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Transcranial direct current stimulation for upper extremity spasticity rehabilitation in stroke survivors: A systematic review of randomized controlled trials

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Running head: tDCS for spasticity rehabilitation post-stroke

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Sources of funding
The authors have no source of funding or

Conflict of interest
The authors have no potential conflicts of interest to disclose.

Acknowledgments
None

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/pmrj.12804

Abstract

Objectives: This review aimed to examine the effects of transcranial direct current stimulation (tDCS) on upper extremity spasticity post-stroke and to define the most effective tDCS parameters.

Literature survey: Systematic review in the following databases: PubMed, SCOPUS, PEDro, CINAHL, MEDLINE, REHABDATA, AMED, and Web of Science databases. Studies up to June 2020 were included.

Methodology: Studies were included if the sample was composed of individuals with stroke, the intervention followed a tDCS intervention (alone or combined with another intervention), and the study was a randomized controlled trial including at least one measurement assessing upper extremity spasticity. Two authors independently screened the included studies. Conflicting decisions between authors were resolved by discussion with the third author. The methodological quality was assessed using the Cochrane Collaboration's tool. The authors determined that the meta-analysis was not feasible due to the heterogeneity in the protocols among the included studies.

Synthesis: After the screening of 1204 records, a total of seven studies met the specified inclusion criteria and involved 320 participants (Mean age= 60.28), 31.1% of whom were females. Patients with ischemic stroke comprised 77.2% of the total patients, and 42.2% were with right hemispheric stroke. Six studies exhibited "high" quality and one exhibited "moderate" quality. Five of the selected studies that combined the tDCS intervention and other traditional interventions showed a significant reduction in upper extremity spasticity post-stroke following tDCS intervention. The other two studies that delivered tDCs alone did not show a significant difference.

Conclusion: The evidence for the effect of tDCS on upper extremity spasticity post-stroke was limited. The optimal tDCS treatment dosage remains unclear. Additional studies with large sample sizes and long-term follow-up are strongly warranted.

Keywords: Stroke; spasticity; neurological disorders; movement disorders; brain injury.

Introduction

Stroke is the third leading cause of disability worldwide [1]. Approximately 30% to 80% of the patients with stroke have spasticity. The incidence of spasticity is 27% at the first month, 28% at the third month, 23-43% at the sixth month, and 34% at 18 months following stroke [2,3]. Spasticity is a velocity-dependent motor disorder characterized by an increase in tonic stretch reflexes [4]. It is associated with pain, soft tissue stiffness, and joint contracture, which may decrease the individuals' function [5,6]. Early management of spasticity may increase function and independence in patients with stroke [7]. Spasticity presents more frequently in the upper extremities than in the lower extremities in patients with stroke [8,9]. It is frequently found in the upper limb flexors (fingers, wrist, and elbow flexors), specifically in the elbow (79% of stroke cases), wrist (66% of stroke cases), and shoulder (58% of stroke cases) [10]. Upper extremity spasticity following a stroke usually limits patients' activities of daily living [6].

Many surgical, pharmacological, and physical interventions are used for reducing spasticity in patients with stroke [10-13]. Medications such as Botulinum toxin are frequently used for managing spasticity in individuals with stroke [11]; however, the common side effects for these agents include muscle weakness, malaise, and painful sensations at the injection site [11]. Additionally, oral anti-spastic medications such as Baclofen can cause muscle weakness and disturb functional activities in individuals with stroke [14]. Surgical procedures are considered following the failure of pharmacological and non-pharmacological interventions [15]. Treatments are often used in combination with other therapeutic modalitieswith an interdisciplinary rehabilitation approach [15,16].

Recently, many non-pharmacological interventions have been used in the treatment of spasticity post-stroke, such as transcutaneous electric nerve stimulation, electromyography biofeedback, therapeutic ultrasound, acupuncture, vibration, and orthotics [6,17-20]; however, their effects on spasticity are still limited [6,17-20]. In recent years, transcranial direct current stimulation (tDCS) has emerged as a promising tool and has attracted significant attention [21,22]. The tDCS technique uses a weak electrical current applied to the scalp to alter the transmembrane potentials of neurons [23,24]. The anodal tDCS shifts neural membrane potentials toward a greater depolarization and it increases cortical excitability and causes increased neural firing rates [23]. The cathodal tDCS moves the membrane potential toward a greater hyperpolarization which reduces cortical excitability and suppresses neural firing rates [23,24]. Damage to the motor cortex leads to loss of

descending inhibitory input through the corticospinal tracts and results in increased excitability of the motoneurons, causing spasticity [4]. tDCs of the motor cortex (M1) can decrease spasticity by either diminishing the unaffected hemisphere excitability with cathodal tDCS [23] or by promoting the affected hemisphere excitability by anodal tDCS [24]. It has been shown that tDCS promotes motor performance, mobility, lower extremity muscle strength, and aphasia in patients with stroke [25].

