

Research Article

The Impact of Transcranial Direct Current Stimulation Combined with Task-Oriented Training on EEG-Based Measures of Motor Recovery in Chronic Stroke: A Randomized Clinical Trial Study

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Running Title: *Effect of tDCs on EEG power spectrum*

Abstract

Introduction: Upper limb motor disability, with a prevalence of approximately 77%, is the most common complication after stroke. Despite advancements in rehabilitation, many patients face persistent upper limb deficits. Adopting an approach combining top-down and bottom-up interventions may enhance neuroplasticity and improve upper limb function. This study aims to determine the effect of motor cortical trans-Cranial Direct Current stimulation (tDCs) as a top-down approach combined with Task-Oriented Training (TOT) as a down-to-top intervention on changes in Electroencephalography (EEG) spectral power in chronic stroke patients.

Materials and Methods: Thirty chronic hemiparetic stroke survivors were randomly assigned to receive real or sham stimulation targeting the primary motor cortex (C3/C4) at 2 mA for 20 minutes and TOT daily over 15 sessions. Electroencephalography was conducted pre- and post-intervention, with a 3-month follow-up, and the relative powers of delta to gamma frequency bands were recorded during the movement task with each hand (healthy and involved).

Results: Significant differences in theta ($P=.000$), alpha ($P=0.004$), beta ($P=0.000$), and gamma ($P=0.003$) relative powers were observed between groups at follow-up. Additionally, Friedman tests revealed a significant decrease in alpha and beta bands' relative powers in the healthy hand of the control group at follow-up ($P=0.001$). The experimental group displayed increased alpha and beta powers and decreased theta, without statistical significance.

Conclusion: The increase in the relative power of low frequencies and the decrease in high frequencies in the sham group, which were more prominent than the increases in alpha and beta bands' relative power and the decrease in theta in the experimental group, can indicate that the presence of real-tDCs has been able to prevent the recovery drop of relative powers. Due to the inconsistent effects of tDCs on the EEG power spectrum in stroke patients, conventional tDCs administration may require adjustments for optimal application to brain target points.

Keywords: *Electroencephalography, stroke, Task, transcranial direct current stimulation, Upper Extremity*

Introduction

Upper limb motor disability, with a prevalence of approximately 77%, is the most common complication after stroke and significantly impacts quality of life. The majority of stroke patients suffer from ischemic hemiplegia, affecting about 80% of stroke patients, which manifests more upper-limb than lower-limb neuromuscular disability in motor control (1-2). Despite rehabilitation efforts, the recovery of the affected upper extremity is significantly limited compared to the affected lower extremity(1;3-4). At best, up to 50% of survivors may not achieve functional recovery in the involved arm (5). Therefore, it would be beneficial to develop a low-risk, innocuous, and

clinically practicable treatment technique to improve upper limb motor deficits. While most traditional rehabilitative strategies use top-down approaches by training distal body parts to influence neural systems without directly linking movements and brain activity, several studies have addressed the clinical effects of top-down approaches such as brain stimulation to induce neuroplastic changes in the sensorimotor network, particularly in stroke survivors (6-10). Establishing a connection between movement and brain activity is crucial for motor skill learning and forming central-peripheral links (11-12). Due to the lack of this link in top-down approaches, recovery can be slow and suboptimal because the time it takes to transfer the effect of training to the brain and its reorganization is considerably long. As Tara Swart reported, it requires variously four and a half months, 144 days, or even three months to remap the motor cortex, depending on the complexity of a certain activity to learn (13). However, in transcranial direct current stimulation (tDCS) as a top-down approach, due to direct stimulation of cortical neurons, neuroplastic changes can occur in a shorter time interval. Recent studies reported that tDCS accelerates the recovery of impaired brain function after neurological lesions by directly modulating brain activity(14-15). Leveraging this innate and robust motor learning circuitry and harnessing brain plasticity may be the next step toward improving patient outcomes (11;16). The conclusive effects of tDCS on improving motor function in stroke remain elusive due to insufficient evidence (17). This ambiguity may stem from previous studies primarily focusing on functional and behavioral aspects of motor impairments and recovery post-treatment, neglecting the associated brain regions. Since tDCS directly targets the brain, overlooking its impact on these areas could contribute to the uncertainty surrounding its efficacy. This study aims to bridge this gap by investigating the impact of tDCs on cortical oscillatory changes in stroke patients, as assessed through EEG recordings. Currently, attention is focused on approaches that prepare the primary motor cortex to be more excitable, thereby enhancing the prospect of experience-dependent plasticity (18). In this regard, studies suggest that tDCS can affect motor function on the involved side by changing the excitability of the stimulated area, leading to neuroplastic changes in the cerebral cortex (19-21). tDCS as a noninvasive brain stimulation (NIBS) is an appealing approach that can be incorporated with training as a key element of rehabilitative therapy. Therefore, we seek to unravel how tDCS, in comparison to Task-Oriented Training (TOT), which has moderate to strong evidence in the improvement of upper extremity motor function in stroke patients, can augment recovery effects in the motor cortex (22). For this purpose, Quantitative Electroencephalography (QEEG) is a reliable, economical, non-invasive, portable, feasible, and high-time-resolution method for assessing brain oscillations. Unlike Transcranial Magnetic Stimulation (TMS) or Electromyography (EMG), QEEG allows the study of cortico-cortical interaction and brain-motor cortex activity without passing through sensory pathways, subcortical structures, and motor pathways. This feature is essential for tracking the direct and immediate effect of tDCS on the brain (23). Previous studies have associated both cortical plasticity and brain stimulation with changes in brain rhythms and synchronization (24-25). Conversely, strong evidence suggests that neurological conditions also translate into brain oscillatory activity changes. Neurological damage from stroke leads to decreased cortical excitability, which travels down the spinal cord and reduces motor nerve excitement. In particular, the primary motor area (M1) has a principal role in inducing peripheral muscle contractions to create movements (26-27). Joeri et al. in 2016 reported that pathologic changes in the thalamocortical system due to stroke can act as an infrastructural mechanism for symptoms caused by ischemia, including sensory-motor or cognitive deficits. Electrophysiological studies comparing stroke patients with healthy control groups have revealed special features of thalamocortical dysrhythmia (28). In other words, thalamocortical oscillations are the alphabet of cortical plasticity,

neurological disorders, and brain stimulation effects, as they are widely used for the assessment of brain stimulation effects (24). Frequency-specific changes have been indicated in studies of brain networks after stroke. Sensorimotor task-based studies in stroke patients demonstrate pathologic changes in alpha and beta band activity, with reduced activity near the damaged area and augmented bilateral delta and theta band power (29-30). At present, little is known about the effect of tDCS on EEG activity and how existing neural dynamics interact with this stimulation. Therefore, in the present study, we investigated the effects of tDCS on cortical oscillatory changes in stroke patients by recording QEEG.

