


RESEARCH ARTICLE



Comparison of a single session of tDCS on cerebellum vs. motor cortex in stroke patients: a randomized sham-controlled trial

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ABSTRACT

Objective: The purpose of this study was to determine whether a single session of trans-cranial direct current stimulation (tDCS) of the cerebellum and M1 has any advantages over one another or sham stimulation in terms of balance, gait and lower limb function.

Methods: A total of 66 patients who had experienced their first ever stroke were recruited into three groups for this double-blinded, parallel, randomized, sham-controlled trial: cerebellar stimulation group (CbSG), M1 stimulation group (MSG) and sham stimulation group (SSG). A single session of anodal tDCS with an intensity of 2 mA for a duration of 20 min was administered in addition to gait and balance training based on virtual reality using an Xbox 360 with Kinect. Balance, gait, cognition and risk of fall were assessed using outcome measures before intervention (T0), immediately after intervention (T1) and an hour after intervention (T2).

Results: Across group analysis of all outcome measures showed statistically non-significant results ($p > .05$) except for Six Minute Walk Test (p value T0 = .003, p value T1 = .025, p value T2 = .016). The training effect difference showed a significant difference in balance, gait and cognition, as well as cerebral and cerebellar stimulation, in comparison to sham stimulation ($p < .05$). The risk of falls remained unaffected by any stimulation ($p > .05$).

Conclusions: In addition to Xbox Kinect-based rehabilitation training, a single session of anodal tDCS to the M1 or cerebellum may be beneficial for improving lower limb function, balance and gait performance.

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Introduction

Despite many efforts, stroke remains the leading cause of death and disability [1]. Worldwide, nearly 70% of stroke survivors have motor impairments [2] and 80% have mobility impairments [3], culminating in long-term disabilities [4]. In view of this fact, one of the top priorities is the optimization of neuro-rehabilitation of stroke survivors [5,6]. Despite rehabilitation therapies, 25% of stroke survivors experience severe gait and motor impairments, and must engage in the rehabilitation process [7]. Moreover, recovery of independent ambulation demands extensive practice and prolong

rehabilitation therapy [8,9]. Stroke prevalence is projected to increase rapidly [10,11]; therefore, it is imperative that researchers develop effective rehabilitation techniques to support functional improvement and quality of life in stroke survivors, which will have a significant socioeconomic impact [12–14].

Non-invasive brain stimulation (NIBS) has emerged as an essential adjuvant therapy for stroke-related gait rehabilitation [15]. NIBS modulates neuronal processes non-invasively and conveniently [16,17]. Because of its neuroplasticity, NIBS has been used to boost crucial intrinsic brain healing mechanisms for decades [16,18]. NIBS can alter neuronal networks and cortical

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excitability, causing long-term neurological events [18,19] thereby, improving motor deficits [19]. A very common technique of NIBS is trans-cranial direct current stimulation (tDCS) with a portable, user-friendly tDCS device that can change cortical excitability. TDCS, a neuromodulator, alters cortical activity by either tonic depolarization or hyperpolarization [18,20]. Polarity affects tDCS, Anodal stimulation increases neuronal activity while cathodal stimulation decreases [20–22]. TDCS has been used as a potential aid in natural recovery from stroke over the past years [23,24].

The cerebellum and motor cortex M1 are both essential for upright movement and balance. Researchers have employed tDCS stimulation in both sites and its effectiveness to improve motor function, balance and gait is also strongly supported by evidence [25–27]. After suffering a stroke, the affected hemisphere of the brain becomes less active in contrast to the intact hemisphere, making the intact hemisphere more active of the two. An imbalance in interhemispheric inhibition is linked to the severity of motor impairments following stroke, which may limit sensorimotor recovery [28,29]. Anodal tDCS of the lesioned M1 improves hemispheric imbalance by increasing corticospinal excitability [28,30]. Tahtis et al. found that a single session of tDCS application on the M1 was effective in enhancing gait performance in stroke patients [31]. Recently, Navarro-López et al. in their meta-analysis also investigated the effect of tDCS on M1 and found it to be effective in improving gait balance and mobility in stroke patients [32].

A recent meta-analysis also highlighted that after a stroke, M1 was stimulated in most investigations [33], but that the mechanisms underlying cerebellar stimulation are distinct from those causing M1 stimulation. The cerebellum is linked to predictions of the consequences of movement rather than direct motor commands [34]. Cerebellar tDCS has the potential to generate comparable neurophysiological modifications as M1 stimulation for LL (M1), which is why it has gained interest as a target stimulation site [35]. The cerebellum supports adaptive learning processes for several behaviours, including walking [36,37]. Cerebellar cortical network activation improves stroke recovery in animal models [38,39]. In stroke patients, contra-lesional cerebellar activity correlated with gait recovery [40]. Patients must relearn cerebellum-controlled simple motor skills [41]. NIBS approaches improve cerebellar-mediated motor learning types, especially for gait and balance tasks [37,42]. Error-based motor adaptation has drawn attention to the cerebellum [41,43]. In cortical lesions, tDCS can change the cerebellum's excitability and control over the cortex [44].

Cerebellar tDCS can aid motor adaptation when used with other motor adaptation tasks [37]. Nevertheless, the cerebellum is a very promising candidate for improving gait and balance [45–47], and future research must produce more proof in support of the use of non-invasive stimulation of regions other than M1 [33].

Many researchers have examined the effects of tDCS on M1 and cerebellum, but few have compared their effects on lower limb, gait and balance function. Our research team has planned two clinical studies to examine the effects of single and short-term anodal tDCS on stroke patients' gait and lower limb function. After short-term stimulation, both stimulation sites were effective [48]. This article discusses single-session outcomes. Two investigations examined M1 and cerebellar tDCS stimulation in healthy people and found both to be beneficial [49,50]. Based on the cerebellum's function, stimulation may only benefit those who need to enhance balance, which is unusual in healthy people. Stroke patients have clinical problems [51–53]. So, the objective of the current research was to find out if a single session of tDCS stimulation of the M1 and cerebellum has any benefits over the two stimulation sites or over sham stimulation in terms of improving the lower limb, walking, balance or cognitive function.

Materials and methods

Study design

A double-blind, randomized, sham-controlled clinical trial was conducted to investigate the effects of brain stimulation in a single session. A total of 66 patients with a first ischaemic stroke were recruited from Akbar Hospital, Gujrat, Pakistan. The sample size was calculated using G Power 3.1 [54] (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany). G*Power3, a program for statistical power analysis, was utilized to calculate the sample size and power [54]. Based on our pilot study of the primary outcome measure (Berg Balance Scale (BBS)), we computed the effect size (0.18). Calculation of the sample size for ANOVA (repeated measures, within-between interaction) revealed that 66 subjects should comprise the entire sample to achieve 80% power and a significance level of .05. Once the required sample size is obtained, excluding dropouts, data collection is completed. The participants had the option to leave the trial at any time of their personal choice.

The effects of a single tDCS session with standard parameters can persist for up to a few hours [55].

Improving the intensity from 1 to 3 mA and increasing the duration from 15 to 30 min can improve neuroplastic changes [56,57]. Knowing this fact and based on evidence that some researchers have also measured the effects of single-session tDCS for durations from 20 min to 1 h [58–61] post-intervention, we assessed outcome measures at three levels. A baseline assessment of primary and secondary outcome measures was performed prior to the intervention (T0), immediately after the treatment session including tDCS stimulation and Xbox Kinect training (T1), and 1 h after treatment (T2). Each assessment took almost 15–20 min and patients had a resting time (30–40 min after T1) between assessments to avoid fatigue.