Decreased motor cortex excitability occurs due to brain lesions, unbalanced transcallosal inhibition, or both [26]. In the brains of patients with unilateral brain lesions, there is decreased cortical excitability in the lesioned hemisphere and increased excitability in the contralesional hemisphere [26]. Two major strategies of modulation of the motor cortex (M1) excitability using non-invasive brain stimulation (NIBS) have been used to restore the balance of interhemispheric inhibition between affected and nonaffected brain hemispheres through upregulation of the affected hemisphere M1 excitability and downregulation of the nonaffected hemisphere M1 excitability [27]. Nitsche and Paulus, 2000 have demonstrated that tDCS can ameliorate brain asymmetry in patients with unilateral brain lesions and has great potential in restoring the interhemispheric balance [28, 29]. tDCS can alter cortical excitability and can lead to improved rehabilitation outcomes [30]. The tDCS intervention reduces spasticity by decreasing the non-affected hemisphere excitability using the cathodal tDCS, or y increasing the affected hemisphere excitability using the anodal tDCS [31]. Various physiotherapy techniques in neurological disorders can normalize the M1 cortical excitability [31]. The tDCS intervention may lower the threshold of these physiological changes following training, and then tDCS can improve this plasticity and keep it for longer [31].

Recent studies of tDCS have reported that the anodal tDCS stimulation typically increases cortical excitability, whereas the cathodal tDCS stimulation decreases cortical excitability[29,32]. In 2013, Marquez et al. conducted a systematic review to collate the available evidence in adults with residual motor impairments as a result of stroke [25]. The authors included “impairment or functional measures (any validated tool of physical function or impairment e.g., Fugyl-Meyer assessment, Jebsen-Taylor test of hand function, grip strength, reaction time)” [25]. They found that tDCS is likely to be effective in improving motor performance in the short-term when applied selectively to patients with stroke [25]. To date, no published systematic reviews have examined the role of tDCS in spasticity rehabilitation post-stroke. Therefore, this review aimed

to investigate the immediate and long-term effects of tDCS on upper extremity spasticity in patients with stroke and to define the most effective tDCS parameters.

Methods

Search strategy

A systematic search was conducted in PubMed, SCOPUS, PEDro, CINAHL, MEDLINE, REHABDATA, AMED, and Web of Science databases from inception until June 2021 (Fig. 1). The key search terms were: ("transcranial direct current stimulation" OR "tDCS" OR "brain stimulation") AND ("stroke [Mesh]" OR "cerebrovascular accident OR CVA") AND ("muscle spasticity [Mesh]" OR "muscle stiffness" OR "muscle hypertonia [Mesh]" OR "tone") AND ("upper extremity [MeSH]" OR "upper limb" OR "arm [MeSH]" OR "hand [MeSH]") (Appendix A). This review was followed all Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [33].

Selection criteria

Studies were included if they met the following criteria and exclusion criteria framed in the PICOTS format.

(P) Population: Adults ≥18 years of age with a clinical diagnosis of stroke.

(I) Interventions: tDCS (alone or combined with another intervention).

(C) Comparison: Passive (i.e. placebo, wait-list, no intervention) or active control group.

(O) Outcome: Measures assess upper extremity spasticity (e.g., Modified Ashworth Scale, H-reflex). The Modified Ashworth Scale (MAS) was designed to assess the level of spasticity. Score 0 indicates normal muscle tone, and 5 indicates rigid limb [34]. H-reflex is modulated by inhibitory reciprocal neurons, which are conversely under control of inhibitory descending fibers.

(T) Timing: Immediate, short-term, and long-term after stroke.

(S) Study design: randomized controlled trials (RCTs) published in English.

Studies were excluded if (a) the patients had other neurological (i.e. traumatic brain injury, multiple sclerosis) or musculoskeletal (i.e. fractures) conditions, (b) the studies used animal models, (c) the tDCS combined other stimulation forms (i.e. repetitive transcranial magnetic stimulation), and (d) the studies were not RCTs. Two authors independently screened the included studies by reading titles and abstracts of the extracted studies. If the abstracts were ambiguous and had no sufficient details, the authors would read the full text to make the final decision. Conflicting decisions between authors were resolved by discussion with the third author.

Data extraction

The following data in this review were extracted separately: (a) study design; (b) characteristics of the study (i.e., sample size, age, stroke type, affected hemisphere, stroke duration); (c) spasticity severity; (d) parameters of tDCS and treatment protocols (i.e., device, mode of application, size of electrode, placement of electrode, current intensity and density, sessions duration, sessions number); (e) experimental and control groups outcomes measures; and, (f) harm or adverse effects (Table 1). Table 2 displays the outcome measures of the included studies. The following data were documented: (a) outcome measures; (b) assessment time; (c) experimental group; (d) control group; and, (e) the results. After reviewing the results of the included studies, the authors determined that the meta-analysis was not feasible because the protocols varied significantly among the included studies.