Methods

The present study is a double-blind, randomized, parallel trial that was carried out between February 2022 and January 2023. Patients with chronic hemiparesis stroke enrolled in 3 weeks (15 sessions, 5 sessions per week) in two groups including Anodal or Sham tDCs, along with TOT for 15 sessions organized in IRAN (Iran University of Medical Science). More specifically, real-tDCs was compared to TOT. The relative power of the frequency spectrum of EEG has been measured at baseline, after 15 sessions (3 weeks) of treatment, and at 15 weeks follow-up (from the start of the scheduled intervention). The participant flowchart through the study is shown in Fig.1. The Modified Ashworth Scale (MAS) was utilized to measure muscle tone in the affected elbow and wrist while participants were seated. The MAS quantifies muscle tone on a scale from 0, indicating no increase in tone, to 4, signifying a limb that is rigid in flexion or extension. This assessment of spasticity in the upper limb was conducted to determine the recovery stages according to the Brunnstrom approach (31).

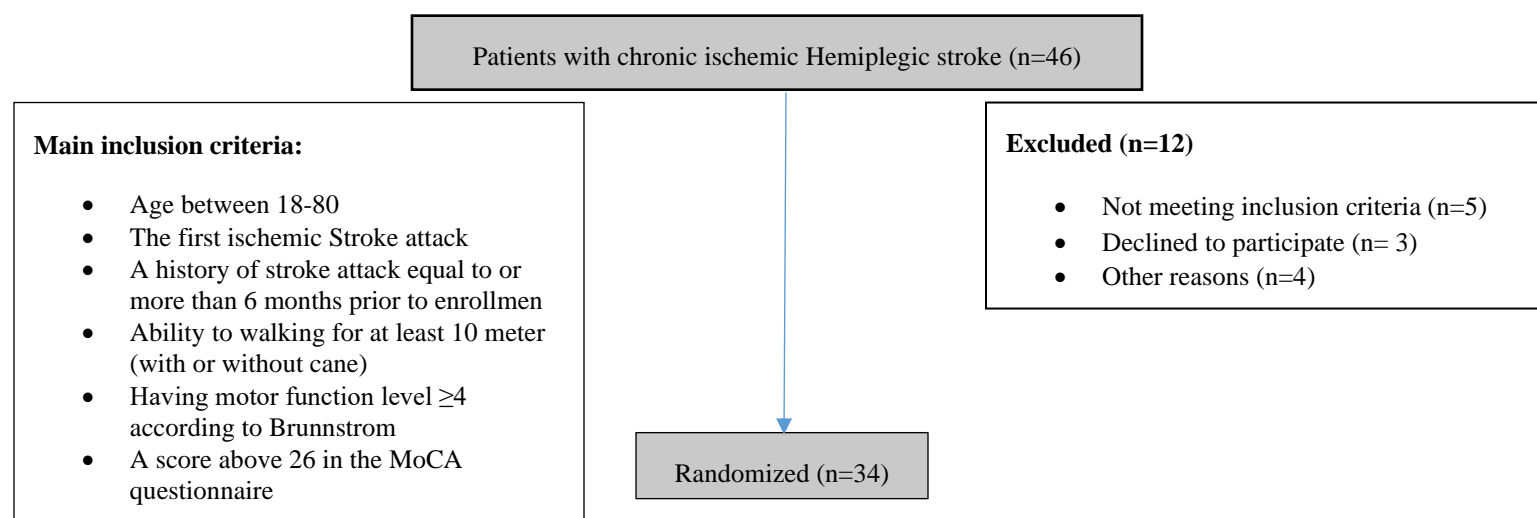
The study population included 30 Chronic ischemic hemiparetic stroke patients. The demographic and clinical characteristics of the patients are written in Table 1. This study was conducted in the physiotherapy clinic in the School of Rehabilitation Sciences of Iran University of Medical Sciences, Tehran, Iran

Table 1. Demographic and clinical characteristics of participants

Group	Age (year)	BMI (Kg/m²)	Gender (M/F)	Handedness	Involved side	months since stroke attack	Brunnstrom stage (n)
Experimental	58.46 (±13.79)	27.60 (±3.36)	7 / 9	13 Right 3 Left	7 Right 9 Left	Mean: 39 months	stage 4 (8) stage 5 (6) stage 6 (2)
Control	63.26 (±8.72)	26.90 (±3.09)	10 / 5	13 Right 2 Left	10 Right 5 Left	Mean: 36 months	stage 4 (7) stage 5 (5) stage 6 (3)