All procedures of the study were carried out in accordance with the Declaration of Helsinki and the study was permitted by the 'Research Ethical Committee' on 10 October 2021, of Riphah College of Rehabilitation Sciences Riphah International University, Islamabad under ID number (Ref: RIPHAIH/RCRS/REC/Letter-01141) and is registered in the U.S. National Library of Medicine within ClinicalTrials.gov (clinicaltrials.gov) on 22 November 2021 (NCT05129683). Prior to participation in the research experiment, all participants provided written informed consent, and all procedures and risk factors were thoroughly explained.

Patient population

This study recruited individuals who had experienced a first-ever stroke and were capable of walking without assistance. The participants included both males and females, with ages ranging from 40 to 80 years. Participants with a score of 6 or above on the John Hopkins Fall Risk Assessment Tool (JHFRAT) were included in the study because their functional status was suitable for participating in the Xbox Kinect training. In the context of this scholarly investigation, specific exclusion criteria were implemented during the process of selecting patients. Patients were recruited regardless of time elapsed since stroke or location of stroke, and both haemorrhagic and ischaemic strokes were included. Exclusion criteria for this study were patients diagnosed with neurological disorders such as Parkinson's disease and Alzheimer's disease, individuals with a documented history of psychiatric illnesses, those who had undergone electrotherapy that impacted the nervous system during a two-week period before the commencement of the trial, and patients with cerebellar problems. Furthermore, participants who had taken sedative medications prior to the commencement of the study, exhibited indications of amnesia and depression, obtained a score below 21

on the Mini-Mental State Examination (MMSE) test for memory disorders, or demonstrated severe motor disorders in the lower extremity resulting in restricted movement or deformities were excluded from the sample. Additional exclusion criteria included the presence of radiculopathy or involvement of the lumbar spinal cord roots, visual or auditory impairments, vertigo, the use of a heart rate regulator, structural deformities in the lower extremities or spine, abnormalities in the vestibular system, a recent history of fracture, and an inability to ambulate without assistance. Patients who had worsening symptoms or recurrent stroke attacks were also excluded. The initial assessment included around 121 participants, but data from those who successfully completed the study, excluding dropouts, are shown in Figure 1.

Randomization and blinding procedure

As the current study was double-blinded, group allotment and treatment were kept hidden from the patients, examiners and therapists. Patient allocation was performed by an independent administrator. Randomization was performed using a centralized computer-generated randomization service (<https://www.sealedenvelope.com/>). Physical therapists with appropriate credentials administered the treatments, while an objective observer blinded to the stimulation site collected the data. Patient identification was kept private and personally identifiable information was not required for the research.

Intervention

The patients were trained and evaluated at the rehabilitation centre of the hospital where they received outpatient therapy. The patients received a single session of tDCS and Xbox Kinect-based gait and balance rehabilitation training. Participants were randomly assigned to one of three groups, with 22 participants in each group: cerebellar stimulation group (CbSG), M1 stimulation group (MSG) and sham stimulation group (SSG). All participants were administered a training program utilizing Xbox Kinect technology to improve lower limb function, mobility and balance. This training was supplemented with concurrent brain stimulation.

Trans-cranial direct current stimulation

The current study employed a battery-powered brain stimulator (The Brain Stimulator v3.0 Deluxe tDCS Kit)

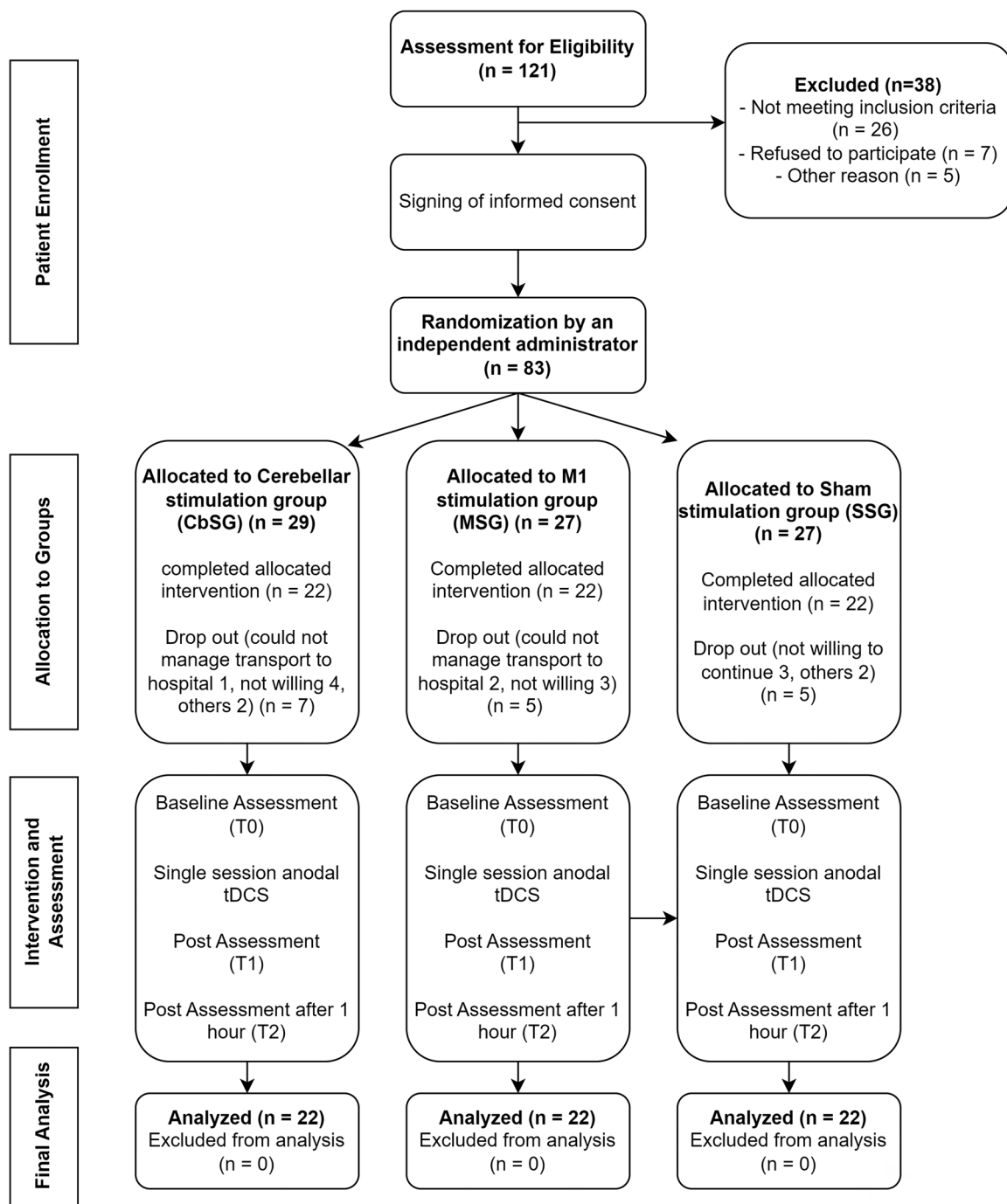


Figure 1. CONSORT flowchart.

for brain stimulation. Each group underwent a solitary session of anodal tDCS with an intensity of 2mA for 20min. Professional 3" × 3" Amrex Sponge Stimulating Electrodes were used, and the skin was cleaned with an antibacterial solution prior to electrode placement. During the first and last 10s of anodal tDCS application [62], the stimulation was progressively raised or decreased [21,63] to prevent any unexpected beginning or ending of the stimulation [21,63] during the first and last 10s of anodal tDCS application [62].