Quality assessment

Two authors evaluated the methodological quality using the Cochrane Collaborations tool [35]. The Cochrane tool is considered the standard tool to assess the risk of bias in randomized clinical trials [36,37]. The Cochrane Collaboration tool consists of six main items (sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, other bias) [36,37]. A risk of bias judgement of 'high', 'low' or 'unclear' was determined for each of these main items. Any disagreements in the quality assessment were resolved by discussion between the authors.

Results

Study selection

An electronic search of PubMed (yielding 62 articles), SCOPUS (209), PEDro (16), REHABDATA (9), MEDLINE (89), CINAHL (68), AMED (74), and Web of Science (677) produced a total of 1204 citations. After removing duplicates, 779 citations were reviewed. Of those, 620 publications were excluded because their abstracts did not match the inclusion criteria of the population (i.e., stroke) and intervention (i.e., tDCS). After that, 159 publications were reviewed in full because eligibility could not be determined by the abstracts. Subsequently, 152 articles were eliminated due to the following reasons: (a) non-randomized controlled trials; (b) assessed other neurological disorders; and, (c) evaluated other motor impairments. A total of seven randomized controlled trials were included in this systematic review. Figure 1 displays the process of article selection.

Study Characteristics

Participants

Patients, Intervention, Control, Outcomes, Timing, and Study design (PICOTS) approach was followed [38]. Seven randomized clinical trials met the inclusion criteria. A total of 320 patients were included in this analysis, 31.1% of whom were women. The mean age for all patients was 60 years. Ischemic stroke was found in 247 (77.2%) patients, with 135 (42.2%) were reported as right hemispheric stroke. Prior to the intervention, three studies included patients with onset between three weeks and six months (acute and sub-acute) [39-41], 3-6 months (sub-acute) (n=1) [42], more than six months (chronic) (n=1) [43], and 2-9 months (acute, sub-acute, and chronic) (n=2) [31,44]. Four studies included stroke survivors with a score of 1-4 in the initial MAS, [31,39-41], 2-4 (n=2) [42,43], and 1-3 (n=1) [44]. Two studies did not provide information about the affected hemisphere [31,42]. Table 1 shows the characteristics of the included studies.

Intervention

Various simulators were used in the selected studies including, (TransQE, IOMED, Salt Lake City, UT),38 (Siemens Therapie, Neuroton 827, Munich, Germany) [39], (Phoresor II Auto Model PM850) [40], (DC Stimulator Plus; neuroConn, Ilmenau, Germany) [43], (IS200) [44], and (Striat, IBRAMED, Brazil) [41]. One study did not provide information about the stimulator type [42]. Table 1 summarizes the characteristics of the transcranial direct current stimulation protocols.

The tDCS application mode was determined by the arrangement of electrode position over the ipsilesional or contralesional side of the brain. Two studies used the anodal tDCS [41,42], two used the cathodal tDCS [40,44], two studies used the anodal tDCS compared with the cathodal tDCS [39,43], and one used the cathodal tDCS compared with the dual tDCS [31].

In the anodal mode, the anodal electrode was placed over the ipsilesional primary motor cortex (M1) of the arm area (centered on C3/C4) [39,41,42]. The reference electrode was placed over the contralateral supraorbital region [42] and the contralateral orbit region [39,43]. In the cathodal mode, the cathodal electrode was placed over the contralesional primary motor cortex (M1) of the arm area, which centered on C3/C4 [31,39,40,43]. One study placed the cathode over the ipsilesional sensorimotor cortex (centred on C3/C4) [44]. The reference electrode was placed over the contralateral supraorbital region [31,43], contralateral orbit region [39,40], and contralateral shoulder [44]. Finally, in the dual-mode, the cathode was placed contralesional primary motor cortex (M1) of the arm area (centered on C3/C4), whereas the anode was placed over the ipsilesional primary motor cortex (M1) of the arm area [31].

The current intensity ranged from 1–2 mA, electrode sizes were 25–35 cm^2, and current densities were 0.029-0.080 mA/cm^2. One study did not provide information about the current intensity and density [44]. The session duration range was 10-30 minutes, and the session numbers range was 5-30 sessions.

