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Quantitative EEG Metrics for Determining HD-tDCS Induced Alteration of Brain Activity in Stroke Rehabilitation

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Abstract

High-definition transcranial direct current stimulation (HD-tDCS) is a promising approach for stroke rehabilitation, which may induce functional changes in the cortical sensorimotor areas to facilitate movement recovery. However, it lacks an objective measure that can indicate the effect of HD-tDCS on alteration of brain activity. Quantitative electroencephalography (qEEG) has shown promising results as an indicator of post-stroke functional recovery. Therefore, this study aims to determine whether qEEG metrics could serve as quantitative measures to assess alteration in brain activity induced by HD-tDCS. Resting state EEG was collected from stroke participants before and after (1) anodal HD-tDCS of the lesioned hemisphere, (2) cathodal stimulation of the non-lesioned hemisphere, and (3) sham. The average power spectrum was calculated using the Fast Fourier Transform for frequency bands alpha, beta, delta, and theta. In addition, delta-alpha ratio (DAR), Delta-alpha-beta-theta ratio (DTABR), and directional brain symmetry index (BSI) were also evaluated. We found that both anodal and cathodal stimulation significantly decreased the DAR and BSI over various frequency bands, which are associated with reduced motor impairments and improved nerve conduction velocity from the brain to muscles. This result indicates that qEEG metrics DAR and BSI could be quantitative indicators to assess alteration of brain activity induced by HD-tDCS in stroke rehabilitation. This would allow future development of EEG-based neurofeedback system to guide and evaluate the effect of HD-tDCS on improving movement-related brain function in stroke.

Keywords

stroke, transcranial direct current stimulation, quantitative electroencephalogram (qEEG), delta alpha ratio, delta-theta alpha-beta ratio (DTABR), brain symmetry index

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Introduction

In ischemic stroke, blood flow to the brain is blocked, preventing brain tissue from getting oxygen and nutrients, causing lasting neurological deficits. Of all strokes, 87% are ischemic, with a global prevalence of 68.16 million in 2020 (Tsao et al., 2023). The prevalence of stroke continues to increase each year, with nearly 4% of the adult US population projected to have experienced a stroke by the year 2030 (Tsao et al., 2023). Long-term effects of stroke include cognitive impairment and motor deficits, leading to difficulty with activities of daily living and returning to work (Tsao et al., 2023). Stroke recovery is highly variable since the long-term effect is determined by the site and size of the initial lesion. Specifically, a lesion on the motor or sensory cortices will causes focal damage to the cortices and to their descending pathways (Nudo et al., 1996). Individuals post stroke can experience continued upper extremity motor impairment including hemiparesis, loss of sensation in the extremity, spasticity, and loss of fine motor skills (Winstein et al., 2016).

Neuromodulation is a promising approach for reducing post-stroke motor impairment. Non-invasive brain stimulation technologies, such as transcranial direct current stimulation (tDCS), are safe and easy-to-manage neuromodulation approaches to modulate cortical excitability. Current research suggests that anodal stimulation to the lesioned hemisphere and cathodal stimulation to the non-lesioned hemisphere can improve upper extremity motor function for patients in stroke recovery (Elsner et al., 2017; Santos Ferreira et al., 2019). However, the effect is limited as conventional tDCS uses large sponge electrodes making it difficult to target a specific area of the patient′s brain. Therefore, our research focuses on a targeted high-definition tDCS (HD-tDCS) technique using few small electrodes, navigated by subject-specific MR-based computer simulation (Mackenbach et al., 2020) and verified by TMS localization. This protocol has been shown to have promising results to improve upper limb motor function post stroke and our early phase analysis has been published (Williamson et al., 2023).

One of the most widely used methods to assess motor recovery post intervention are clinical assessments such as the fugl-meyer motor assessment (FMA), the National Institude of Health Stroke Scale (NIHSS), and the modified rankin scale (mRS) (Santisteban et al., 2016). Specifically, the FMA is sensitive to motor gains and has well-established reliability and validity as an indicator of motor impairment throughout stroke recovery (Duncan et al., 1983; Gladstone et al., 2002). However, the FMA is relatively subjective and is an indirect measure of neural deficits (Saes et al., 2019). Therefore, recent studies and review have indicated the benefit of objective measures in conjunction to the FMA to obtain optimal evaluation of the motor state (Boyd et al., 2017; Dahlby et al., 2024; Stinear, 2017; Ueyama et al., 2023). In fact, in a recent Stroke Recovery and Rehabilitation Roundtable (SRRR) task force, they note there is an urgent need for complementary neural biomarkers in addition to clinical assessments to optimize the accuracy of evaluating motor recovery (Boyd et al., 2017). It has not yet established a quantitative measure that evaluates the neuro-effect of HD-tDCS to the brain.