Evidence strongly supports the use of bilateral hemispheric cerebellar stimulation in improving posture and balance, therefore in the current study, we used bilateral hemispheric stimulation of cerebellum [49,64,65]. In CbSG, the active (anode) and returning (cathode) electrodes were placed bilaterally over the cerebellum (1–2cm below theinion of the occipital bone) and the right buccinator muscle, respectively [65,66]. For the MSG, the cathode was placed over the right (contralateral) supraorbital area, whereas the

anode was placed over the lesioned M1 (C3, International 10–20 system). Because of the large size of the electrodes (3 in. × 3 in.), the active electrode covered a large area, including the M1 area for the hand, arm, trunk and lower limb [65,67,68]. In the SSG, participants received stimulation for 30s before the current was reduced and eventually turned off. The electrode position was similar to that of MSG; the anode was positioned over the lesioned M1, while the cathode was positioned over the contralateral supraorbital area [65,67,68].

Xbox 360 Kinect training

Recently, evidence showed that balance and gait impairments after stroke can be effectively treated using a combination of standard rehabilitation techniques and commercial video game systems [69]. In addition, virtual reality (VR) training using the Xbox Kinect (Sports Pack) [70–73] has been shown to be an effective treatment technique for strengthening motor function, gait and balance in stroke rehabilitation [70,73]. Consequently, tDCS stimulation and Xbox-based training were used in this investigation. Each patient played soccer for 20min, beach volleyball for 15min and basketball for 15min, with 5min resting time between games, on Xbox Kinect. TDCS was administered before VR training and withdrawn after the stimulation period in the resting interval between games.

Outcome measures and measurement outline

Berg Balance Scale, Timed Up and Go Test (TUG) and Balance Evaluation Systems Test (BESTest) measured balance. BBS is a robust and accurate 14-item evaluation scale that quantifies a patient's ability (or inability) to maintain balance throughout planned tasks [74]. Alghadir et al. recommended utilizing the TUG with the BBS to measure stroke patients' balance and mobility [75,76]. TUG has strong test–retest reliability [77]. The BESTest is the best scale for assessing stroke patients' balance because of its responsiveness and accuracy [78–80]. The BESTest evaluates 36 balance control items in six domains: biomechanical constraints, limits of stability, anticipatory postural adjustments, postural responses, sensory orientation and gait stability [81].

Secondary outcome measures included the Montreal Cognitive Assessment (MoCA), Mini-mental state examination (MMSE), JHFRAT, Timed 25-Foot Walk Test (T25-FW), Six Minute Walk Test (6MWT) and tDCS adverse effects questionnaire. Stroke patients'

cognitive abilities [82] are often evaluated using either the MMSE [83] or MOCA [84–86].

In stroke patients, the reliable and sensitive JHFRAT scale measured fall risk [87,88]. The T25-FW is used by clinicians to assess functional ambulation after a stroke since it is simple and objective [89]. T25-FW objectively assesses lower limb function and mobility [90]. The 6MWT is a functional walking test that measures aerobic capacity and endurance in stroke patients [91]. tDCS is safe and well-tolerated. Sensory side effects are rare and mild. The tDCS adverse effects questionnaire will examine side effects [92]. The study's outcome measures were supported by literature [71,72,93,94] and rigorous evaluation was done to detect any slight alterations in lower limb, gait and balance function.

Statistical analysis

The data were collected using semi-structured questionnaires. The questionnaire included information related to demographic data (age, sex, stroke type, duration since stroke, and hemiplegic side) and outcome measures, and statistical analysis of the sample was conducted using IBM SPSS 26 (Armonk, NY). The normality of the distribution was tested using the Shapiro–Wilk test, and for variables that were normally distributed (BBS 0.073 and MoCA 0.164), parametric test over time (T0, T1 and T2) for across group analysis was applied (two-way mixed-design ANOVA or Split Plot ANOVA). For within-group analysis, the assumption of sphericity in Mauchly's test of sphericity was not satisfied; therefore, we employed the Friedman test. Most variables were not normally distributed (TUG 0.002, 6MWT <0.001, T25FWT <0.001, JHFRAT <0.001 and MMSE 0.003), and the across group analysis was conducted using Kruskal–Wallis test and within-group analysis was conducted using the Friedman test. Pairwise comparisons across each pair of groups were conducted using the Mann–Whitney *U*-test. Statistical significance was set at $p < .05$.

Results

The final analysis of the 66 participants who completed the study yielded results. Table 1 compares the demographic characteristics of the three groups. The average age, gender distribution, kind of stroke, and lesioned hemisphere of the participants in all three groups are nearly the same; however, the MSG's length since the stroke attack was shorter than that of CbSG and sham stimulation.

Table 1. Demographic characteristics of study population.

Variable	Cerebellar stimulation group (CbSG) (n = 22)	M1 stimulation group (MSG) (n = 22)	Sham stimulation group (SSG) (n = 22)	p Value
Age (mean \pm SD)	59.00 \pm 4.61	55.77 \pm 6.30	57.95 \pm 5.45	.159
Gender (male, female)	16, 6	18, 4	18, 4	.706
Stroke type (ischaemic, haemorrhagic)	15, 7	15, 7	14, 8	.937
Hemisphere affected (right, left)	13, 9	14, 8	12, 10	.835
Dominant hemisphere (right, left)	1, 21	3, 19	0, 22	.16
Ashworth scale for spasticity (mean \pm SD)	1.04 \pm 0.2	1.27 \pm 0.6	0.68 \pm 0.6	.122
Duration (months) (mean \pm SD)	16.50 \pm 11.8	11.23 \pm 7.73	16.41 \pm 10.26	.118

Table 2. Baseline scores (T0) (mean standard \pm deviation, *p* value) for all variables.

Variable	Cerebellar stimulation group (CbSG) (n = 22) (mean \pm SD)	M1 stimulation group (MSG) (n = 22) (mean \pm SD)	Sham stimulation group (SSG) (n = 22) (mean \pm SD)	p Value
Berg Balance Scale	41.68 \pm 5.54	43.77 \pm 5.14	45.14 \pm 6.14	.747
Timed Up and Go Test	16.75 \pm 6.32	14.20 \pm 4.87	10.38 \pm 2.82	.084
Six Minute Walk Test (km)	0.13 \pm 0.03	0.13 \pm 0.03	0.16 \pm 0.6	.068
25 Feet Walk Test (s)	18.15 \pm 10.94	14.52 \pm 6.34	11.27 \pm 6.56	.03
Johns Hopkins Fall Risk Assessment Tool	11.50 \pm 4.10	13.14 \pm 3.17	10.64 \pm 2.67	.238
BESTest Balance Evaluation – Systems Test	64.36 \pm 12.76	60.09 \pm 16.85	75.22 \pm 8.06	.001
Mini-Mental State Examination	22.64 \pm 3.74	20.95 \pm 5.08	23.23 \pm 4.80	.501
Montreal Cognitive Assessment	18.27 \pm 4.18	18.50 \pm 4.46	19.32 \pm 3.60	.787

Table 2 shows the baseline scores (mean and standard deviation) for all variables tested in each of the three groups, as well as the *p* values (homogeneity of variances) calculated by ANOVA. Based on the Shapiro–Wilk score, it can be clearly indicated that the data are not homogeneous; therefore, statistical tests were chosen for the analysis of these variables, as stated in the statistical analysis section.