BMI: Body Mass Index

Patients were eligible for this study if they had the following: age between 18 and 80, first ischemic hemiparesis post-stroke as confirmed by the MRI or CT-Scan, At least 6 months have passed since the unilateral stroke (18;29), the ability to walk for at least 10 meter (with or without cane), motor dysfunction in upper limb with a degree of recovery equal or more than 4 according to the recovery stages of Brunnstrom (32), a score equal or more than 26 in the "Montreal Cognitive Assessment" (18). The most important exclusion criteria were as follows: any evidence of specific medical diagnosis include other neurological disorders, a thalamic stroke or central pain syndrome (Dejerine Roussy Syndrome) (11;26), Seizure history in the last two years and taking anticonvulsant drugs up to one month before the start of the current study, received Botox up to 6 months ago (to enter the study, patients must not have received Botox in the past 6 months), having a contracture in the wrist and fingers of the affected side, moderate to severe depression (a score of 19 or higher on the "Beck" depression scale) (26), Pain in the patient's shoulder (having a score of less than 12 based on the Pain Assessment section of the Fugle-Meyer assessment of upper extremity), pacemaker or other stimulation or ferromagnetic implants, Using drugs that affect the central nervous system, Pregnancy, lack of cooperation or consent to continue treatment, the presence of serious and persistent skin complications or sleep and concentration disorders due to stimulation with tDCs, Not completing the treatment period or causing an accident that affects the motor function or brain activity, Incidence of allergy to the gel of electroencephalography electrodes. During a face-to-face meeting, the researcher who conducted the evaluations explained the method and purpose of the study in detail to each participant and answered all their questions about the study. Then the participants were asked to fill out the consent form, which included information such as the title of the study, the name of the researchers, registered information, the background of the research, how the study will be conducted, what the participants should do during the study, treatment plans and obligations.



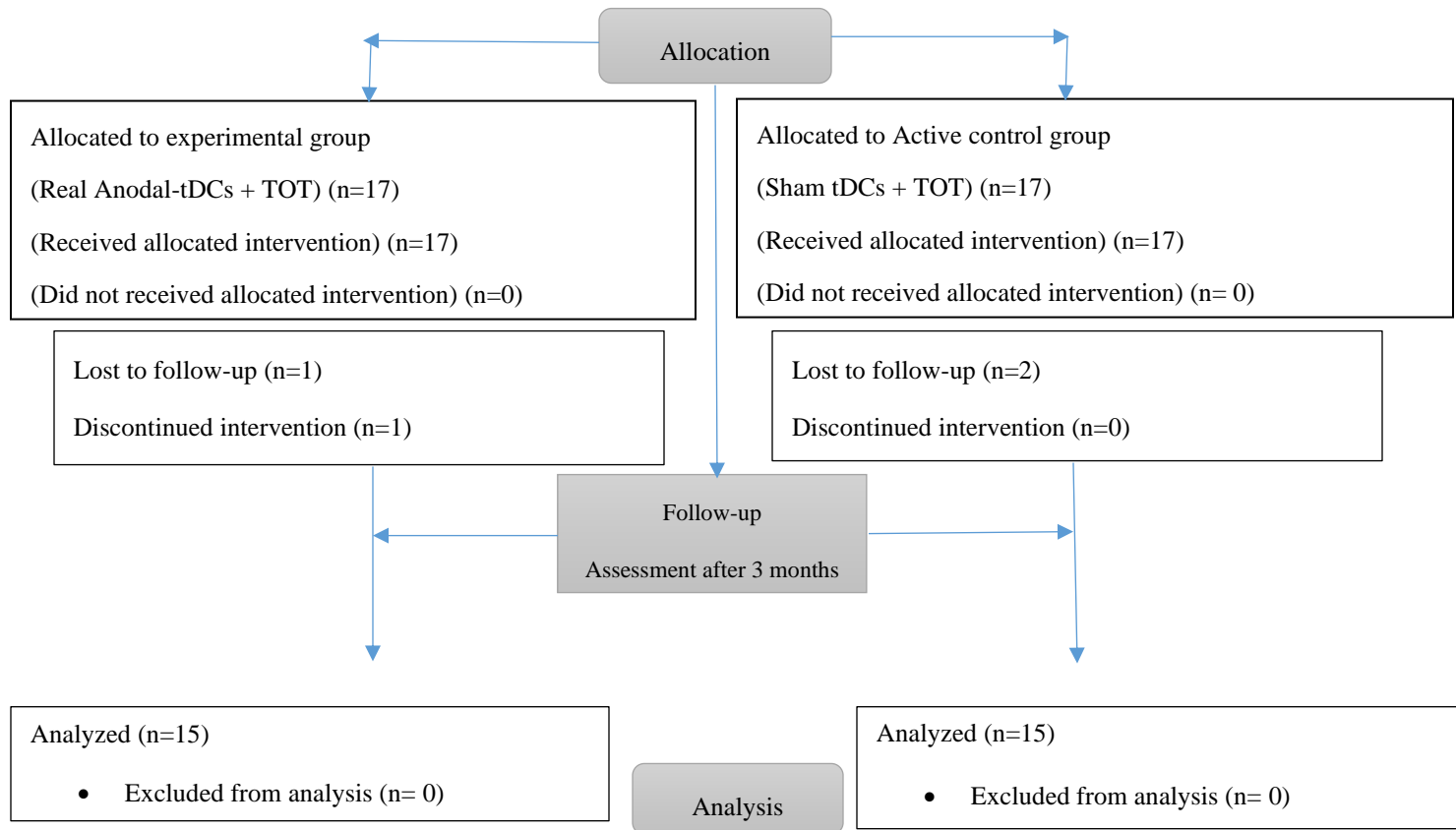


Fig.1. Flow chart of research design.

Concealment and Randomization

After obtaining written informed consent, baseline measurements were performed. The participants were randomized to either active control (sham tDCs with TOT) or experimental group (Real tDCs with TOT) (1:1 ratio) by an independent researcher not involved in outcome assessments. According to the sample size of 30 that has been determined, 15 double blocks were created using the online site www.sealedenvelope.com. To apply concealment in the randomization process, unique codes were used on the envelopes in which the

type of tDCs was specified by an analyst. Stratification was used to have the same distribution in terms of the “involved side” (right or left hemiplegia) in both groups. Participants were blinded to which of the two treatment groups (trans cranial stimulation with anodal direct current) and control (task-oriented therapeutic exercise) they had been placed in. The person who was in charge of the evaluation process of the study was blinded to the allocation of treatment and control groups. Data extraction and evaluation was done by a third person who was a physical therapist with experience of EEG recording and blinded to the groups of study and their evaluation and treatment. Allocation sequence, participant enrollment, and participant assignment to interventions were performed by an independent investigator who was not involved in assessments, interventions, or any other part of the research.