Electroencephalography (EEG) is a non-invasive technique that measures cortical brain activity with a high degree of temporal resolution (Nunez & Srinivasan, 2006). Mathematical analysis of EEG signals yields quantitative EEG metrics (qEEG) that have been studied as a potential indicator of functional impairment following stroke (Finnigan et al., 2004). The level of cortical deficits after stroke may be quantified by resting-state EEG, as altered resting-state cortical activity is associated with motor dysfunction (Guggisberg et al., 2019). In acute phase of stroke, altered slow-frequency oscillations in the delta (1–4 Hz) and theta (4.1–8 Hz) bands of the EEG signal may be linked to the volume of lesion and edema (Harmony et al., 1995). During the recovery, the increase of slow-frequency is likely associated with the decline in neuronal integrity and poor recovery outcomes (Finnigan & Van Putten, 2013; Saes et al., 2021; Thibaut et al., 2017); while the enhancement of fast-frequency oscillations, alpha (8.1–12.5 Hz) and beta (12.6–30 Hz) bands, is often associated with improved motor function post stroke (Olga, 2012; Pichiorri et al., 2018). A ratio of slow and fast oscillation spectral characteristics can be expressed by the Delta/Alpha Ratio (DAR) (Leon-Carrion et al., 2009) and Delta-Theta/Alpha-Beta ratio (DTABR) (Sheorajpanday et al., 2011). Unilateral stroke may also affect the activity of the cortical areas involved through modified spectral power distributions over the hemispheres, resulting in interhemispheric imbalance (Dodd et al., 2017). This likely caused by increased neural activity in the contralesional hemisphere to compensate the functional loss of the lesioned hemisphere (Mohapatra et al., 2016). The hemispheric asymmetry of neural activity can be quantified via the pairwise-derived brain symmetry index (BSI) or the direction BSI (dirBSI) (Finnigan et al., 2007; Saes et al., 2019; van Putten & Tavy, 2004).

These qEEG metrics, when measured early post stroke, have been found to be predictors of future motor neurological deficits (Bentes et al., 2018; Doerrfuss et al., 2020; Finnigan & Van Putten, 2013). In patients with acute middle cerebral artery stroke, frontal lobe DAR assessed within 72 h post-stroke correlated with cognitive function assessed 3.5 months post-stroke (Schleiger et al., 2014). A recent study has shown these changes also occur longitudinally. BSI calculated over delta band was longitudinally associated with FMA and DAR, BSI, BSI over delta and theta were longitudinally associated with NIHSS (Saes et al., 2020). However, it is yet to explore the potential of qEEG parameters as quantitative indicators for evaluating the effectiveness of HD-tDCS on modulating neural activity in the brain and its relationship with motor function

changes. Therefore, the goal of this study was to determine whether qEEG metrics could serve as quantitative measures to assess alteration in brain activity induced by HD-tDCS and are related to improved motor function.

Methods

The human subject study was approved by the internal review board (IRB # 14011 and #12550) of the University of Oklahoma Health Sciences Center and conducted in its entirety in the Neural Control and Rehabilitation Lab within that University.

Power Analysis

A power analysis was performing using commercial software Statistical Analysis Systems (9.4, SAS, Carey, NC, USA). Proc Power was used for a paired t-test for mean difference using the Fugl-Meyer Upper Extremity test as primary outcome measure. Utilizing a normal distribution, with the exact method, a difference in the means of 6 points (which is the minimally clinically significant difference), a standard deviation of 5 points, a power of 0.8 and an alpha = 0.05, the number of participants needed was 10 (Hiragami et al., 2019).

Participants

Fourteen individuals (4 female) provided written consents for the study and were recruited from January 18, 2022, to May 12, 2023. The participants were at least three months post stroke and had an ischemic unilateral, subcortical stroke lesion confirmed by a physician through their most recent clinical or radiological report. The subjects also had paresis confined to one side and capacity of provide informed consent. Exclusion criteria included muscle tone abnormalities and motor or sensory impairment in the unimpaired limb, severe concurrent medical problems (e.g., cardiorespiratory impairment), use of a pacemaker, metal implants in the head, known adverse reaction to TMS and tDCS, and pregnancy. Demographics of participants are provided in Table 1.

Table 1. Stroke Participants Demographics.

Subject ID	Lesion Side	Age	Sex	Time post stroke	FM-UE (Total:66)
1	L	64	M	33 months	8
2	R	72	M	17 months	14
3	L	81	F	14 months	10
4	Both	55	M	6 months	46
5	L	44	M	3 months	26
6	R	62	M	30 months	48
7	L	43	M	87 months	53
8	R	59	M	33 months	46
9	R	65	M	14 months	16
10	L	73	F	92 months	23
11	R	57	F	7 months	15
12	L	67	M	11 months	16
13	R	75	F	5 months	-
14	R	38	M	4 months	38

Baseline Assessment and Subject Selection

One participant (S13) was lost to follow up before the screening visit. The rest of the participants (n = 13) were screened at their baseline using the Fugl-Meyer upper extremity (FM-UE) score [12] and transcranial magnetic stimulation (TMS)-induced motor evoked potentials (MEP), details on these methods can be found in our previous publication (Williamson et al., 2023).

After the baseline assessment, eight of the participants (S2, S3, S5, S9, S10, S11, S12, and S14) met the inclusion/exclusion criteria and within the FM-UE score range (10–40) of a registered pilot clinical trial (ClinicalTrials.gov Identifier: NCT05174949, IRB # 14011). Three of the participants whose FM-UE scored above 40 (S4, S7, and S8) signed an additional consent form through a separate IRB (IRB # 12550) – this allowed mildly impaired participants with the higher FM-UE score to continue with the same procedure for intervention and data collection. S1 and S5 did not meet the criteria to continue. Therefore, a total of eleven participants' data were included in the data analysis study to develop qualitative EEG metrics for determining HD-tDCS induced alteration of brain activity in stroke rehabilitation. Based on our power analysis, the number of participants is sufficient for the proposed analysis.