Across group and within group analysis

Between-subjects analysis was conducted, and no statistically significant difference was found after a single

session of stimulation ($p = .241$, df_2 , partial eta squared 0.037). However, the within group analysis showed a significant difference among all three groups ($p \leq .001$, df_2 , partial eta squared 0.221). However, the mean difference variable analysis clearly indicated a negligible difference in the SSG compared to the cerebellar and cerebral stimulation groups. The across-group analysis of TUG and BESTest like BBS scores showed non-significant statistical differences across the three groups. Within-group analysis was significant in all three groups, with minimal differences in the SSG. The details of the three primary balance outcome measures are shown in Figure 2.

The 6MWT showed significant improvement across groups. No significant result was found for 25FWT and JHFRAT during the across-group analysis, with *p* values higher than .05. Within subjects' analysis showed significant differences between baseline and final assessments for 6MWT and 25FWT but for JHFRAT, there was no significant result within any group. The details of these scores are shown in Figure 3.

Across- and within-group analyses for cognitive assessment measures are shown in Figure 4. No significant difference was found between subjects; however, within-group analysis showed significant *p* values with minimal training effect differences.

Post hoc analysis

Multiple group analysis was performed using Bonferroni's procedure for pairwise comparisons to further emphasize the substantial influence of each group relative to the other two groups, as shown in Table 3. However, as most of the variables were not normally distributed, a significant difference was observed in the baseline scores. At 1-h post-intervention, both M1 and cerebellar stimulation exhibited significant differences in BBS scores compared to sham stimulation. The TUG test demonstrated a significant difference for cerebellar stimulation compared to sham stimulation at all three levels. At baseline, immediately after the intervention, and 1 h later, the BESTest reveals a statistically significant *p* value for the comparison of M1 and cerebellar stimulation, as well as cerebellar and sham stimulation. The 6MWT, JHFRAT and MoCA all showed no statistically significant changes. Comparing cerebellar and sham stimulation on the 25FWT yielded statistically significant *p* scores at all three time points (pre-intervention, post-intervention and 1-h post-intervention). At T1 and T2 post-intervention assessments, the MMSE indicated statistically significant differences between M1 and sham stimulation and cerebellar and sham stimulation. Table 3 contains complete information on all *p* values.

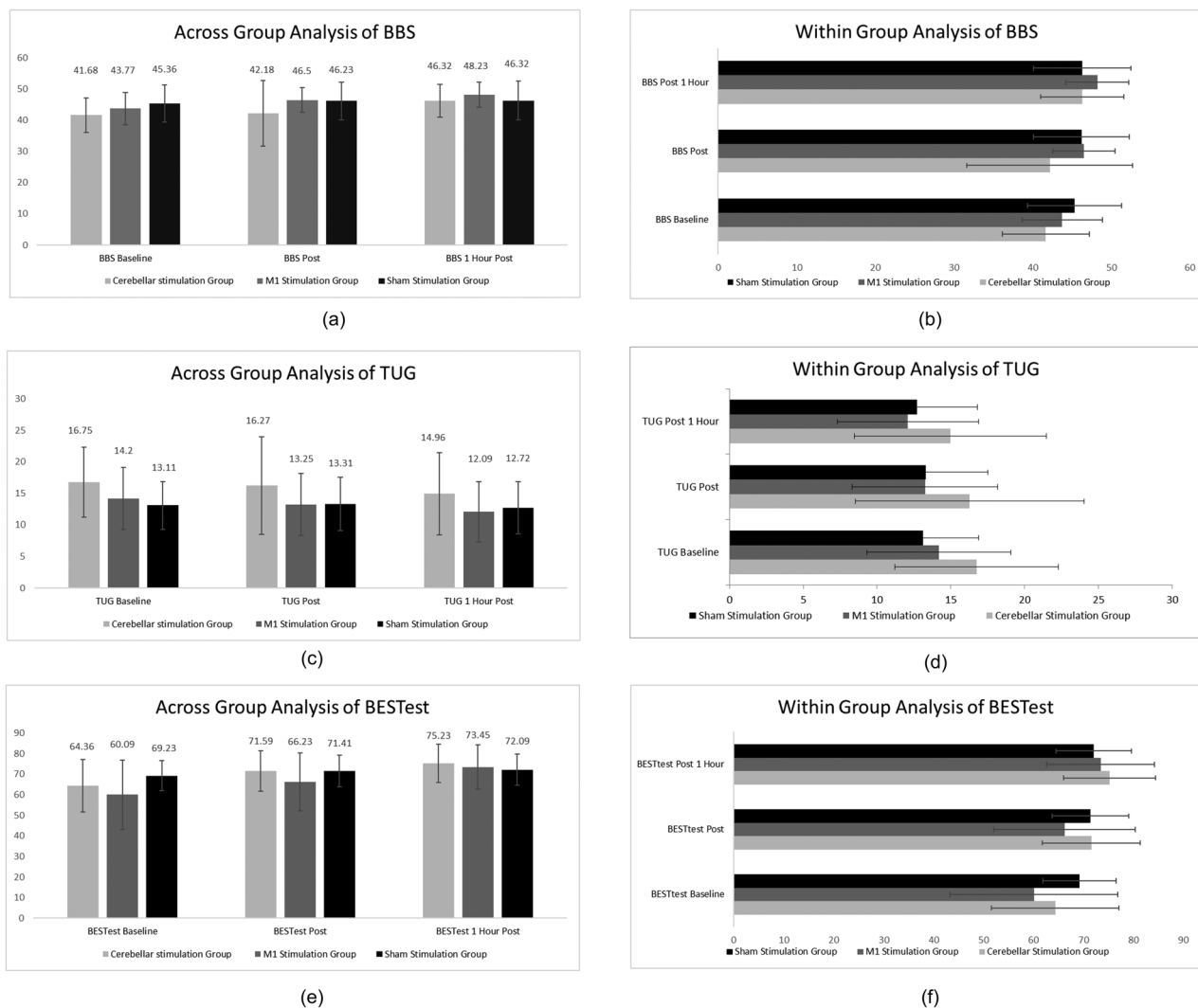


Figure 2. Across group analysis and within group analysis for primary outcomes (Berg Balance Score (BBS), Timed Up and Go Test (TUG) and BESTest balance Evaluation – Systems Test (BESTest)).

Training effect difference analysis

We used SPSS's compute variable feature to create a training effect difference variable, as our within-group analysis revealed statistically significant differences between groups. Differences in scores were determined between pre- and post-intervention levels, as well as between pre- and post-intervention levels and after 1 h. Both the BBS and TUG showed that stimulating the cerebral cortex had the same effect as stimulating the cerebellum. The BESTest scores of the MSG changed significantly ($p = .01$) between post-intervention and 1 h later. Table 4 displays the statistically significant differences between the two stimulation groups and the SSG.

Although within-group analysis for the 6MWT showed significant improvement in all three groups, no significant difference was found by measuring the

training effect difference for the same scale at any level. For the 25FWT, only a significant difference was found between cerebellar stimulation and sham stimulation with $p = .002$ and $p = .013$ between baseline and post-intervention, and baseline at 1 h post-intervention, respectively. The training effect difference for JHFR remained non-significant at each of the three levels measured, as shown in Table 5.