Experimental group

Participants received tDCs, along with task-oriented therapeutic exercises in both experimental and control groups. In the experimental group, Anodal-tDCs on the ipsilesional hemisphere was administered along with a series of TOT for the first 20 minutes of each session, and the remaining 40 minutes were only included exercises. Training presented in this study, including 15 exercises focused on active and auxiliary movements to increase the range of motion of the upper limbs, grasping skills, grasping and moving, and releasing objects. Interventions in both groups were conducted for three weeks, 5 sessions per week and each session lasted 60 minutes (15 sessions in total). The current of tDCs was provided to patients by the anode electrode on the damaged hemisphere (ipsilesional hemisphere M1-C3/C4) and the cathode electrode on the contralesional supraorbital for 20 minutes in each session, and during the intervention, the physical and mental conditions of the patient was carefully monitored, and necessary measures were taken. So that the first 20 minutes of the intervention sessions were exercise therapy with the application of tDCs, and the remaining 40 minutes consisted only of exercise. The application of stimulation before performing exercises in this study was planned based on the results of previous studies, as reported that applying tDCs, if it is before the start of motor exercises, compared in conditions where it is applied during or after movement training, better therapeutic effects follow (33).

Active control group

Patients in this group received sham tDCs along with TOT. In this group, the device setting and connecting the electrodes on the patient's head were the same as the method performed in the experimental group. But the current was different. At the beginning of the session, the current was gradually reaching the intensity of 2 mA for 30 seconds, and after that second, the current was cut off for 20 minutes. Then, at the end, the current was restored for 30 seconds and finally, the device was turned off. After 20 minutes of sham tDCs, TOT was continued for 40 minutes. This group's TOT included the same exercises that were given to the experimental group.

Data Collection

The brain function was recorded (bandwidth is 0.2–70 Hz, the impedance ≤ 20 kHz, and the sampling rate = 512 Hz) with 64 channel amplifiers (MicroMed, Italy) according to the international 10/20 system, from 20 Ag/AgCl surface electrodes and a diameter of 6mm electrode sites distributed throughout the whole head of the participants. The 20 electrodes were placed in Fp1, Fpz, Fp2, F7, F3, Fz,

F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, and O2, using a Medium-large sized EEG-Cap which all of 20 electrodes had been fixed on it. The EEG recording was done in an acoustic-magnetic insulated chamber and under two conditions: 1) resting state with closed eyes and 2) during the motor task of "catching and releasing the tennis ball".

The ground electrode was stuck on the skin of the radius bone's end prominence in the unaffected hand. The reference electrodes A1 and A2 were placed on the patient's left and right earlobes, respectively. Therefore, the absolute and relative power of the frequency spectrum of EEG were extracted from recorded EEG raw data as the main outcome of the present study.

Absolute power is the actual voltage or power of each of the rhythms recorded in the EEG (including delta, theta, alpha, beta, and gamma). This power is expressed in square microvolts. The absolute power of a rhythm is obtained by summing up all the power within that rhythm. The absolute power for each rhythm across all the electrodes (in the present study, all 20 electrodes) is the algebraic sum of all the powers calculated from all electrodes. Relative power is the percentage of the power of each EEG rhythm compared to the total power of all EEG rhythms (34), according to the following formula:

$$R(h) = 100 * (E(h) / E \text{ total})$$

E (h): Sum of the absolute power of each frequency band

E total: Absolute power of all frequency bands

The relative power values reported in this study are the average of all relative power values for each frequency band across all electrodes.

Sample size

The sample size was determined using G*Power 3.1.9.4 (Düsseldorf, Germany), considering the therapeutic effects on both absolute and relative power, as well as a 10% dropout rate over a 3 month. The calculations were based on a t-test with an alpha level of 0.05, the standard Cohen's effect size (d) of 0.5, a desired power of 0.80 and the number of groups = 2. Consequently, the total estimated sample size was 30 patients. The allocation ratio (N2/N1) was set to 1, resulting in 15 patients in the intervention group and 15 patients in the control group.

The statistical analysis was performed using the SPSS version 22 and sLORETA software. We performed an intention-to-treat analysis for dropout participants. The intraclass correlation coefficient (ICC) was used to assess the reliability of the QEEG measures. In all analyses, the level of significance was set at 0.05. The normality of the distribution of data was examined using the Kolmogorov-Smirnov test. Due to the small sample size, nonparametric tests were employed for multivariate analysis. To compare quantitative demographic variables between the two groups, the nonparametric equivalent of the t-test (Mann Whitney-U test) was used. A comparison of the relative power values within each group (experimental or control) between the three time-points (time stages) during performing the task by involved or healthy hands was done by the Friedman test. The Kruskal-Wallis test was performed to compare the relative power changes from T0 (before intervention) to T1 (after intervention) and T2 (follow-up) stages in each frequency band between the two groups.

Results

Comparison of involved and healthy hands between two groups

Results of the Mann-Witney U test between the Healthy and Involved hands for all frequency band power in T0 or before section, indicated no significant difference and showed matching of these frequencies between the two groups. The comparison between the two groups after intervention (T1) by the Mann-Witney U test indicated there are no significant differences in involved and healthy hands similar to T0 section. But in T2 or the Follow-up section, QEEG analysis for relative power indicated a significant difference between the two groups from theta to gamma rhythms (Tables 2 and 3).

Table 2) Comparison between groups for relative power in involved hand.