Study Design

Eleven of the participants (Subject no. 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, and 14) participated in randomized, double-blind (Participant, Outcomes Assessor) cross-over studies (with three visits lasting about 2 h each: (1) anodal high-definition transcranial direct stimulation (HD-tDCS) over the ipsilesional M1, (2) cathodal HD-tDCS over contralesional PMd, (3) sham stimulation, with a two-week washout period to mitigate any carry-over effect of intervention. The cross-over design reduced variability and controlled for unknown confounding factors, as each subject served as their own control. The biostatistician prepared the randomization program and enrolled and consented each patient. The investigator randomized each patient and placed them into one of three intervention sequences based on a computer-generated randomization program, unavailable to the FM-UE evaluators. Detailed methods for subject specific HD-tDCS hot-spot identification, HD-tDCS parameters, and collection of TMS-included motor evoked potentials (MEP) and FM-UE are recorded in our previous analysis (Williamson et al., 2023), with

the calculation of the current density and total charge density explained below.

In HD-tDCS, current density (J) refers to the amount of electric current flowing through a given area on the scalp. This is particularly important in HD-tDCS because the electrodes used are smaller and provide a more focused stimulation compared to conventional tDCS. The formula for current density is:

$$J = \frac{I}{A} \tag{1}$$

where J is the current density (measured in amperes per square meter, A/m²), I is the total current applied by the electrodes (measured in amperes, A), and A is the area of the electrode(s) in contact with the scalp (measured in square meters, m²).

In our study, the area of an electrode is 1 cm² and the applied current is 2 mA at the central electrode and 2 mA/4 = 0.5 mA at four surrounding electrodes. Therefore, the current density at the central electrode is 20 A/m² and at the surrounding electrodes is 5 A/m².

The total charge density (ρ) in HD-tDCS refers to the amount of electric charge distributed within the brain tissue during stimulation. The charge density can be calculated using the following formula:

$$\rho = \frac{Q}{V} \tag{2}$$

where ρ is the total charge density (measured in coulombs per cubic meter, C/m³), Q is the total charge delivered by the stimulation over a period of time (measured in coulombs, C), and V is the volume of brain tissue exposed to the stimulation (measured in cubic meters, m³). The total charge delivered is a product of the current applied and the duration of stimulation. Thus, the charge delivered over time can be calculated as:

$$\rho = I \times t \tag{3}$$

where I is the applied current (in amperes, A) and t is the duration of stimulation (in seconds, s).

To calculate charge density, we then divide the total charge by the volume of brain tissue that is being stimulated. The total charge depends on the geometry of the electrode and the spread of current in the brain tissue, which can be influenced by factors such as the electrode configuration, skin-electrode contact, and tissue conductivity.

Therefore, to precisely calculate the current distribution in a specific brain region, we use the Finite Element Method. This method helps simulate how the current flows in the brain, considering the electrode configuration and the conductivity of different brain tissues. A common software for this purpose is SimNIBS (Hendrickson et al., 2023). SimNIBS helps model the current flow in the brain, taking into account the individual anatomy and electrode setup, providing accurate results for current density and charge distribution. Once the current distribution is calculated, total charge density can be determined by using the formula mentioned above, considering the specific volume and stimulation time.

In our study, we applied 2 mA (0.002 A) for 20 min (1200 s). Thus, the total charge delivered is 0.002 × 1200 = 2.4 C and charge density is 2.4/V (V is the volume of the stimulated area which is subject-specific in this study due as the brain volume varies from subject to subject).

EEG Data Collection

The EEG was recorded before and after HD-tDCS stimulation using the OpenBCI Cyton Daisy Biosensing Boards (OpenBCI, New York, United States) sampled at 125 Hz and established wireless communication with a computer using the BLE (Bluetooth Low Energy) module. Each participant was fitted with a 16 channel OpenBCI Gel Free Electrode Cap. The participants were instructed to sit quietly, eyes closed, in a dark room without noise for the duration of the 3 min. The EEG data was preprocessed using EEGLAB v 2020.0 toolbox in MATLAB (EEGLAB v. 2020.0, Swartz Center for Computational Neuroscience) (Delorme & Makeig, 2004). The data was visually inspected for artifact removal. In some participants' data, some electrodes had "noisy" data, typically due to poor contact between the electrode and the scalp or excessive blinking artifacts. In these cases, these electrodes were removed from the calculation.

Outcome Measures

Spectral Power. The power spectrum was calculated average using the Fast Fourier Transform. From this, mean power was computed across the following frequency bands: delta (1–4 Hz), theta (4.1–8 Hz), alpha (8.1–12.5 Hz), and beta (12.6–30 Hz) (Finnigan et al., 2004) for electrodes in the sensorimotor area (C3/C4, F3/F4, and P3/P4) of the 16 channel EEG.