By analysing the training effect difference for cognitive measures, there was a significant difference in MMSE scores between the cerebral and CbSG ($p = .039$ and $p = .016$ at post-intervention and 1 h post-intervention score, and baseline score at 1 h post-intervention score, respectively). Cerebral stimulation also showed a significant improvement compared to sham stimulation (Table 6). The training effect difference for MOCA did not show any statistically significant scores at any of the three levels of difference.

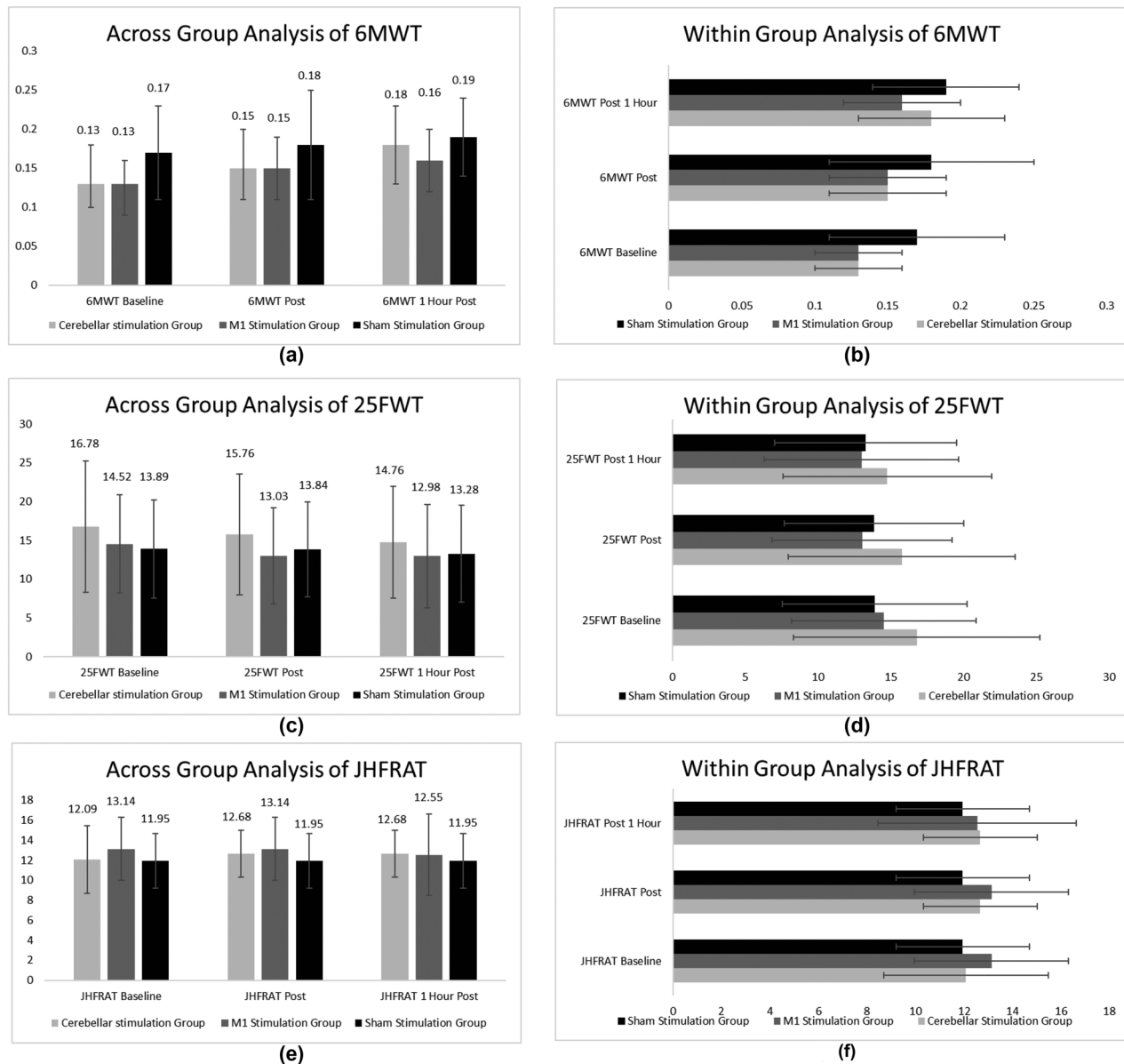


Figure 3. Across group analysis and within group analysis for Six-Minute Walk Test (6MWT), 25 Feet Walk Test (25FWT) and John Hopkins Fall Risk Assessment Tool (JHFRAT).

Adverse effects of tDCS stimulation

Trans-cranial direct current stimulation was well tolerated by all three interventional groups with little side effects or adverse effects. Figure 5 shows the mean and standard deviation scores for all aberrant sensations reported among the three groups. Only four aberrant sensations (headache, tingling, itching and skin redness) were reported by participants across all groups, out of a total of 11. A score of 1 indicated no symptoms, 2 indicated mildness, 3 indicated moderateness, 4 indicated severity and 5 indicated that tDCS stimulation was the primary cause of the symptoms. Fourteen people in the CbSG reported headache, four

people reported tingling (all scored 5: definite) and two people reported skin redness (all scored 5: definite). Two subjects in the MSG had moderate headaches, four reported tingling sensations (two reported severe, two reported definite) and three reported itching (two reported moderate, and one reported definite). One person in the SSG experienced a headache, tingling and itching, all of which were rated a 5.

Discussion

The purpose of this study was to determine if a single session of cerebellar tDCS stimulation or cerebral tDCS