Variable		Delta	Theta	Alpha	Beta	Gamma
Before (T0)	Mann-Whitney U	88.00	66.00	85.00	81.00	91.00
	Wilcoxon W	208.00	186.00	205.00	201.00	211.00
	Z	-1.01	-1.92	-1.14	-1.30	-.89
	Asymp. Sig. (2-tailed)	.31	.05	.25	.19	.37
	Exact Sig. [2*(1-tailed Sig.)]	.32	.05	.26	.20	.38
After (T1)	Mann-Whitney U	95.00	68.00	93.00	103.00	92.00
	Wilcoxon W	215.00	188.00	213.00	223.00	212.00
	Z	-.72	-1.84	-.80	-.39	-.85
	Asymp. Sig. (2-tailed)	.46	.06	.41	.69	.39
	Exact Sig. [2*(1-tailed Sig.)]	.48	.06	.43	.71	.41
Follow-up (T2)	Mann-Whitney U	83.00	32.00	45.00	25.00	43.00
	Wilcoxon W	203.00	152.00	165.00	145.00	163.00
	Z	-1.22	-3.33	-2.80	-3.62	-2.88
	Asymp. Sig. (2-tailed)	.221	.001	.005	.000	.004
	Exact Sig. [2*(1-tailed Sig.)]	.233	.000	.004	.000	.003

Table 3. Comparison between groups for relative power in healthy hand

Variable		Delta	Theta	Alpha	Beta	Gamma
Before (T0)	Mann-Whitney U	109.00	93.00	83.00	83.00	109.00
	Wilcoxon W	229.00	213.00	203.00	203.00	229.00
	Z	-.14	-.80	-1.22	-1.22	-.14
	Asymp. Sig. (2-tailed)	.88	.41	.22	.22	.88
	Exact Sig. [2*(1-tailed Sig.)]	.90	.43	.23	.23	.90
After (T1)	Mann-Whitney U	109.00	87.00	110.00	89.00	105.00
	Wilcoxon W	229.00	207.00	230.00	209.00	225.00
	Z	-.14	-1.05	-.10	-.97	-.31
	Asymp. Sig. (2-tailed)	.88	.29	.91	.33	.75
	Exact Sig. [2*(1-tailed Sig.)]	.90	.30	.93	.34	.77
Follow-up (T2)	Mann-Whitney U	89.00	20.00	23.00	35.00	66.00
	Wilcoxon W	209.00	140.00	143.00	155.00	186.00
	Z	-.97	-3.83	-3.71	-3.21	-1.92
	Asymp. Sig. (2-tailed)	.33	.00	.00	.00	.05
	Exact Sig. [2*(1-tailed Sig.)]	.34	.00	.00	.00	.05

Comparison of interventions

1- Experimental Group:

The results of comparing relative power during T0, T1, and T2 within the experimental group were not significant between the healthy hand and the involved hand in any frequency band (Table 4).

The Friedman test for analysis of three conditions (T0, T1, and T2) in two sides separately (involved and healthy) in the experimental group indicated that there is no significant difference between the above conditions for all frequency rhythms.

Table 4. Comparison between healthy and involved hand in the experimental group.

Variable		Delta	Theta	Alpha	Beta	Gamma
Before (T0)	Wilcoxon W	213.00	208.00	227.00	226.00	220.00
	Z	-0.81	-1.02	-0.23	-0.27	-0.52
	Asymp. Sig. (2-tailed)	0.42	0.31	0.82	0.79	0.60
	Exact Sig. 2*(1-tailed Sig.)	0.44	0.33	0.84	0.81	0.62
After (T1)	Wilcoxon W	214.00	216.00	231.00	229.00	222.00
	Z	-0.77	-0.68	-0.06	-0.15	-0.44
	Asymp. Sig. (2-tailed)	0.44	0.49	0.95	0.88	0.66
	Exact Sig. 2*(1-tailed Sig.)	0.46	0.51	0.97	0.90	0.68
Follow-up (T2)	Wilcoxon W	223.00	222.00	186.00	231.00	201.00
	Z	-0.39	-0.44	-1.93	-0.06	-1.31
	Asymp. Sig. (2-tailed)	0.69	0.66	0.05	0.95	0.19
	Exact Sig. 2*(1-tailed Sig.)	0.71	0.68	0.06	0.97	0.20

2- Control Group:

Comparison between T0, T1, and T2 for relative power within the control group was not significant between the healthy hand and the involved hand in any of the frequency bands (Table 5).

Table 5. Comparison between healthy and involved hand in the control group.

Variable		Delta	Theta	Alpha	Beta	Gamma
Before (T0)	Wilcoxon W	224.00	227.00	226.00	231.00	219.00
	Z	-0.35	-0.23	-0.27	-0.06	-0.56

After (T1)	Asymp. Sig. (2-tailed)	0.72	0.82	0.79	0.95	0.58
	Exact Sig. 2*(1-tailed Sig.)	0.74	0.84	0.81	0.97	0.60
	Wilcoxon W	226.00	227.00	192.00	222.00	217.00
	Z	-0.27	-0.23	-1.68	-0.44	-0.64
	Asymp. Sig. (2-tailed)	0.79	0.82	0.09	0.66	0.52
	Exact Sig. 2*(1-tailed Sig.)	0.81	0.84	0.10	0.68	0.54
Follow-up (T2)	Wilcoxon W	187.00	214.00	226.00	210.00	221.00
	Z	-1.89	-0.77	-0.27	-0.93	-0.48
	Asymp. Sig. (2-tailed)	0.06	0.44	0.79	0.35	0.63
	Exact Sig. 2*(1-tailed Sig.)	0.06	0.46	0.81	0.37	0.65

In the control group, the Friedman test for analysis of three conditions (T0, T1, and T2) indicated there is no significant difference between the above conditions for all frequency rhythms in the involved hand, but in the healthy hand, there are significant differences just in alpha and beta frequencies in the three above conditions (Table 6).