Regarding the treatment programs: one study applied tDCS alone as an experimental intervention compared with the sham stimulation control intervention [39]. Wu *et al*. (2013) compared the tDCS plus conventional physiotherapy (CPT) experimental intervention to the sham plus CPT control intervention [44]. Del Felice *et al*. (2016) compared the tDCS experimental intervention to the dual tDCS control intervention [31]. In the study of Ochi *et al*. (2013), the cathodal tDCS plus arm training (AT) experimental intervention was compared to the anodal tDCS plus arm training (AT) control intervention [43]. Viana *et al*. (2014) compared tDCS plus

virtual reality (VR) to the sham plus VR control intervention [41]. One study compared tDCS alone to tDCS plus VR experimental interventions with VR control intervention [40]. Finally, the study of Halakoo *et al*. (2020) compared functional electrical stimulation (FES) plus tDCS to the sham plus FES and FES alone [42]. Four studies did follow-up assessment at one week [31], one month [31,42,44], two months [31], and three months [39] after the tDCS intervention.

Adverse events

Except for the study by Halakoo *et al*. (2020) [42], no adverse effects were demonstrated after tDCS in any study. In the study by Halakoo *et al*. (2020), anodal tDCS intervention was tolerated very well with minimal adverse effects (i.e. itching) by all participants. No side effects were reported by the patient's following completion of the stimulation sessions [42].

Effects of tDCS alone on upper extremity spasticity

Table 2 shows the main outcomes for the upper extremity spasticity post-stroke. Two studies investigated the effects of tDCS intervention alone on upper extremity spasticity in patients with stroke [39,40]. Hesse *et al*. (2014) reported that the patients in the anodal tDCS of the affected hemisphere, the cathodal tDCS of the non-affected side, and sham tDCS groups did not show significant improvements in the total upper extremity MAS scores after the intervention [39]. Lee *et al.* (2014) showed no significant improvements in the total upper extremity MAS scores after the cathodal tDCS, virtual reality, and cathodal tDCS plus virtual reality interventions [40].

Effects of combined tDCS with other interventions on upper extremity spasticity

Five studies investigated the effects of combined tDCS with other interventions on upper extremity spasticity post-stroke [31,41-44]. In the study by Del Felice *et al*. (2016), the combined cathodal tDCS over contralesional M1of the arm area and sham tDCS intervention was superior to dual tDCS (i.e. cathodal tDCS: contralesional M1 of the arm area; anodal tDCS: ipsilesional M1 of the arm area) plus sham tDCS intervention in reducing upper extremity distal spasticity immediately after treatment (cathodal > dual: P = .023) and

provided a higher and longer lasting reduction at proximal regions after one week (cathodal > dual: P = .042), after four weeks (cathodal > dual: P = .028), and after eight weeks form the stimulation (cathodal > dual: P = .05). These results are supported by an H-reflex modulation (overall time effect P > .002) [31]. The authors proposed that the rationale for decreasing cM1 excitability, possibly coupled with an induced increase of lesional motor area excitability in dual tDCS, is backed by the neurophysiological phenomenon of imbalance in primary M1 excitability [31]. In the study by Ochi *et al*. (2013), the mean improvement in finger MAS in patients with right hemispheric stroke was significantly larger with the cathodal tDCS of the contralesional M1 of the arm area plus arm training than with the anodal tDCS of the ipsilesional M1 of the arm area plus arm training (median –1 vs 0; Wilcoxon signed-rank test, p = 0.03). In patients with an affected left hemisphere, improvements were similar for the cathodal tDCS of the unaffected right hemisphere and the anodal tDCS of the affected left hemisphere [43]. The authors suggested that the use of cathodal stimulation of the unaffected hemisphere was based on the hypothesis that this stimulation would suppress activity locally and release the damaged hemisphere from possible excessive transcallosal inhibition, potentially allowing some functional improvement [43]. The study by Wu *et al*. (2013), the active cathodal tDCS over the ipsilesional M1 of the arm area plus conventional physiotherapy intervention compared with the sham tDCS plus conventional physiotherapy intervention had significantly more patients with a clinically important difference after treatment (80% and 78% vs 6% and 9%, elbow and wrist, respectively) and at follow-up (84% and 82% vs 7% and 4%, elbow and wrist, respectively) [44]. It could be inferred that cathodal tDCS over ipsilesional M1 had the effect of inhibition of M1 hyperactivation, which caused a significant reduction in muscle tone [44]. Additionally, in the study by Viana *et al.* (2014), the patients in the virtual reality plus anodal tDCS over the ipsilesional M1 of the arm area experiment group demonstrated significant improvement in the total upper extremity MAS scores for upper extremity spasticity (p = 0.01) compared with the virtual reality plus sham tDCS group [41]. It is possible that the anodal tDCS increased neural activity in the injured hemisphere and, consequently, reduced the spasticity levels [41]. Finally, in the study by Halakoo *et al.* (2020), the total upper extremity MAS scores in the primary motor cortex (M1) in the anodal tDCS over the ipsilesional M1 of the arm area plus FES intervention was significantly decreased immediately and one month after intervention (p = 0.01) compared with the sham tDCS plus FES and FES alone control groups [42]. The authors suggested

that the reduction of agonist spasticity with tDCS may modulate the agonist-antagonist balance, which can release antagonist muscle from reciprocal inhibition and promote a better antagonist muscle activation [42].