Delta Alpha Ratio (DAR) and Delta Theta Alpha Beta Ratio (DTABR). DAR is defined as the ratio of delta power to alpha power. DTABR is defined as the ratio of delta and theta power to alpha and beta power. For every channel *c* the power of each frequency band was determined as the mean of the spectral power $P_c f$. With these mean values, DAR and DTABR were calculated using the following formulas (Saes et al., 2019):

$$DAR_c = \frac{(P_c(f))f = 1, \ldots, 4\ Hz}{(P_c(f))f = 8.1, \ldots, 12.5\ Hz} \tag{4}$$

$$DTABR_c = \frac{(P_c(f))f = 1, \ldots, 4\ Hz + (P_c(f))f = 4.1, \ldots, 8\ Hz}{(P_c(f))f = 8.1, \ldots, 12.5\ Hz + (P_c(f))f = 12.6, \ldots, 30\ Hz} \tag{5}$$

These values were averaged all N channels of the sensorimotor areas.

Table 2. Statistical Summary for Individual Power Bands and Power Ratios.

	Alpha	Beta	Delta	Theta	DAR	DTABR
Anodal						
Mean Change	0.50	0.03	−15.9	−0.09	−3.1	−1.1
SD	15.9	4.3	388.7	48.2	4.0	1.1
Cathodal						
Mean Change	−14.3	−5.5	−254.6	−35.3	−4.3	−0.98
SD	31.2	13.0	608.7	81.7	3.0	1.4
Sham						
Mean Change	2.2	0.42	47.6	6.8	−0.17	−0.04
SD	15.9	3.8	339.6	43.1	3.1	1.9
GEE Analysis of Group*Time						
Anode v Sham	$p = 0.655$	$p = 0.818$	$p = 0.694$	$p = 0.727$	$p = 0.026$	$p = 0.104$
Cathodal v Sham	$p = 0.105$	$p = 0.120$	$p = 0.178$	$p = 0.145$	$P = 0.011$	$P = 0.259$

$$DAR = \frac{1}{N}\sum_{1}^{N} DAR_c \tag{6}$$

$$DTABR = \frac{1}{N}\sum_{1}^{N} DTABR_c \tag{7}$$

Brain Symmetric Index (BSI). The BSI was defined as the mean of the absolute value of the difference in mean hemispheric power in the frequency range from 1 to 25 Hz. Traditional BSI does take the direction of the asymmetry into account; therefore, we calculated directional BSI. Directional BSI ranges from −1 to +1. BSI = 0 represents perfect symmetry. Positive values represent higher power in the right hemisphere compared to the left hemisphere, vice versa for negative values. The BSI for each channel pair (*cp*) was calculated using the following formula (Saes et al., 2019).

$$BSI_{cp} = \frac{P_{C_{Right}}(f) - P_{c_{Left}}(f)}{\left[P_{C_{Right}}(f) + P_{c_{Left}}(f)\right]_{f=1,\ldots,25\ Hz}} \tag{8}$$

These values were averaged over N channel pairs of the sensorimotor areas:

$$BSI = \frac{2}{N}\sum_{cp=1}^{N/2} BSI_{cp} \tag{9}$$

BSI was also determined separately for the delta, theta, alpha, and beta frequency bands.

Statistical Analysis

All statistical analysis was completed using commercial software Statistical Analysis Systems (9.4, SAS, Carey, NC, USA) with alpha = 0.05. After checking for and finding no evidence of a non-normal outcome measure distribution using Proc Univariate, the outcome measures were analyzed using generalized estimating equations (GEE) in PROC GENMOD. The fixed factors were group (anodal, cathodal, sham), time (pre and post intervention), with their interaction, and the random factor as subject ID. This technique used correlated linear models for each outcome variable. This method was selected due to its ability to improve the power in small-sample studies in which the temporal spacing of outcomes was the same for each subject. Specifically, we used a modified empirical sandwich covariance matrix estimator within correlation structure selection criteria and test statistics. Use of this estimator can improve the accuracy of selection criteria and increase the degrees of freedom to be used for inference (Westgate & Burchett, 2016). Glimmix was used to determine correlation between Fugl-Meyer Upper Extremity (FM-UE) score and qEEG outcome measures.

DAR Topography

Topography maps of EEG channels were generated using MNE-Python library(Gramfort et al., 2013). Individual component analysis (ICA) was done for all 16 channels, and from 2 to 4 components were selected to filter out the artifacts and identify channels with signals based on the subject's lesion. The data arrays were then aligned so that the lesion side will be on the left, meaning all the arrays with lesion on the right were reversed. Using the selected ICAs, DAR values were plotted for each channel to generate a topography map. This was completed for all participants before and after each visit. The individual maps were averaged together to create mean topography maps before and after stimulations.

