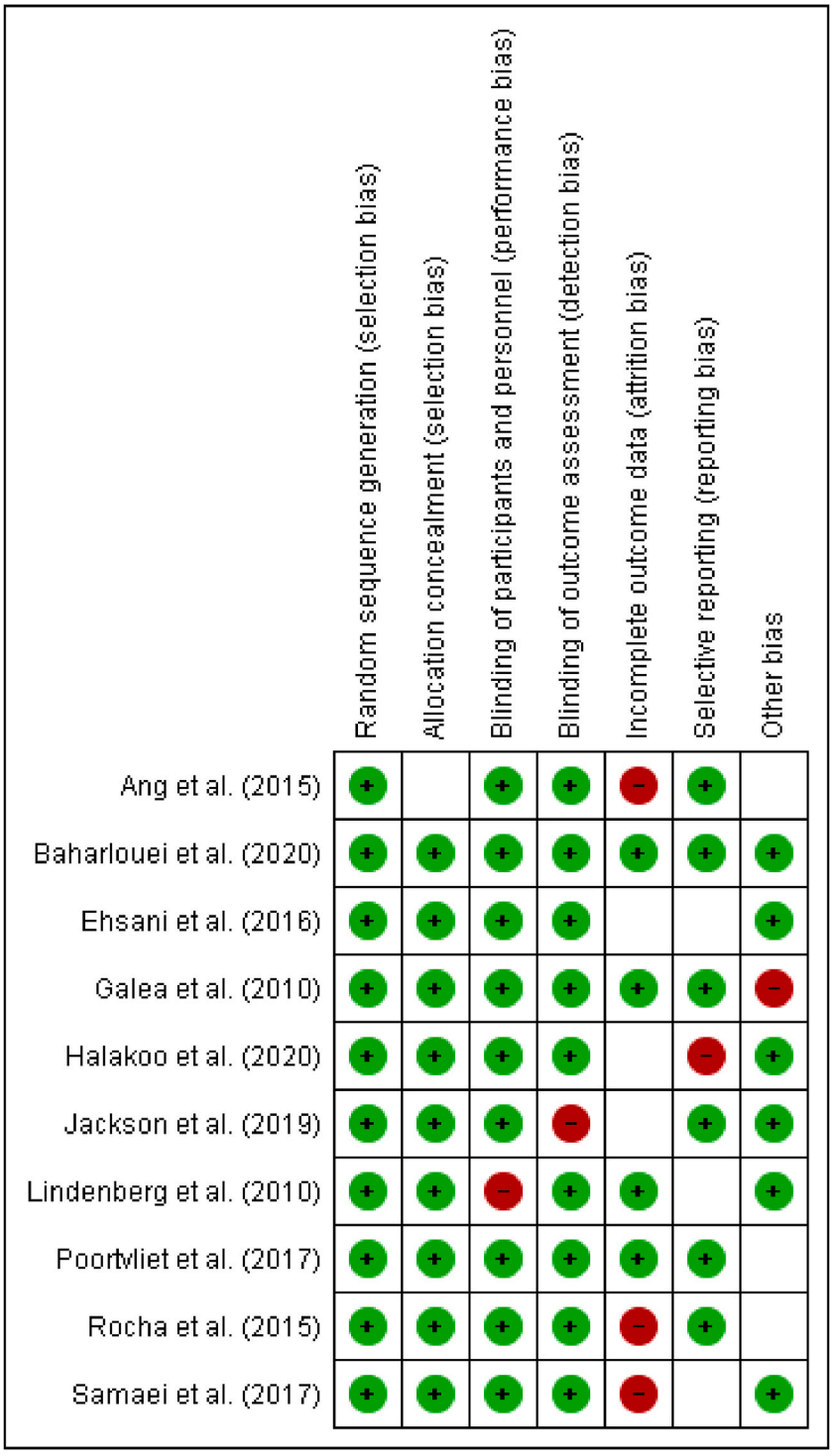

Fig. 17. Risk of bias summary of the included studies from the quality appraisal in RoB2.

blood flow (rCBF). Others include modulating neuronal excitability and plasticity, activating the ipsi-lesional motor cortex, facilitating neuroplasticity and brain reorganization, and enhancing the levels of cerebellar activity [35,44].

5. Limitations

The primary limitation of this study is the scarcity of statistical data on individual outcomes of interest. There is a high probability of bias because there were varied intrinsic differences between particular trials focusing on diverse aspects. In many cases, studies did not provide sufficient data on within, and between-group testing. The included trials also failed to state the blinding procedures for the therapists, participants, and assessors, further contributing to selection bias. Subgroup analyses were not possible in every outcome analysis owing to the few studies that met the eligibility criteria for inclusion.

6. Conclusion

In this systematic and meta-analysis, we can conclusively state that tDCS is safe without any adverse effects reported. Expectedly, mild discomfort might be experienced during the stimulation. Itching and tingling sensation were the most common side effects and were significantly prevalent in sham interventions ($P < 0.00001$). Moreover, this study could not find any significant difference between the efficacy levels of m1-tDCS versus ctDCS ($P = 0.18$), m1-tDCS versus sham ($P = 0.92$), and ctDCS versus sham ($P = 0.19$). With the limited data pooled from these analysis groups, it was not possible to offer conclusive results on the superiority of the intervention. However, the descriptive review uncovers that m1-tDCS and ctDCS offer almost similar levels of efficacy, affecting various physiological mechanisms to improve motor function.

Data availability statement

Data associated with the study has not been deposited into a publicly available repository. However, it can be available on request to the corresponding author.

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CRediT authorship contribution statement

Qurat ul-ain: Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Saad Ilyas:** Software, Methodology, Investigation, Formal analysis, Data curation. **Hamid Ali:** Writing – original draft, Formal analysis. **Ijaz Ali:** Software, Investigation, Formal analysis. **Riaz Ullah:** Project administration, Methodology, Investigation. **Hafsah Arshad:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Sana Khalid:** Writing – review & editing, Data curation, Conceptualization. **Muhammad Ehab Azim:** Validation, Methodology, Investigation, Conceptualization. **Tian Liu:** Conceptualization, Data curation, Funding acquisition, Supervision. **Jue Wang:** Supervision, Resources, Project administration, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Jue Wang reports financial support was provided by National Natural Science Foundation of China.

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