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Quality assessment

Two studies met five criteria [41,42], four met four criteria [31,39,40,43], and one met three criteria [44] for low risk of bias (Table 3). Random sequence generation and blinding were adequately reported in all included studies. Moreover, five studies were considered at low risk of attrition bias and did not show reporting bias [39-43]. In terms of other biases, five studies were considered free from other sources of bias [31,39,41,42,44].

Discussion

To our knowledge, this is the first systematic review to clarify the effectiveness of tDCS on spasticity in patients with stroke. It included seven randomized controlled trials of tDCS on upper extremity spasticity following stroke. The selected studies included patients with stroke with an initial MAS score ≥1. The included tDCS treatments showed mixed evidence on the benefits of tDCS for the upper extremity spasticity outcomes. Ang-uea *et al*. (2014) found that anodal tDCS reduces spasticity in patients with cerebral palsy [45]. The quality of included studies was varied. The included studies failed to conceal allocation [31, 39-44], which could produce selection bias.

Hesse *et al*. (2011) ascribed the lack of effectiveness of the anodal and cathodal tDCS on spasticity to the fact that most of the included patients exhibited either a large anterior circulation infarct, with both cortical and subcortical involvement, or a partial anterior circulation infarct leading to a predominantly cortical involvement [39]. Stroke survivors with a subcortical infarct, thus, intact cortical connectivity, might benefit more from tDCS [39]. Lee and Chun (2014) attribute the lack of differences between the treatment groups because the patients in the tDCS plus VR group had more cortical lesions than the other groups [40].

There was heterogeneity in the treatment protocols, which may have led to conflicting results. The tDCS parameters were heterogeneous among the included studies. Hence, the optimal tDCS treatment parameters could not be identified. The studies by Del Felice *et al*. (2016) and Ochi *et al*. (2013) demonstrated significant

reductions in spasticity following the cathodal tDCS, anodal tDCS, and dual tDCS interventions [31,43], though greater reductions occur following the cathodal tDCS [31,43]. No significant reduction in spasticity was reported after a 1-month follow-up [44]. Treatment administration varied among studies – tDCS was administrated after sham tDCS [31], or before VR [40], AT [43], and CPT [44] interventions. Only one study applied tDCS and FES at the same time [42].

Overall, there is evidence that using tDCS as a priming technique concurrent with other rehabilitation interventions could induce more positive effects than its application before or after these interventions or its applications as a stand-alone technique [46-49]. Different physiotherapy techniques in neurological conditions can normalize the M1 cortical excitability [50]. The tDCS may lower the threshold of these physiological changes following training, and then the tDCS could improve this plasticity and increase duration of the effect [50]. Recently, many rehabilitation interventions have demonstrated effectiveness on spasticity in patients with various neurological disorders, such as mental practice (MP) [51], focal muscle vibration (FMV) [16,20], FES [52], task-oriented [53], and whole-body vibration (WBV) [19]. Thus, this systematic review indicated that combining tDCS with one of these interventions at the same time might show a significant reduction in spasticity post-stroke.

Three studies included a small sample size (<20) [31,41,43] which made it not feasible to calculate differences [54]. , thus it is not possible to establish the clinical importance of the reported effects. With the exception of the study of Halakoo *et al*. (2020) [42], the included studies did not report adverse events after administration of tDCS, so while the clinical effectiveness has not been demonstrated clearly, tDCS appears to be a safe and well-tolerated intervention for patients with stroke.

As the included studies used different treatment protocols of tDCS, including different parameters, devices, and applications, we were not able to determine the optimal treatment parameters for treating upper extremity spasticity in patients with stroke. Moreover, the included studies did not report details about the tDCS devices, which makes it difficult to homogenize the outcomes. Reporting characteristics of the tDCS device in future research would address this issue. Additionally, due to the lack of follow-up assessments, the long-term effects of tDCS remain unclear. Furthermore, the stroke population (i.e., cortical, sub-cortical) who most likely would benefit from tDCS remains unclear. Future studies should focus on investigating the effects of combining

tDCS with other rehabilitation interventions, such as focal muscle vibration (FMV), whole-body vibration (WBV), functional electrical stimulation (FES), task-oriented, and mental practice at the same time. High-quality studies with large sample sizes are warranted to determine the most effective tDCS treatment parameters.

There are some limitations to this review. The MAS scale was used in the included studies to assess the upper extremity spasticity. Although it is likely the most common tool for assessing spasticity [55], it is had methodological limitations [55]. One of these limitations is the lack of a standardized method for evaluating spasticity [34]. For example, some clinicians evaluate limb spasticity from the resting position without any previous limb stretching, while others move the limb many times in the flexion-extension pattern before examination. This difference in performing the test may affect the results because the excitability of the stretch reflex may be different in two conditions [34]. As well, in the MAS, one grade (i.e. 1+) added to the five grade original Ashworth scale; hence, it should be considered as an ordinal scale [34].