Results

Spectral Power and Power Ratios

Table 2 displays the descriptive statistics and results of GEE analysis for individual bands and power ratios DAR and DTABR. No significant differences were found in the analysis of individual power bands alpha, beta, delta, and theta between anode or cathode and sham stimulation (Figure 1). GEE

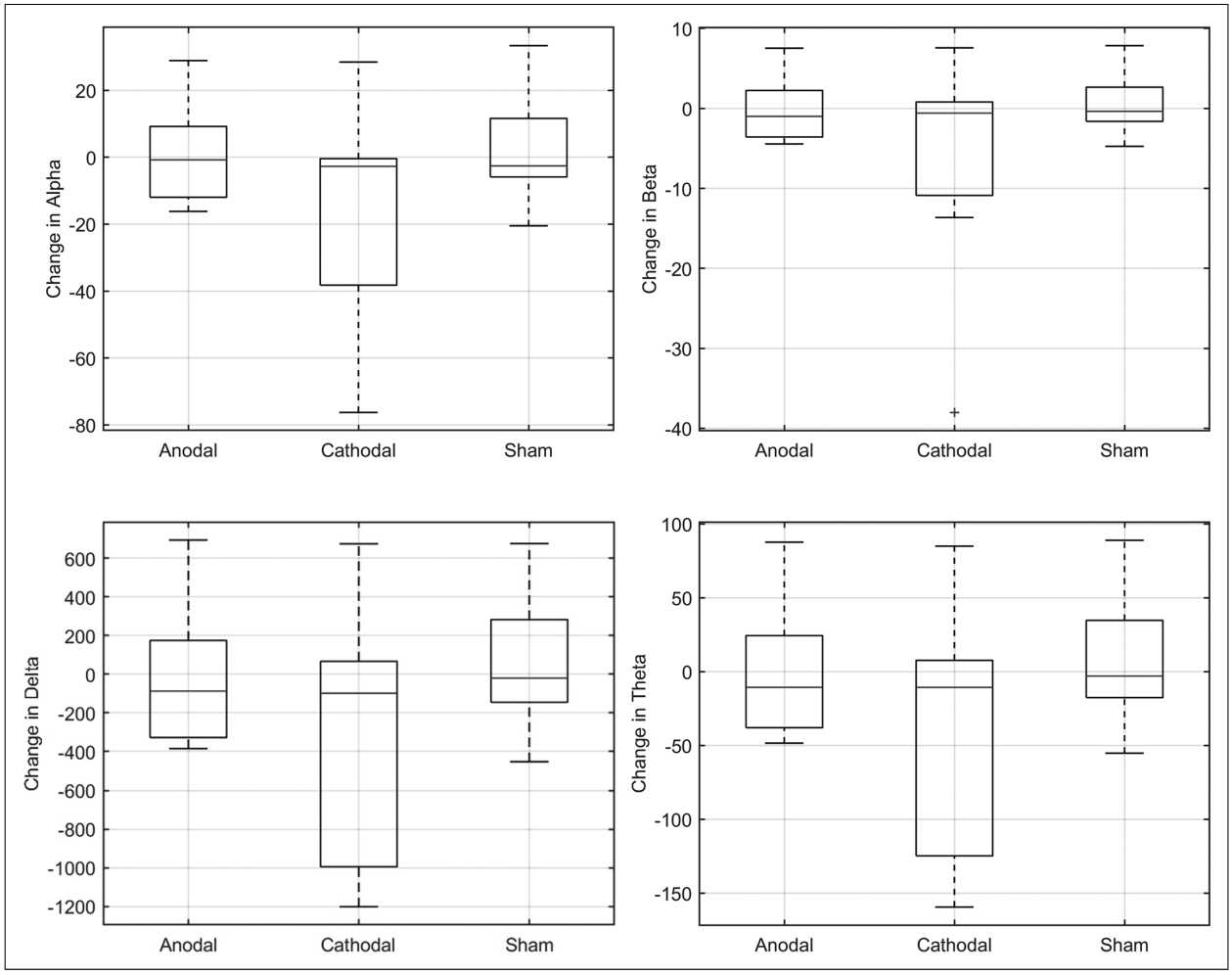

Figure 1. Boxplots of Mean Changes of Individuals Power Bands (Alpha, beta, delta, and Theta) Before and After Stimulation for Anodal, Cathodal, and Sham.

analysis did reveal that anodal stimulation (group*time) altered the DAR significantly as compared to sham stimulation, with a beta estimate of −2.9215, z = −2.23, $p = 0.0260$. Cathode stimulation (group*time) also decreased DAR significantly in comparison to sham stimulation, with a beta estimate of −4.1047, z = −2.55, $p = 0.0108$. For DTABR, while the mean change for cathode (−0.98) and anode (−1.06) are greater than the sham (−0.04) there were no statistically significant changes found between cathode and anode compared to sham over time. This can be visually displayed in Figures 2 and 3. Figure 2 also displays means changes of FM-UE and Latency of M1 MEP for comparison.

Brain Symmetry Index

Table 3 displays the descriptive statistics and results of GEE analysis for BSI and BSI of individual frequency bands. GEE analysis of the BSI revealed that anodal stimulation significantly changed the BSI over time in individual frequency bands, BSI_{Alpha}, BSI_{Beta}, BSI_{Delta}, and BSI_{Theta}, compared to the sham. Cathodal stimulation significantly changed the BSI_{Alpha} over time compared to the sham. There were no significant differences in standard BSI over frequency 1–25 Hz. This is also displayed in Figure 4.

Association Between qEEG Metrics and Motor Impairment

There was no statistically significant correlation found between the initial (pre intervention) qEEG metrics with initial FM-UE scores. There also no statistically significant correlations found in the changes of qEEG metrics (post minus pre intervention) with the changes in FM-UE score. These values are shown in Table 4.