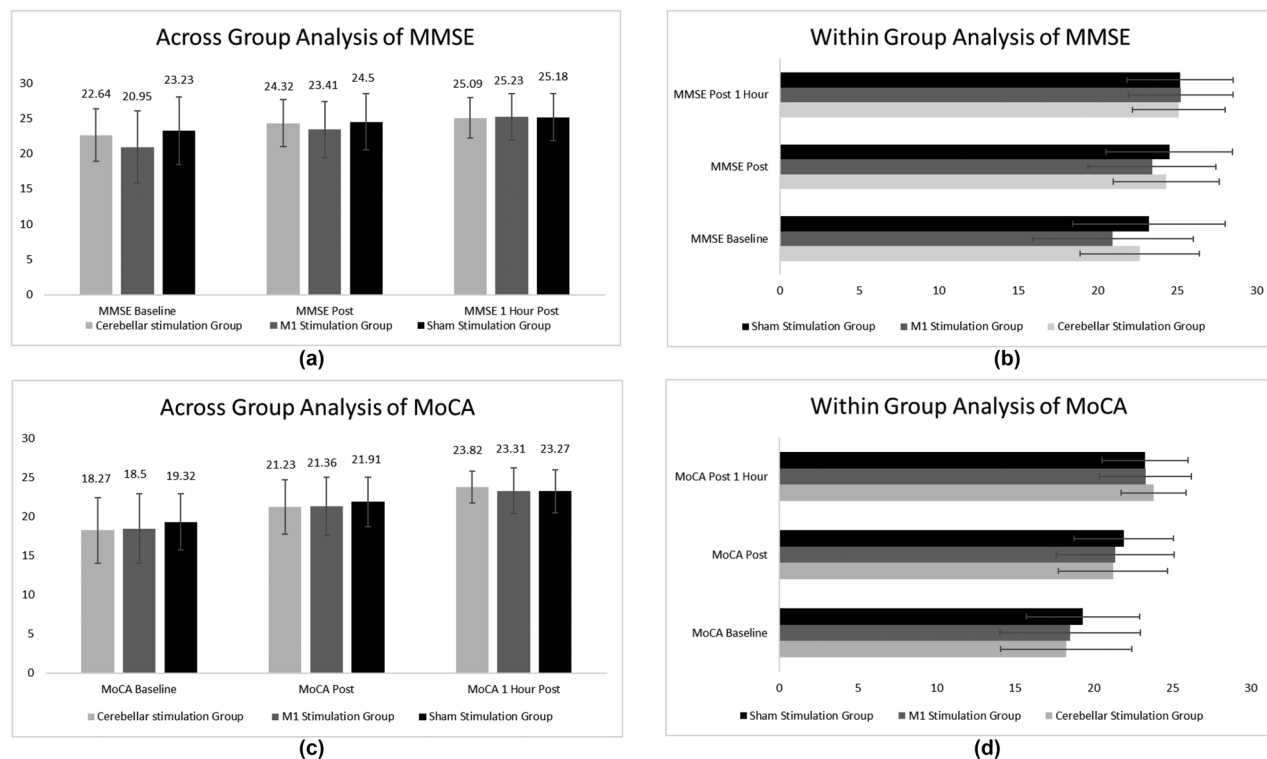


Figure 4. Across group analysis and within group analysis for Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment Tool (MoCA).

stimulation has any extra therapeutic effects beyond those of sham stimulation. All balance-related outcomes (BBS, TUG and BESTest) in the current study showed that cerebral and cerebellar stimulation versus sham stimulation was more successful in improving balance. Interestingly, BESTest evaluation showed that all pairs improved from post-intervention to 1h post-intervention, but the MSG showed the most marked improvement. TUG and BBS showed no improvement from post-intervention to 1h post-intervention. When comparing the training effect differences between the dynamic mobility and endurance scales (6MWT, 25FWT), the 6MWT showed no improvement, whereas the 25FWT favoured cerebellar stimulation. According to the JHFRAT, none of the stimulations used reduced the risk of falling. One session of brain stimulation may also have beneficial benefits on cognitive function in stroke patients, as measured by MMSE scores.

While there has been research into the effects of both M1 stimulation [95,96] and cerebellar stimulation [26,97], comparing the two is lacking evidence, particularly in stroke patients. Our results demonstrated that stimulating either the M1 or the cerebellum improved balance function in stroke patients. Craig and Dumas also found that both stimulation sites were equally

effective in enhancing balance function, but contrary to our findings, they conducted a study on young and older adults. Moreover, they did not compare the effect of the two stimulation sites [64].

While Baharlouei et al. [50] evaluated static balance and found comparable findings, we found that dynamic balance was also enhanced by stimulating M1 and the cerebellum. In a related study, Yosephi et al. [65] compared the effects of multi-session postural training using anodal cerebellar tDCS, anodal M1 tDCS and sham stimulation on balance and postural stability in older persons at risk of falling. Although we showed that M1 stimulation was more successful than cerebellar stimulation in improving dynamic postural control, other research contradicts our findings and shows that both types of stimulation are equally helpful in improving dynamic balance. As measured by the 25-Foot Walk Test, we discovered that cerebellar stimulation significantly improved both lower-limb mobility and endurance/aerobic capacity.

Both the M1 and cerebellum have good physiological grounds that allow them to improve balance and motor ability, making it difficult to establish which stimulation site in the M1 or cerebellum can be more favourable. M1 is a part of the cortico-basal ganglia network, which plays a crucial role in maintaining

Table 3. Bonferroni's method for pair wise multiple comparisons for Berg Balance Scale (BBS), Timed Up and Go Test (TUG), BESTest Balance Evaluation – Systems Test (BESTest), Six Minute Walk Test (6MWT), 25 Feet Walk Test (25FWT), Johns Hopkins Fall Risk Assessment Tool (JHFRAT), Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA).

Group pair			p Value
<i>Berg Balance Scale (BBS)</i>			
BBS (T0)	M1	Cerebellar	1
	M1	Sham	.976
	Cerebellar	Sham	.085
BBS (T1)	M1	Cerebellar	.279
	M1	Sham	.081
	Cerebellar	Sham	.076
BBS Post (T2)	M1	Cerebellar	.869
	M1	Sham	.009
	Cerebellar	Sham	.006
<i>Timed Up and Go Test (TUG)</i>			
TUG (T0)	M1	Cerebellar	.087
	M1	Sham	.042
	Cerebellar	Sham	<.001
TUG (T1)	M1	Cerebellar	.076
	M1	Sham	.371
	Cerebellar	Sham	.001
TUG (T2)	M1	Cerebellar	.114
	M1	Sham	.399
	Cerebellar	Sham	.002
<i>BESTest Balance Evaluation – Systems Test (BESTest)</i>			
BESTest (T0)	M1	Cerebellar	<.001
	M1	Sham	.064
	Cerebellar	Sham	.020
BESTest (T1)	M1	Cerebellar	.001
	M1	Sham	.050
	Cerebellar	Sham	<.001
BESTest (T2)	M1	Cerebellar	<.001
	M1	Sham	.073
	Cerebellar	Sham	<.001
<i>Six Minute Walk Test (6MWT)</i>			
6MWT (T0)	M1	Cerebellar	1
	M1	Sham	.270
	Cerebellar	Sham	.090
6MWT (T1)	M1	Cerebellar	1
	M1	Sham	.03
	Cerebellar	Sham	.157
6MWT (T2)	M1	Cerebellar	1
	M1	Sham	.180
	Cerebellar	Sham	.12
<i>25 Feet Walk Test (25FWT)</i>			
25FWT (T0)	M1	Cerebellar	.368
	M1	Sham	.667
	Cerebellar	Sham	.020
25FWT (T1)	M1	Cerebellar	.417
	M1	Sham	.527
	Cerebellar	Sham	.017
25FWT Post (T2)	M1	Cerebellar	1
	M1	Sham	.279
	Cerebellar	Sham	.040
<i>Johns Hopkins Fall Risk Assessment Tool (JHFRAT)</i>			
JHFRAT (T0)	M1	Cerebellar	.370
	M1	Sham	.055
	Cerebellar	Sham	1
JHFRAT (T1)	M1	Cerebellar	1
	M1	Sham	.090
	Cerebellar	Sham	.059
JHFRAT (T2)	M1	Cerebellar	1
	M1	Sham	.413
	Cerebellar	Sham	.148
<i>Mini-Mental State Examination (MMSE)</i>			
MMSE (T0)	M1	Cerebellar	.534
	M1	Sham	.030
	Cerebellar	Sham	1

(Continued)

Table 3. Continued.

	Group pair		p Value
MMSE (T1)	M1	Cerebellar	.845
	M1	Sham	.041
	Cerebellar	Sham	.064
MMSE (T2)	M1	Cerebellar	1
	M1	Sham	.026
	Cerebellar	Sham	.031
<i>Montreal Cognitive Assessment (MoCA)</i>			
MoCA (T0)	M1	Cerebellar	1
	M1	Sham	1
	Cerebellar	Sham	1
MoCA (T1)	M1	Cerebellar	1
	M1	Sham	1
	Cerebellar	Sham	.925
MoCA (T2)	M1	Cerebellar	1
	M1	Sham	1
	Cerebellar	Sham	1

Significant p values are given in bold.

balance [98]. Spinal network, corticospinal tract and cerebral cortical activity may all be impacted by tDCS, according to multiple studies [99,100]. Different balancing challenges, as well as anodal tDCS, have been shown to improve balance by increasing synaptic activity [101]. The cerebellum receives information from the vestibular, visual, somatosensory and auditory systems to direct the muscles used for maintaining balance [98,102]. Cerebellar white matter connections link the cerebellum to the rest of the brain, and the vermis is pivotal for maintaining balance [103]. Anodal tDCS can improve posture and balance by modulating the vermis's function and the intricate pathways connecting the M1 and cerebellum. Anodal tDCS can also boost vermis and white matter tract activation by stimulating Purkinje cells [41]. So, it is important to learn more about how tDCS stimulation works based on individual and combined cerebellar and M1 characteristics.