The search strategy was limited by studies published in English; this can introduce bias because studies with significant findings are more likely to get published in English than studies which failed to show significant results [56]. Therefore, reviewing only studies published in English could lead to an overestimation of treatment effects [36]. Finally, the meta-analysis was not performed because of the heterogeneity in the treatment protocols tested area between the included studies.

Conclusion

The tDCS intervention might be safe and well-tolerated in patients with stroke. The evidence for the effect of tDCS on the upper extremity spasticity post-stroke was limited. Applying the cathodal tDCS over the non-affected side of the brain, or the anodal tDCS over the affected side, in combination with other concurrent rehabilitation interventions may result in significant spasticity reduction. The optimal tDCS treatment dosage

remains unclear. Further randomized controlled trials with larger sample sizes and long-term follow-up are warranted.

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Table 1: Study characteristics

Reference	Participants characteristics and study design	tDCS protocol	Experimental group	Control group	Adverse effects
Del Felice *et al.* (2016) [31]	Study design: Cross-over double-blinded RCT Sample size: 10 Gender (M/F): 7/3 Age (Mean): 62 Stroke type (I/H): 10/0 Affected hemisphere (L/R): NA Stroke duration (months): < 9 Spasticity severity (MAS): ≥1	Device: TransQE, IOMED, Salt Lake City, UT Intensity (mA): 1 Current density (mA/cm^2): 0.040 Size (cm^2): 25 Duration: 20 minutes Sessions (n): 5	Sham tDCS + cathodal tDCS +Sham tDCS Anode: contralateral supraorbital region Cathode: contralateral M1	Sham tDCS + dual tDCS + Sham tDCS Anode:M1 of the affected hemisphere Cathode: contralateral M1	No
Halakoo *et al.* (2020) [42]	Study design: double-blinded RCT Sample size: 32 Gender (M/F): 21/11 Age (Mean): 62.61 Stroke type (I/H): 32/0 Affected hemisphere (L/R): NA Stroke duration (months): 3-6 Spasticity severity (MAS): >1	Device: NA Intensity (mA): 2 Current density (mA/cm^2): 0.057 Size (cm^2): 35 Duration: 20 minutes Sessions (n):10	FES+ tDCS Anode: M1 of the affected hemisphere Cathode: contralateral supraorbital region FES (20 min, pulse width of 250μs, frequency of 50 Hz, and stimulation cycles of 1:2).	Control 1: FES+Sham Control 2: FES	Yes (itching, tingling, burning sensations, headache, pain)
Hesse *et al.* (2011) [39]	Study design: double-blinded RCT Sample size: 91 Gender (M/F): 59/32 Age (Mean): 65 Stroke type (I/H): 91/0 Affected hemisphere (R/L): 51/40 Stroke duration (months): 3-8 weeks (acute-subacute) Spasticity severity (MAS): ≥1	Device: Siemens Therapie, Neuroton 827, Munich, Germany Intensity (mA): 2 Current density (mA/cm^2): 0.057 Size (cm^2): 35 Duration: 20 minutes Sessions (n): 30	*Experimental 1:* Anodal stimulation of of the lesioned hemisphere Anode: The presumed hand area of the lesioned hemisphere (C3) according to the 10-20 system) Cathode: The contralateral orbit (C4) *Experimental 2*: Cathodal stimulation of the contralateral hemisphere Anode: contralateral orbit (C4). Cathode: presumed hand area of the non-lesioned hemisphere (C3).	Sham stimulation	No
Lee and Chun (2014) [40]	Study design: Pilot RCT Sample size: 59 Gender (M/F): 31/28 Age (Mean): 61.3	Device: Phoresor II Auto Model PM850 Intensity (mA): 2 Current density (mA/cm^2): 0.080 Size (cm^2): 25	*Experimental 1: tDCS* *Experimental 2: tDCS+ VR*	VR The VR training protocol (bird and ball, conveyor; and	No