Table 6) Comparison of relative power for health hand in control group

Variable	Alpha			Beta		
	Before(T0)	After (T1)	Follow-up (T2)	Before(T0)	After (T1)	Follow-up (T2)
<i>Control group</i>						
<i>Health hand</i>						
Mean Rank	1.87	2.60	1.53	2.00	2.53	1.47
Chi-Square	8.93			8.53		
Asymp. Sig. (2-tailed)	0.01			0.01		

DISCUSSION

Based on the results, no significant differences were observed between the experimental and control groups for either the involved hand or the healthy hand in the after-intervention stage (T1). However, in the follow-up stage, there were significant differences in relative powers between the two groups across all frequency bands. The question arises as to why these significant changes were observed during the follow-up phase. Similar findings were reported by Tjreed et al. (2016), who noted that changes in the power spectrum were more pronounced at later measurement time points occurring after a significant interval from the end of the stimulation. Despite tDCs being a top-down approach, the expectation of producing rapid effects on cortical brain oscillations may be more feasible during online EEG, conducted simultaneously with tDCs administration, as observed in previous studies (24). Our study protocol consisted of offline EEG and perhaps immediate effects of tDCs dissipate soon after stopping the stimulation, but during the repeated sessions and after a long-term follow-up, brain cells may gradually react, resulting in an accumulative effect. This phenomenon aligns with the findings of Ulam F. et al. (2014), who noted improvements in working memory among patients with Transient Brain Injury (TBI) extending beyond the period associated with the immediate effects of tDCs. This suggests the potential for a cumulative change in cortical excitability. Similarly, previous investigations into motor recovery in stroke patients following tDCs administration have shown that at the 6-month follow-up, tDCs led to greater improvements in motor function (35).

If we consider the increasing effect of anodal-tDCs on brain excitability as an assumption, the results of this study can be viewed from a different perspective. Keith C. Dodd (2017) highlighted that while ipsilesional hemispheric reorganization is often presumed to be crucial for efficient recovery, the role of the contralesional motor cortex has been somewhat overlooked. Interestingly, some well-improved stroke patients demonstrate contralesional motor activity and exhibit decreased functional ability when the contralesional hemisphere is inhibited (36). In line with this, Hummel et al. (2006) demonstrated that cathodal-tDCs applied to the contralesional hemisphere may be unfavorable for some stroke patients, as the contralesional hemisphere becomes activated during motor tasks executed by the paretic hand. (37). Considering that anodal stimulation of the ipsilesional hemisphere increases its excitability, it can be inferred that anodal stimulation on the ipsilesional hemisphere may have inhibitory effects on the contralesional hemisphere. In the control group where anodal stimulation was absent, such an inhibitory effect on the contralesional hemisphere was not observed. Therefore, the observed recovery changes in the present study, including a significant increase in the alpha and beta frequency bands and a decrease in the theta band, may be attributed to this absence of inhibitory effects on the contralesional hemisphere.

An increasing trend was observed in the alpha and beta band's relative power in the real-tDCs (experimental) group. Despite recent beliefs about the increase of the beta band relative power following the anodal tDCs, this stimulation did not produce such an effect at a significant level in the current experiment. This discrepancy can be explained by the variability of anatomy and cortical reorganization after stroke lesions, leading to alterations in local conductivity and resulting in differences in electric current pathways in the brain between healthy individuals and stroke patients, as well as within stroke patients themselves, influenced by factors such as lesion location, size, and conductivity. Another possible reason for the conflicting and inconsistent effects of tDCs in stroke studies is that brain functional reorganization caused by stroke can alter different brain areas that tDCs are intended to target. After stroke, functional

reorganization may occur in different motor areas including the ipsilesional dorsal premotor cortex and the contralesional primary motor cortex areas, which are not targeted with conventional tDCs electrode configurations. Previous studies have demonstrated that traditional tDCs resulted in highly variable electric fields within the motor hand projection in chronic stroke patients. Joris van der Crujsen et al. (2022) applied three types of targets to stimulate the hand-related motor cortex with tDCs: structural targets using T1- MRI, functional targets by recording EEG during stimulation and simultaneous MRI, and optimized electrode configurations by a software computational model called SIM NIBS 3.2 to create finite element volume conductor models of the head for simulation of NIBS. In healthy individuals, the intended target was found on the contralateral hemisphere in EEG, but in stroke patients, the functional target was detected on the ipsilesional hemisphere in 45% of subjects and on the contralesional cortex in the rest of the participants, which was localized in different cortical areas of the ipsilesional and contralesional hemisphere: the premotor cortex/supplementary motor cortex (BA6), primary motor cortex (BA4), Wernicke's area (BA22), intermediate frontal cortex (BA8), Pars opercularis (BA44), primary somatosensory cortex (BA1), somatosensory association cortex (BA5), and the supramarginal gyrus (BA40). After optimization of the electrode positioning, the stimulation strength significantly increased in the stroke group but was not as strong as the stimulation in healthy subjects. Considering the individual brain structure and functional motor targets is necessary for utilizing tDCs in chronic stroke patients and also, to a lesser extent, in healthy subjects (38). In this regard, as Salazar and colleagues (2023) introduced, there are several software optimization models that can help researchers to individualize tDCs electrode placement and dosimetry (39).

Unexpectedly, according to the results of the intervention comparison, relative power changes in the control group were statistically significant, whereas the experimental group results were not significant. There was an increasing trend in the theta band and a significant decrease in the alpha and beta bands following sham stimulation in the healthy hand of the control group at the follow-up stage. Previous studies' results are incoherent on this issue. For example, Alex I. Wiesman (2018), Mc Dermott (2018), and Anirban Dutta (2015) demonstrated that anodal tDCs elevated baseline theta relative power compared with cathodal or sham stimulation in bilateral cortical areas(40-42). Tjreed W. B et al. (2016), similar to our results, reported a significant increase in spectral power at lower frequencies after sham tDCs (24). Although methodological differences could impact research outcomes and findings, larger electrodes (35 cm²), with a corresponding reduced current density, produced a greater motor response compared with smaller electrodes (20), maybe because of the lower total charge (which is influenced by current density and stimulation duration) in sham tDCs having a greater effect on spectral power. An increase in low-frequency oscillations has been reported along with a decreased level of cognitive activity and probably reflects conditions of low arousal such as drowsiness and fatigue (41;43). Maybe due to the concise duration of the current (30s start +30s end) and feeling the current on the scalp, patients fell asleep in the sham group, thus increasing their low-frequency cortical oscillations during the EEG recording. On the other hand, it supports anodal stimulation effects in the experimental group. Since theta band relative power increased in the control group, and it decreased (although statistically insignificant) in the experimental group, consistent with previous studies (24), real anodal stimulation preventing the theta increase and alpha and beta reduction, created changes in cortical activity in favor of motor and cognitive recovery after stroke (44).