Trans-cranial direct current stimulation has been studied extensively, with numerous research looking at its effects on cognition, motor function of the upper and lower limbs, gait and balance in a variety of populations after just one session. We observed that it improved both balance and lower-limb function in the current investigation. When compared to the findings of other research that have looked at the effects of a single tDCS session, ours are generally consistent. Tahtis et al. found that a single session was effective in enhancing gait performance in patients with subacute stroke [31]. Similarly, Jackson et al. investigated the effect of a single session of cerebellar stimulation in enhancing motor function and reported that it was effective [104]. Foot placement in patients with chronic stroke was improved after just one session of cerebellar stimulation, according to research by Mohammadi et al. [97]. Similar to our findings, Klomjai et al. [105] reported

Table 4. Training effect difference across pairs of group for primary outcome measures using Mann–Whitney's *U*-test.

Variable	Groups	Mean \pm SD	p Value		
Training effect difference across pairs of group (multiple comparison)					
Between BBS (T0) and BBS (T1)	Cerebellar stimulation group	0.50 \pm 8.4	.851	–	.97
	M1 stimulation group	2.73 \pm 2.9		.459	–
	Sham stimulation group	0.86 \pm 0.77	–		.97
Between BBS (T1) and BBS (T2)	Cerebellar stimulation group	4.13 \pm 9.6	.118	–	.5
	M1 stimulation group	1.73 \pm 1.2		.601	–
	Sham stimulation group	0.09 \pm 0.5	–		.5
Between BBS (T0) and BBS (T2)	Cerebellar stimulation group	4.64 \pm 2.9	.091	–	<.001
	M1 stimulation group	4.45 \pm 3.4		<.001	–
	Sham stimulation group	0.95 \pm 0.7	–		<.001
Training effect difference across pairs of group (multiple comparison)					
Between TUG (T0) and TUG (T1)	Cerebellar stimulation group	0.48 \pm 2.4	.332	–	.026
	M1 stimulation group	0.95 \pm 1.9		.095	–
	Sham stimulation group	0.20 \pm 1.3	–		.026
Between TUG (T1) and TUG (T2)	Cerebellar stimulation group	1.32 \pm 4.7	.335	–	.359
	M1 stimulation group	1.16 \pm 1.7		.605	–
	Sham stimulation group	0.59 \pm 0.8	–		.359
Between TUG (T0) and TUG (T2)	Cerebellar stimulation group	1.79 \pm 3.2	.972	–	.5
	M1 stimulation group	2.12 \pm 1.6		<.001	–
	Sham stimulation group	0.38 \pm 1.3	–		.5
Training effect difference across pairs of group (multiple comparison)					
Between BESTest (T0) and BESTest (T1)	Cerebellar stimulation group	7.23 \pm 5.1	.351	–	<.001
	M1 stimulation group	6.14 \pm 4.3		<.001	–
	Sham stimulation group	2.18 \pm 1.8	–		<.001
Between BESTest (T1) and BESTest (T2)	Cerebellar stimulation group	3.64 \pm 1.2	.01	–	<.001
	M1 stimulation group	7.23 \pm 5.5		<.001	–
	Sham stimulation group	0.68 \pm 1.1	–		<.001
Between BESTest (T0) and BESTest (T2)	Cerebellar stimulation group	10.86 \pm 5.5	.279	–	<.001
	M1 stimulation group	13.36 \pm 8.7		<.001	–
	Sham stimulation group	2.86 \pm 2.0	–		<.001

Significant *p* values are given in bold.**Table 5.** Training effect difference across pairs of group for Six Minute Walk Test, 25 Feet Walk Test and Johns Hopkins Fall Risk Assessment Tool using Mann–Whitney's *U*-test.

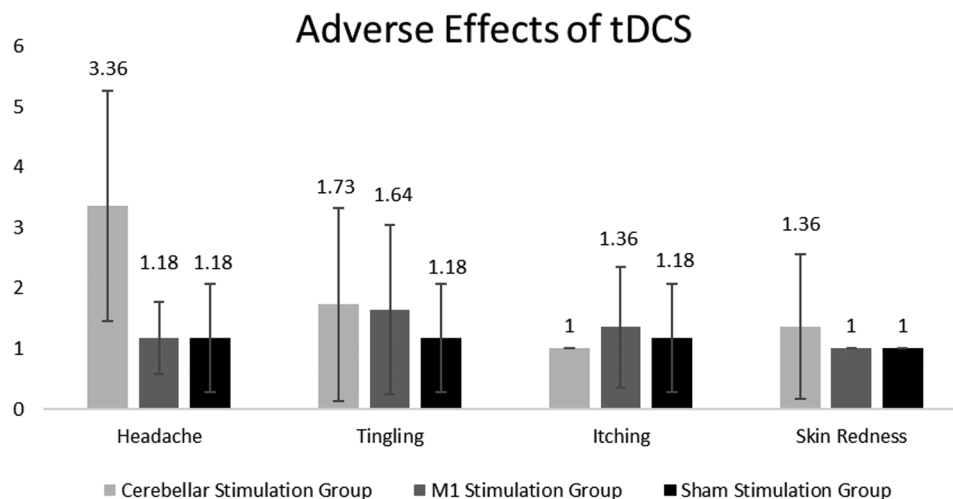
Variable	Groups	Mean \pm SD	p Value		
Training effect difference across pairs of group (multiple comparison)					
Between 6MWT (T0) and 6MWT (T1)	Cerebellar stimulation group	0.03 \pm 0.03	.151		.182
	M1 stimulation group	0.02 \pm 0.01		.856	
	Sham stimulation group	0.02 \pm 0.02			
Between 6MWT (T1) and 6MWT (T2)	Cerebellar stimulation group	0.01 \pm 0.01	.496		.547
	M1 stimulation group	0.01 \pm 0.01		.238	
	Sham stimulation group	0.01 \pm 0.02			
Between 6MWT (T0) and 6MWT (T2)	Cerebellar stimulation group	0.04 \pm 0.03	.255		.563
	M1 stimulation group	0.03 \pm 0.02		.837	
	Sham stimulation group	0.03 \pm 0.03			
Training effect difference across pairs of group (multiple comparison)					
Between 25FWT (T0) and 25FWT (T1)	Cerebellar stimulation group	1.03 \pm 1.9	.888	–	.002
	M1 stimulation group	1.49 \pm 2.4		.102	–
	Sham stimulation group	0.06 \pm 0.8	–		
Between 25FWT (T1) and 25FWT (T2)	Cerebellar stimulation group	0.99 \pm 1.6	.154	–	.533
	M1 stimulation group	0.06 \pm 2.2		.29	–
	Sham stimulation group	0.55 \pm 1.1	–		.533
Between 25FWT (T0) and 25FWT (T2)	Cerebellar stimulation group	2.02 \pm 2.4	.445	–	.013
	M1 stimulation group	1.54 \pm 2.4		.379	–
	Sham stimulation group	0.61 \pm 1.3	–		.013
Training effect difference across pairs of group (multiple comparison)					
Between JHFRT (T0) and JHFRT (T1)	Cerebellar stimulation group	0.59 \pm 2.8	.317	–	.317
	M1 stimulation group	0.00 \pm 0.0		1.001	–
	Sham stimulation group	0.00 \pm 0.0	–		.317
Between JHFRT (T1) and JHFRT (T2)	Cerebellar stimulation group	0.00 \pm 0.0	.317	–	1.001
	M1 stimulation group	0.59 \pm 2.8		.317	–
	Sham stimulation group	0.00 \pm 0.0	–		1.001
Between JHFRT (T0) and JHFRT (T2)	Cerebellar stimulation group	0.59 \pm 2.8	.162	–	.317
	M1 stimulation group	0.59 \pm 2.8		.317	–
	Sham stimulation group	0.00 \pm 0.0	–		.317

Significant *p* values are given in bold.