Discussion

These results indicate that DAR significantly decreased after both anodal and cathodal HD-tDCS compared to the sham. No significant differences were observed in

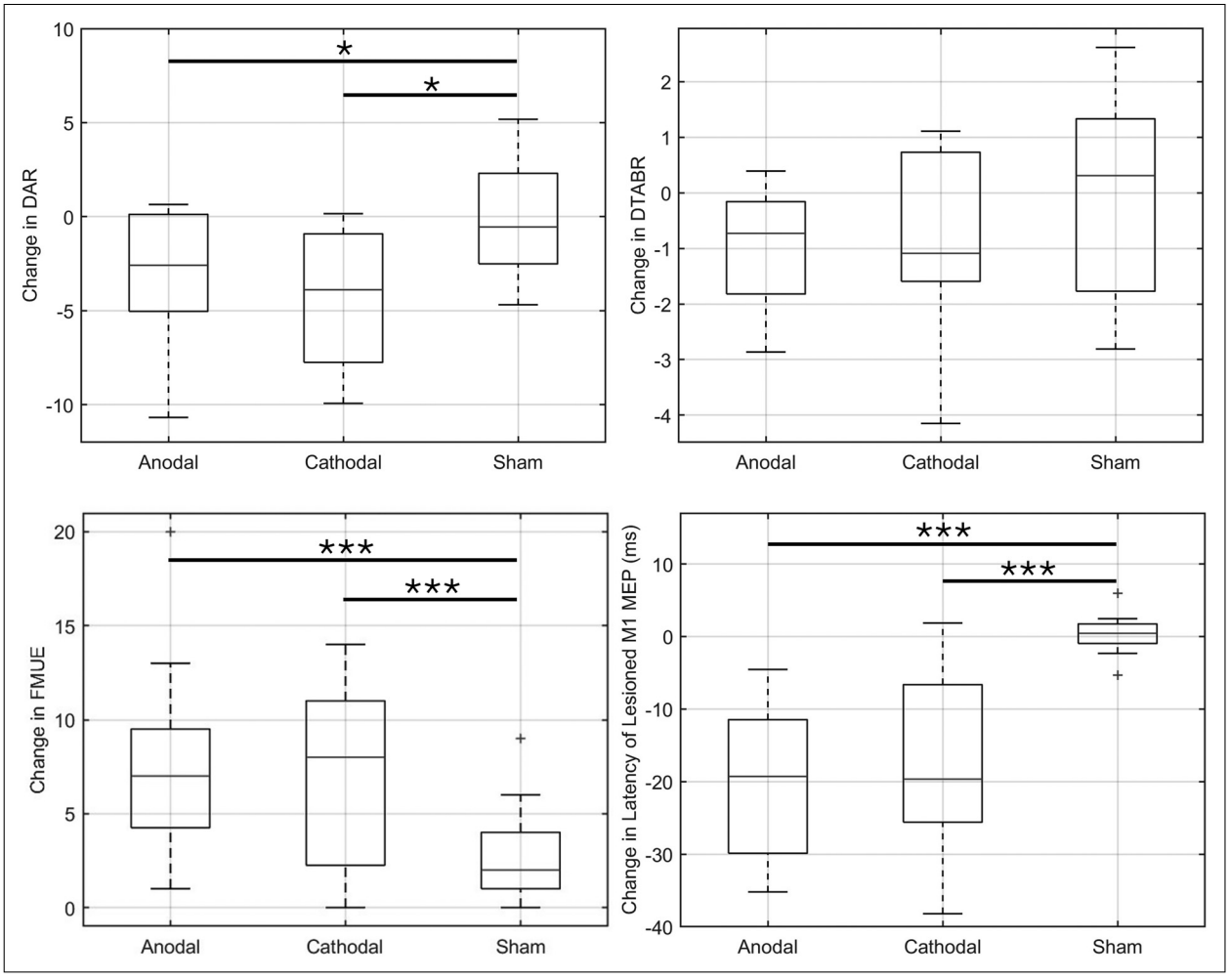

Figure 2. Boxplot of Mean Changes of Power Ratios DAR and DTABR, FM-UE Score, and Latency of Lesioned M1 MEP Before and After Stimulation for Anodal, Cathodal, and Sham. Stars Indicate Statistically Significant Differences between Groups *<0.05, **<0.01, ***<0.001.

individual frequency bands. DAR has consistently been a superior qEEG measure in ischemic stroke identification when analyzed against individual absolute and relative power bands and other power ratios (Claassen et al., 2004; Finnigan et al., 2016; Leon-Carrion et al., 2009). The decrease in DAR reflects an improvement in overall resting state brain function. DAR quantifies the overall signal intensity of abnormal, slow delta activity, relative to that of (healthy) alpha activity (Finnigan & van Putten, 2013). Due to this normalization, this ratio may more sensitively reflect the severity of neurological deficits compared to the individual spectral components (Saes et al., 2021). The mechanism behind the change in DAR may be related to the interaction between thalamocortical circuits and the activity of monoaminergic neurotransmitters. Descending monoaminergic neurotransmitters, norepinephrine and serotonin, have been shown to play a key role in flexion synergy and spasticity expression in chronic hemiparetic stroke (McPherson et al., 2018). The generation of high-frequency waves (alpha) and the reduction of lower-frequency waves (delta) also depend on these neurotransmitters (Hughes & Crunelli, 2005; Saletu et al., 1996). Therefore, DAR may reflect the change in norepinephrine/serotonin level after HD-tDCS stimulation. While mean DTABR was lower after anodal and cathodal stimulation compared to the sham, this difference was not found to be statistically significant. While this ratio has been shown to be associated with post stroke recovery (Vanderschelden et al., 2023), others have argued that theta and beta do not appear to contribute to the predictive capacity of EEG for functional outcome prognosis or monitoring (Finnigan et al., 2004).