	Stroke type (I/H): 35/24 Affected hemisphere (R/L): 27/32 Stroke duration (month): < 1 Spasticity severity (MAS): ≥1	Duration (minutes): 30 Sessions (n): 15	Anode: contralateral orbit of the eye. Cathode: hand area of the unaffected M1.	juggler).	
Ochi *et al.* (2013) [43]	Study design: Cross-over double-blinded RCT Sample size: 18 Gender (M/F): 14/4 Age (Mean): 61.1 Stroke type (I/H): 7/11 Affected hemisphere (R/L): 6/12 Stroke duration (month): >6 Spasticity severity (MAS): >1	Device: DC Stimulator Plus; neuroConn, Ilmenau, Germany Intensity (mA): 1 Current density (mA/cm^2): 0.029 Size (cm^2): 35 Duration (minutes): 10 Sessions (n): 5	tDCS(c)+AT Anode:contralateral supraorbital area Cathode: M1 of the unaffected hemisphere	tDCS(a)+AT Anode: M1 of the affected hemisphere Cathode: contralateral supraorbital areas AT was performed using the Bi-Manu-Track robotic arm trainer (Reha-Stim, Berlin)	No
Wu *et al.* (2013) [44]	Study design: double-blinded RCT Sample size: 90 Gender (M/F): 69/21 Age (Mean): 47.6 Stroke type (I/H): 53/37 Affected hemisphere (R/L): 43/47 Stroke duration (month): > 2 Spasticity severity (MAS): 1-3	Device: IS200 Intensity (mA): NA Current density (mA/cm^2): NA Size (cm^2): 25 Duration (minutes): 20 Sessions (n): 20	tDCS + CPT Anode: unaffected shoulder Cathode: primary sensorimotor cortex of the affected side (C3/ C4)	Sham tDCS + CPT CPT: (maintaining good limb position, chronic stretching via casting or splinting, physical modalities and techniques, and movement training).	No
Viana *et al.* (2014) [41]	Study design: pilot double-blind RCT Sample size: 20 Gender (M/F): 16/4 Age (Mean): 55.5 Stroke type (I/H): 19/1 Affected hemisphere (R/L): 8/12 Stroke duration (month): < 6 Spasticity severity (MAS): ≥1	Device: Striat, IBRAMED, Brazil Intensity (mA): 2 Current density (mA/cm^2): 0.057 Size (cm^2):35 Duration (minutes): 13 Sessions (n): 15	VR+ tDCS Anode: M1 (C3/C4) of the affected hemisphere Cathode: contralateral orbit region	VR+ sham tDCS The VR: ("Wii Sports resortTM", "Wii Play MotionTM", and "Let´s TapTM") for 15 minutes.	No

FES: functional electrical stimulation; tDCS: transcranial direct current stimulation; MAS: Modified Ashworth scale; M/F: male/female; I/H: ischemic/haemorrhagic; NA: not applicable; AT: arm training; tDCS (c) cathode; tDCS (a) anode; CPT: conventional physiotherapy; M1: primary motor cortex.

Table 2: Outcome measures

Reference	Outcome measure	Time of assessment	Experimental group	Control group	Results
Del Felice *et al.* (2016) [31]	MAS-Finger flexion	T1: Pre intervention T2: After real or sham intervention T3: one week after intervention T4: four weeks after intervention T5: eight weeks after intervention	T1 3.1± 1.1 T2 2.2± 1.0 T3 2.3± 1.2 T4 2.5± 1.1 T5 2.5± 1.2	T1 3.2± 1.1 T2 2.5± 1.0 T 32.9± 1.2 T4 3.1± 1.2 T5 3.1± 1.2	Both cathodal and dual tDCS decreased spasticity immediately and lasting up to 1 week.. Cathodal tDCS was superior comapred to dual tDCS.
	MAS-Wrist flexion	T1: Pre intervention T2: After real or sham intervention T3: one week after intervention T4: four weeks after intervention T5: eight weeks after intervention	T1 2.9± 0.7 T2 2.0± 0.8 T3 2.1± 0.9 T4 2.2± 0.8 T5 2.4± 0.7	T1 2.9± 0.7 T2 2.0± 0.6 T3 2.5± 0.8 T4 2.7± 0.8 T5 2.9± 0.7	Both cathodal and dual tDCS decreased spasticity immediately and lasting up to 1 week.. Cathodal tDCS was superior comapred to dual tDCS.
	MAS-Elbow flexion	T1: Pre intervention T2: After real or sham intervention T3: one week after intervention T4: four weeks after intervention T5: eight weeks after intervention	T1 2.9± 1.0 T2 2.1± 0.7 T3 2.2± 0.8 T4 2.4± 0.7 T5 2.5± 0.8	T1 3.2± 0.8 T2 2.4± 1.0 T3 2.9± 0.8 T4 3.1± 0.7 T5 3.2± 0.8	Both cathodal and dual tDCS decreased spasticity immediately and lasting up to 1 week.. Cathodal tDCS was superior comapred to dual tDCS.
	MAS-Shoulder abduction	T1: Pre intervention T2: After real or sham intervention T3: one week after intervention T4: four weeks after intervention T5: eight weeks after intervention	T1 2.3± 0.8 T2 2.0± 0.0 T3 2.0± 0.0 T4 2.2± 0.4 T5 2.2± 0.4	T1 2.6± 0.7 T2 2.1± 0.9 T3 2.5± 0.8 T4 2.6± 0.7 T5 2.6± 0.7	Both cathodal and dual tDCS decreased spasticity immediately and lasting up to 1 week. Cathodal tDCS was superior comapred to dual tDCS.
Malakoo *et al.* (2020) [42]	*MAS-Wrist flexion	T1: pre intervention T2: post intervention T3: 1 month after intervention	T1-T2 1.33 (1.02–1.64) T1-T3 1.41 (1.08–1.74)		Significant reduction of wrist flexors spasticity was reported after experimental intervention (FES+tDCS), lasting up to 1-month after the intervention
Hesse *et al.* (2011) [39]	MAS-UE	T1: pre intervention T2: post intervention T3: 3-month after intervention	Experimental 1: T1 1.6 ± 2.9 T2 3.3 ± 3.6 T3 3.6 ± 6.9 Experimental 2: T1 1.0 ± 1.8 T2 3.5 ± 4.9 T3 3.5 ± 5.0	T1 1.4 ± 2.7 T2 3.5 ± 4.0 T3 3.8 ± 5.5	No significant difference