Conclusion

In conclusion, despite methodological differences in available studies, the diverse and inconsistent effects of tDCs on the power spectrum in stroke patients suggest that conventional tDCs administration may require changes to optimize utility on desired brain target points considered for stroke studies. It is suggested to investigate the effect of individualized tDCs on EEG biomarkers including power spectrum density, in stroke patients in future clinical studies.

Ethical Considerations

This trial gained approval from the Ethics Committee of the Iran University of Medical Sciences (Code: IR.IUMS.REC.1400.1122), and it was registered at the Iranian Registry of Clinical Trials (IRCT) (Code: IRCT20140222016680N9).

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Authors' contributions

All authors made equal contributions to the preparation of all aspects of the research.

Conflict of interest

The authors declared no conflict of interest.

References

1. Kashoo FZ, Al-Baradie RS, Alzahrani M, Alanazi A, Manzar MD, Gugnani A, *et al.* Effect of transcranial direct current stimulation augmented with motor imagery and upper-limb functional training for upper-limb stroke rehabilitation: a prospective randomized controlled trial. *International Journal of Environmental Research and Public Health.* 2022;19(22):15199
2. Donkor ES. Stroke in the century: a snapshot of the burden, epidemiology, and quality of life. *Stroke research and treatment.* 2018;2018
3. Yao X, Cui L, Wang J, Feng W, Bao Y, Xie Q. Effects of transcranial direct current stimulation with virtual reality on upper limb function in patients with ischemic stroke: a randomized controlled trial. *Journal of NeuroEngineering and Rehabilitation.* 2020;17(1):73.[10.1186/s12984-020-00699-x]
4. Van Hoornweder S, Debeuf R, Verstraelen S, Meesen R, Cuypers K. Unravelling ipsilateral interactions between left dorsal premotor and primary motor cortex: a proof of concept study. *Neuroscience.* 2021;466:36-46

5. Tu-Chan AP, Natraj N, Godlove J, Abrams G, Ganguly K. Effects of somatosensory electrical stimulation on motor function and cortical oscillations. *Journal of neuroengineering and rehabilitation*. 2017;14:1-9
6. Dimyan MA, Cohen LG. Contribution of transcranial magnetic stimulation to the understanding of functional recovery mechanisms after stroke. *Neurorehabilitation and neural repair*. 2010;24(2):125-35
7. Liew S-L, Santarnecchi E, Buch ER, Cohen LG. Non-invasive brain stimulation in neurorehabilitation: local and distant effects for motor recovery. *Frontiers in human neuroscience*. 2014;8:378
8. López ND, Monge Pereira E, Centeno EJ, Miangolarra Page JC. Motor imagery as a complementary technique for functional recovery after stroke: a systematic review. *Topics in stroke rehabilitation*. 2019;26(8):576-87
9. Daly JJ, Wolpaw JR. Brain-computer interfaces in neurological rehabilitation. *The Lancet Neurology*. 2008;7(11):1032-43
10. Bhagat NA, Yozbatiran N, Sullivan JL, Paranjape R, Losey C, Hernandez Z, *et al*. Neural activity modulations and motor recovery following brain-exoskeleton interface mediated stroke rehabilitation. *NeuroImage: Clinical*. 2020;28:102502
11. Remsik AB, Williams Jr L, Gjini K, Dodd K, Thoma J, Jacobson T, *et al*. Ipsilesional Mu rhythm desynchronization and changes in motor behavior following post stroke BCI intervention for motor rehabilitation. *Frontiers in Neuroscience*. 2019;13:53
12. Yassin M, Takamjani IE, Talebian S, Maroufi N, Sarrafzadeh J, Ahmadi A, *et al*. Preparatory Brain Activity and Anticipatory Postural Control in cervical myofascial trigger point. *Journal of Modern Rehabilitation*. 2022
13. Swart T, Chisholm K, Brown P. *Neuroscience for leadership: Harnessing the brain gain advantage*: Springer; 2015.
14. Pellegrino G, Maran M, Turco C, Weis L, Di Pino G, Piccione F, *et al*. Bilateral transcranial direct current stimulation reshapes resting-state brain networks: a magnetoencephalography assessment. *Neural Plasticity*. 2018;2018
15. Mondini V, Mangia AL, Cappello A. Single-session tDCS over the dominant hemisphere affects contralateral spectral EEG power, but does not enhance neurofeedback-guided event-related desynchronization of the non-dominant hemisphere's sensorimotor rhythm. *PloS one*. 2018;13(3):e0193004
16. Baharlouei H, Goosheh M, Moore M, Ramezani Ahmadi AH, Yassin M, Jaberzadeh S. The effect of transcranial direct current stimulation on rating of perceived exertion: A systematic review of the literature. *Psychophysiology*. 2024:e14520.[10.1111/psyp.14520]
17. Group MoSRW. VA/DOD Clinical practice guideline for the management of stroke rehabilitation. *Journal of rehabilitation research and development*. 2010;47(9):1-43
18. Rossiter HE, Boudrias M-H, Ward NS. Do movement-related beta oscillations change after stroke? *Journal of neurophysiology*. 2014;112(9):2053-8
19. Cha T-H, Hwang H-S. Rehabilitation interventions combined with noninvasive brain stimulation on upper limb motor function in stroke patients. *Brain Sciences*. 2022;12(8):994
20. Ho K-A, Taylor JL, Chew T, Gálvez V, Alonzo A, Bai S, *et al*. The effect of transcranial direct current stimulation (tDCS) electrode size and current intensity on motor cortical excitability: evidence from single and repeated sessions. *Brain stimulation*. 2016;9(1):1-7