Our results also showed that BSI_{Alpha} significantly increased (closer to perfect symmetry) after anodal and cathodal stimulation. BSI_{Beta}, BSI_{Delta}, and BSI_{Theta} also significantly increased after anodal stimulation. A reduction in interhemispheric imbalance is associated with improved

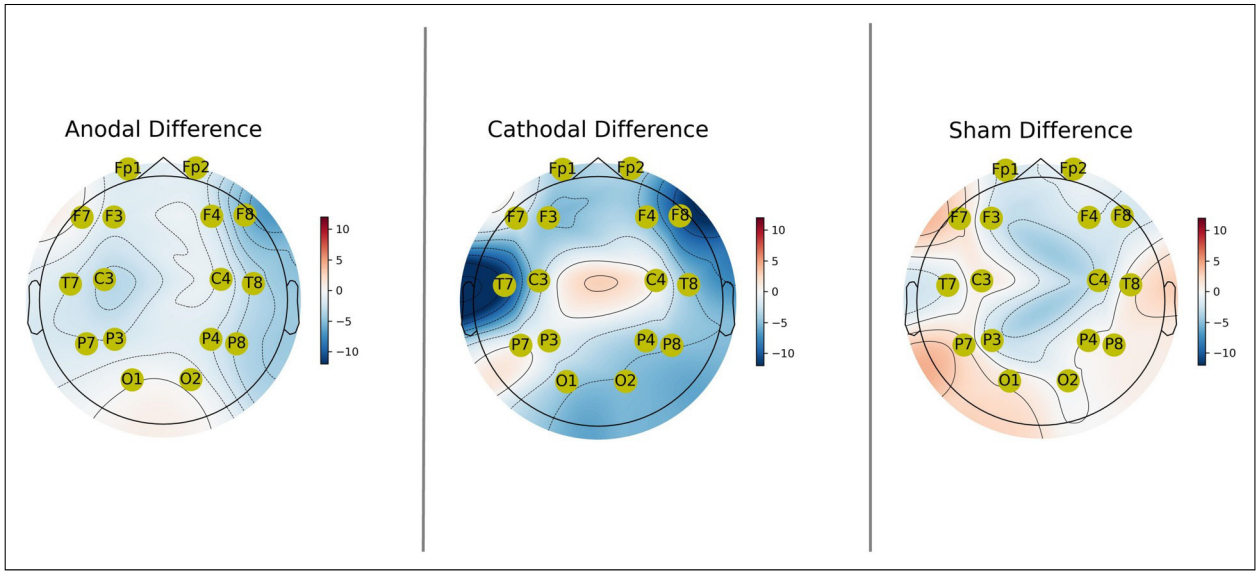

Figure 3. Topography of Difference in DAR Before and After Stimulation for Anodal, Cathodal, and Sham. Data Arrays Aligned to Have Lesion on Left. Blue Indicates Greater Decrease in DAR, Red Indicates Less Decrease in DAR.

Table 3. Statistical Summary for Brain Symmetry Index.

	BSI	BSI_{Alpha}	BSI_{Beta}	BSI_{Delta}	BSI_{Theta}
Anodal					
Mean Change	0.091	0.04	0.03	0.05	0.05
SD	0.35	0.08	0.10	0.16	0.13
Cathodal					
Mean Change	0.099	−0.06	−0.11	−0.12	−0.10
SD	0.39	0.15	0.22	0.25	0.22
Sham					
Mean Change	−0.08	−0.10	−0.12	−0.15	−0.11
SD	0.42	0.18	0.18	0.24	0.21
GEE Analysis of Group*Time					
Anode v Sham	$p = 0.397$	$p = 0.0005$	$p = 0.0091$	$p = 0.0376$	$p = 0.0378$
Cathodal v Sham	$p = 0.233$	$p = 0.0478$	$p = 0.869$	$p = 0.769$	$P = 0.850$

brain function and the reduction of severity of motor impairment post stroke (Berenguer-Rocha et al., 2020). Increase in asymmetry quantified by BSI, has been widely shown in the acute and subacute stages after stroke (Agius Anastasi et al., 2017; Finnigan et al., 2016; Sheorajpanday et al., 2009). However, research in the chronic phase is limited. It has been shown that BSI is correlated with motor impairment in lower frequency bands (Saes et al., 2020, 2021). However, these studies did not include information about individual frequency alpha and beta bands in their analysis. Our results showed that there were no significant correlations between BSI and motor impairment (FM-UE) in individual frequency bands in the chronic phase, as well as changes after anode or cathode HD-tDCS intervention. This research provides new insights into changes in brain symmetry in the chronic phase of stroke. This is important for selecting appropriate parameters to objectively quantify brain stimulation effects. Specifically, these results emphasize the value of taking into account the individual frequency bands when calculating qEEG parameters.