Lee and Chun (2014) [40]	MAS-UE	T1: pre intervention T2: post intervention	Experimental 1: T1 0.7±0.3 T2 0.7±0.8 Experimental 2: T10.4±0.5 T2 0.5±0.8	T1 0.5±0.4 T2 0.7±0.5	No significant difference
Ochi *et al.* (2013) [43]	MAS-Elbow	T1: pre intervention T2: post intervention	T1 2.5±1.2 T2 2.0±1.1	T1 2.4±1.1 T2 2.1±1.1	Both interventions showed significant reduction in spasticity.
	MAS-Wrist	T1: pre intervention T2: post intervention	T1 2.9±1.1 T2 2.4±1.3	T1 3.0±1.1 T2 2.4±1.3	Both interventions showed significant reduction in spasticity. Cathodal tDCS improving distal spasticity more than anodal tDCS.
	MAS-Finger	T1: pre intervention T2: post intervention	T1 2.9±1.2 T2 2.1±1.4	T1 2.8±1.3 T2 2.3±1.4	Both interventions showed significant reduction in spasticity. Cathodal tDCS improving distal spasticity more than anodal tDCS.
Wu *et al.* (2013) [44]	**MAS-Elbow	T1: pre intervention T2: post intervention T3: 1-month post intervention	T2-T1 -5.6 T3-T2 -1.4	T2-T1 -0.6 T3-T2 -5.0	Significant reduction in spasticity after the intervention. Reduced non-significantly at follow up
	**MAS-Wrist	T1: pre intervention T2: post intervention T3: 1-month post intervention	T2-T1 -5.7 T3-T2 -1.9	T2-T1 -5.0 T3-T2 -5.5	Significant reduction in spasticity after the intervention. Reduced non-significantly at follow up
Viana *et al.* (2014) [41]	MAS-Wrist flexion	T1: pre intervention T2: post intervention	T1 1.5 ± 0.52 T2 1.1 ± 0.9	T1 1.5 ± 0.7 T2 1.5 ± 0.7	Significant reduction in spasticity

MAS: Modified Ashworth scale; UE: upper extremity; tDCS: transcranial direct current stimulation; FES: functional electrical stimulation.
*Mean difference (95% CI)
**Wilcoxon signed-rank test

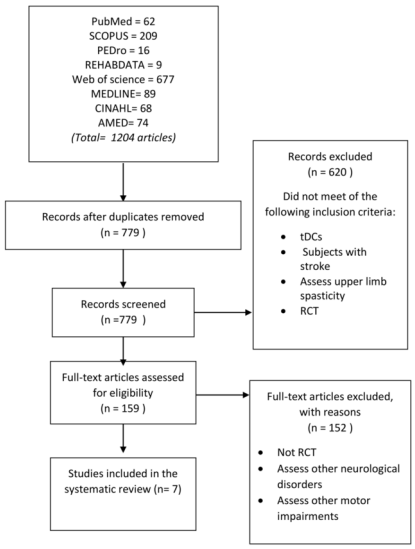
Table 3. Risk of bias assessment

Reference	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias	
Del Felice *et al.* (2016) [31]	+	?	+	+	-	+	4
[illegible]lakoo *et al.* (2020) [42]	+	?	+	+	+	+	5
Hesse *et al.* (2011) [39]	+	-	+	-	+	+	4
[illegible]e and Chun (2014) [40]	+	?	+	+	+	?	4
Ochi *et al.* (2013) [43]	+	-	+	+	+	?	4
[illegible] *et al.* (2013) [44]	+	?	+	-	?	+	3
Viana *et al.* (2014) [41]	+	?	+	+	+	+	5

Note: + = low risk; ? = unclear risk; – = high risk.

[illegible]gure legends

[illegible]igure 1 Summary of literature review process



PMRJ_12804_Figure 1 SUMMARY OF LITERATURE REVIEW PROCESS (1).tiff