21. Afsharipor M, Hejazi-Shirmard M, Irani A, Kalantari M, Baghban AA. Combined Transcranial Direct Current Stimulation with Occupational Therapy Improves Activities of Daily Living in Traumatic Brain Injuries: A Pilot Randomized Clinical Trial. *Journal of Modern Rehabilitation*. 2024;18(1):114-20
22. da Silva ESM, Ocamoto GN, Santos-Maia GLd, de Fatima Carreira Moreira Padovez R, Trevisan C, de Noronha MA, *et al.* The effect of priming on outcomes of task-oriented training for the upper extremity in chronic stroke: a systematic review and meta-analysis. *Neurorehabilitation and Neural Repair*. 2020;34(6):479-504
23. Snyder DB, Schmit BD, Hyngstrom AS, Beardsley SA. Electroencephalography resting-state networks in people with Stroke. *Brain and Behavior*. 2021;11(5):e02097
24. Boonstra TW, Nikolin S, Meisener A-C, Martin DM, Loo CK. Change in mean frequency of resting-state electroencephalography after transcranial direct current stimulation. *Frontiers in human neuroscience*. 2016;10:270
25. Hu J, Li C, Hua Y, Zhang B, Gao B-Y, Liu P-L, *et al.* Constrained-induced movement therapy promotes motor function recovery by enhancing the remodeling of ipsilesional corticospinal tract in rats after stroke. *Brain research*. 2019;1708:27-35
26. Hu M, Ji F, Lu Z, Huang W, Khosrowabadi R, Zhao L, *et al.*, editors. Differential amplitude of low-frequency fluctuations in brain networks after BCI training with and without tDCS in stroke. 2018 40th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC); 2018: IEEE.
27. Cunningham DA, Machado A, Janini D, Varnerin N, Bonnett C, Yue G, *et al.* Assessment of inter-hemispheric imbalance using imaging and noninvasive brain stimulation in patients with chronic stroke. *Archives of physical medicine and rehabilitation*. 2015;96(4):S94-S103
28. Van Wijngaarden JB, Zucca R, Finnigan S, Verschure PF. The impact of cortical lesions on thalamo-cortical network dynamics after acute ischaemic stroke: a combined experimental and theoretical study. *PLoS computational biology*. 2016;12(8):e1005048
29. Bao S-C, Wong W-W, Leung TWH, Tong K-Y. Cortico-muscular coherence modulated by high-definition transcranial direct current stimulation in people with chronic stroke. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*. 2018;27(2):304-13
30. Jomhour S, Talebian S, Vaez-Mousavi M, Sadjadi-Hazaveh SH. Training Interventions Change Relative Power Spectrum of Alpha After Anterior Cruciate Ligament Deficiency in Athletes. *Journal of Modern Rehabilitation*. 2023
31. Naghdi S, Ansari NN, Mansouri K, Hasson S. A neurophysiological and clinical study of Brunnstrom recovery stages in the upper limb following stroke. *Brain Inj*. 2010;24(11):1372-8.[10.3109/02699052.2010.506860]
32. Kim W-S, Kwon BS, Seo HG, Park J, Paik N-J. Low-frequency repetitive transcranial magnetic stimulation over contralesional motor cortex for motor recovery in subacute ischemic stroke: a randomized sham-controlled trial. *Neurorehabilitation and neural repair*. 2020;34(9):856-67

33. Winstein CJ, Stein J, Arena R, Bates B, Cherney LR, Cramer SC, *et al.* Guidelines for adult stroke rehabilitation and recovery: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2016;47(6):e98-e169
34. Yuvaraj R, Murugappan M, Mohamed Ibrahim N, Iqbal Omar M, Sundaraj K, Mohamad K, *et al.* On the analysis of EEG power, frequency and asymmetry in Parkinson's disease during emotion processing. *Behavioral and Brain Functions*. 2014;10(1):12.[10.1186/1744-9081-10-12]
35. Ulam F, Shelton C, Richards L, Davis L, Hunter B, Fregni F, *et al.* Cumulative effects of transcranial direct current stimulation on EEG oscillations and attention/working memory during subacute neurorehabilitation of traumatic brain injury. *Clinical Neurophysiology*. 2015;126(3):486-96
36. Dodd KC, Nair VA, Prabhakaran V. Role of the contralesional vs. ipsilesional hemisphere in stroke recovery. *Frontiers in human neuroscience*. 2017;11:469
37. Hummel FC, Cohen LG. Non-invasive brain stimulation: a new strategy to improve neurorehabilitation after stroke? *The Lancet Neurology*. 2006;5(8):708-12
38. van der Crujisen J, Dooren RF, Schouten AC, Oostendorp TF, Frens MA, Ribbers GM, *et al.* Addressing the inconsistent electric fields of tDCS by using patient-tailored configurations in chronic stroke: Implications for treatment. *NeuroImage: Clinical*. 2022;36:103178
39. Salazar CA, Feng W, Bonilha L, Kautz S, Jensen JH, George MS, *et al.* Transcranial Direct Current Stimulation for Chronic Stroke: Is Neuroimaging the Answer to the Next Leap Forward? *Journal of Clinical Medicine*. 2023;12(7):2601
40. Wiesman AI, Mills MS, McDermott TJ, Spooner RK, Coolidge NM, Wilson TW. Polarity-dependent modulation of multi-spectral neuronal activity by transcranial direct current stimulation. *Cortex*. 2018;108:222-33
41. McDermott TJ, Wiesman AI, Mills MS, Spooner RK, Coolidge NM, Proskovec AL, *et al.* tDCS modulates behavioral performance and the neural oscillatory dynamics serving visual selective attention. *Human brain mapping*. 2019;40(3):729-40.[10.1002/hbm.24405]
42. Dutta A. Simultaneous functional near-infrared spectroscopy (fNIRS) and electroencephalogram (EEG) to elucidate neurovascular modulation by transcranial electrical stimulation (tES). *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation*. 2021;14(5):1093-4
43. Seibt O, Brunoni AR, Huang Y, Bikson M. The pursuit of DLPFC: non-neuronavigated methods to target the left dorsolateral prefrontal cortex with symmetric bicephalic transcranial direct current stimulation (tDCS). *Brain stimulation*. 2015;8(3):590-602
44. Zakaria H, Valentine O, Mayza A. Analysis of quantitative EEG (QEEG) parameters on the effect of transcranial direct current stimulation (TDCS) on post-stroke patients. *AIP Conference Proceedings*. 2021;2344(1):050001.[10.1063/5.0047216]