Table 6. Training effect difference across pairs of group for Mini-Mental State Examination and Montreal Cognitive Assessment using Mann–Whitney's *U*-test and ANOVA with post hoc.

Variable	Groups	Mean ± SD	p Value		
Training effect difference across pairs of group (multiple comparison)					
Between MMSE (T0) and MMSE (T1)	Cerebellar stimulation group	7.23 ± 5.1	.127	–	.222
	M1 stimulation group	1.68 ± 1.1		.028	–
	Sham stimulation group	1.27 ± 1.4	–		.222
Between MMSE (T1) and MMSE (T2)	Cerebellar stimulation group	0.77 ± 0.7	.039	–	.185
	M1 stimulation group	1.82 ± 1.8		.01	
	Sham stimulation group	0.68 ± 1.2	–		.185
Between MMSE (T0) and MMSE (T2)	Cerebellar stimulation group	2.45 ± 1.6	.016	–	.21
	M1 stimulation group	4.27 ± 2.9		.013	–
	Sham stimulation group	1.95 ± 2.2	–		.21
Training effect difference across pairs of group (multiple comparison)					
Between MOCA (T0) and MOCA (T1)	Cerebellar stimulation group	2.95 ± 1.3	.851	–	.811
	M1 stimulation group	2.86 ± 2.8		.889	–
	Sham stimulation group	2.59 ± 1.3	–		.811
Between MOCA (T1) and MOCA (T2)	Cerebellar stimulation group	2.59 ± 2.4	.576	–	.136
	M1 stimulation group	1.95 ± 2.4		.621	–
	Sham stimulation group	1.36 ± 1.3	–		.136
Between MOCA (T0) and MOCA (T2)	Cerebellar stimulation group	5.55 ± 2.8	.723	–	.22
	M1 stimulation group	4.82 ± 4.1		.634	–
	Sham stimulation group	3.95 ± 2.2	–		.22

Significant *p* values are given in bold.

**Figure 5.** Mean score with SD for adverse effects of trans-cranial direct current stimulation (tDCS) among all groups.

that a single session of tDCS did not increase TUG scores compared to sham stimulation, but it did increase sit-to-stand activity. Solanki et al. also discovered that tDCS can help improve balance and gait after just one session [9]. However, several studies have also shown that a single session of tDCS does not yield any significant improvements. In contrast to our results, Utarapichat et al. [106] observed that a single session of tDCS had no effect on the motor activity of the muscles in chronic stroke survivors' lower extremities. Similarly, single-session tDCS on M1 was ineffective in changing gait kinematics in a 2019 study by Kindred et al. [107]. Similar to our findings, Steiner et al. [108] showed that a single session of cerebellar stimulation did not improve dynamic balance in young healthy people.

Some research suggests that tDCS, and specifically cerebellar stimulation [109–111], can improve cognitive

function and may even have an effect on cognition with motor restoration. Because of this, we also used the MMSE and the MoCA test to assess mental functioning. Despite the common belief that cerebellar stimulation is more beneficial, our findings showed that cerebral stimulation improved cognitive performance. This may be due, at least in part, to the large surface area covered by the electrodes, which is not the case with cerebellar stimulation. Another study backs up ours in demonstrating that a single session of cerebellar stimulation does not improve cognitive performance [112].

Lower limb function, such as balance and gait, and overall physical function can be improved with VR-based rehabilitation training, and the effect size is moderate [113]. Recently, Salameh et al. investigated the effect of combined VR and tDCS stimulation and

found it to be effective in the rehabilitation of gait and lower-limb function [114]. In the current study, we also found that the combined therapy was effective; however, other studies that used tDCS stimulation of the M1 and cerebellum together [50,65] did not use a similar intervention combination.

The present study has some limitations that should be considered in future studies. First, we investigated the effects of a single session of anodal tDCS. However, for generalization of the results, long-term stimulation effects could be more convincing and beneficial in terms of their potential clinical applications. There were some clinical variations at baseline as seen for TUG and age of participants. In the current study, we only used electrode mounting of M1 stimulation for SSG instead it would have been better if sham stimulation used mounting similar to both stimulation groups equally. Because of the large number of outcome measures in the current study, it took time to complete assessment and it may affect the immediate effect recorded by the measures assessed in the end (cognitive assessment) after intervention. The response of different stages of stroke (acute, sub-acute and chronic) might be different for anodal tDCS, although we have included all stages equally. Another important factor that should be considered in future studies could be the effect of gender, which we did not consider in the current study. It is recommended that more localized electrodes should be used in future studies. In the current study, we considered motor, balance and cognitive functions, and employed broader scales that covered several aspects of motor learning. Future research with more specific evaluations considering components of posture, gait metrics and simple motor tasks comparing the effects of cerebellar and M1 stimulation should be undertaken.

Conclusions

Based on the results of the current investigation, we concluded that a single session of anodal tDCS to the M1 or cerebellum as an adjunct to Xbox Kinect-based rehabilitation training may be of additional value for enhancing lower limb function, balance and gait performance. However, the specific additional effects at both stimulation sites varied to some extent. Cerebellar stimulation can potentially enhance gait performance better than cerebral stimulation, whereas cerebral stimulation seems to be more helpful in improving balance, and cognitive function can be enhanced by both M1 and cerebellar stimulations, with more

enhanced outcomes with M1 stimulation. One session of tDCS stimulation to the M1 or Cerebellum did not reduce the risk of falls. For stroke patients, we advise clinicians to combine tDCS stimulation on either the cerebellum or cerebral cortex as an adjunct therapy with any type of rehabilitation program based on patients' specific needs regarding balance, gait and lower limb function. However, we urge that future researchers carry out a more in-depth investigation to clarify the advantages of the two stimulation sites over one another, and we recommend conducting a more detailed analysis of specific functions, such as balance alone and the combined effect of M1 and cerebellar stimulation.

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Author contributions

QUA: conceptualization, analysis, investigation, methodology, writing – original draft, writing – review and editing; ZA: methodology, statistical analysis, writing – original draft; Sal: methodology and statistical analysis; Sul: data collection and writing; IT: methodology and supervision; ANM: supervision, review and editing; TL: funding acquisition, methodology, project administration, writing – review and editing; JW: conceptualization, funding acquisition, project administration, resource supervision, writing, review and editing.

Ethics statement

The study was reviewed and approved by the ethics committee of Riphah College of Rehabilitation Sciences, Riphah International University, Islamabad, Pakistan. All participants were aware of the potential risk factors and provided signed informed consent prior to participation.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

The authors will make available raw data that supports the conclusions of this article upon request.

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