This change in observed EEG wave patterns is consistent with prior studies using conventional anodal tDCS on ipsilesional M1 post stroke (Bernardes et al., 2024). However, prior research using cathodal tDCS over contralesional M1 found no change in EEG metrics post stimulation (Wang et al., 2021). Our results indicate that targeted cathodal HD-tDCS over contralesional PMd does improve DAR in the sensorimotor area. This is likely because the PMd is the origin of cortico-reticular projection whose input to the hyperactive reticulospinal tract is known to be a driven of abnormal muscle synergies and spasticity in chronic stroke (Li, 2017; Li et al., 2019; McPherson et al., 2018). This finding provides further evidence for as contralesional PMd a neural target for cathodal HD-tDCS (Williamson et al., 2023).

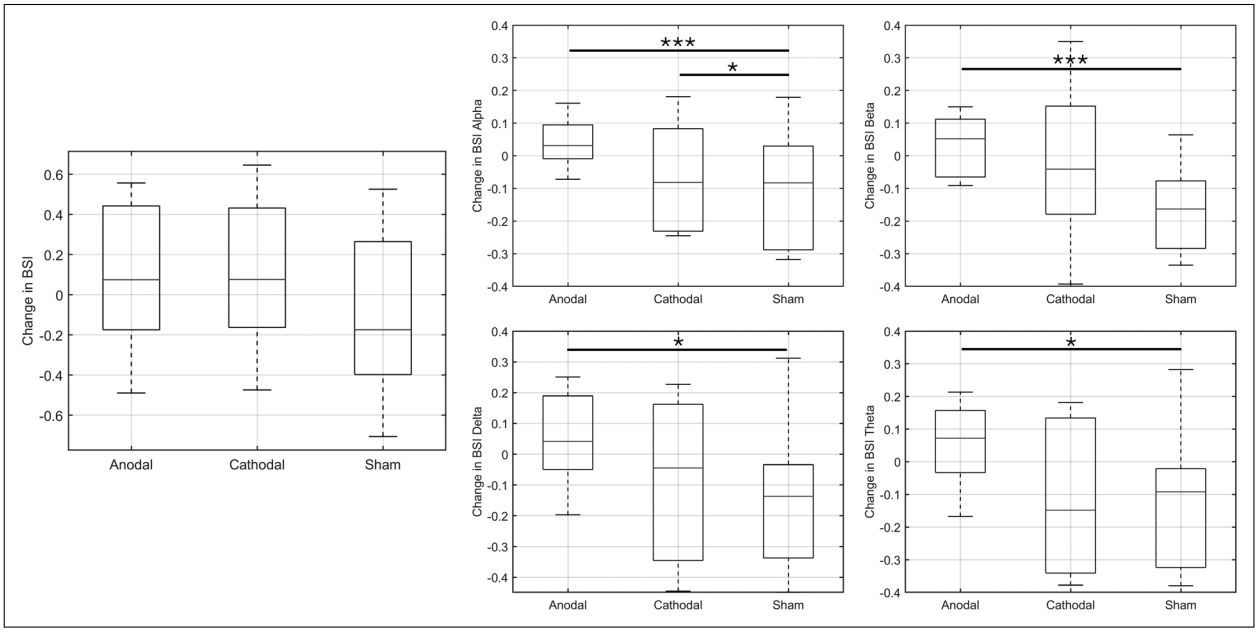

Figure 4. Boxplot of Mean Changes of Directional BSI and BSI Over Alpha, Beta, Delta, and Theta Frequency Bands. Stars Indicate Statistically Significant Differences Between Groups *<0.05, **<0.01, ***<0.001.

Table 4. Correlations Between Fugl-Meyer Upper Extremity Score with qEEG Metrics for Initial Values and Changes After Stimulations.

	Initial		Change after Anodal		Change after Cathodal	
Independent variable	R	*p* value	R	*p* value	R	*p* value
Spectral Power						
Alpha	−0.022	0.953	−0.008	0.984	−0.013	0.971
Beta	−0.101	0.782	−0.031	0.938	0.024	0.948
Delta	0.080	0.826	−0.040	0.918	−0.025	0.946
Theta	0.049	0.893	−0.033	0.933	−0.020	0.955
Power Ratios						
DAR	−0.011	0.976	0.326	0.392	0.046	0.899
DTABR	−0.064	0.861	0.421	0.259	0.130	0.721
BSI						
BSI	0.372	0.289	0.121	0.756	0.276	0.441
BSI_{Alpha}	−0.103	0.777	−0.050	0.899	0.178	0.623
BSI_{Beta}	−0.035	0.924	0.100	0.798	0.149	0.681
BSI_{Delta}	−0.008	0.982	0.405	0.279	0.093	0.798
BSI_{Theta}	−0.042	0.908	0.285	0.457	0.099	0.785

Additionally, this study emphasizes the use of HD-tDCS as compared to conventional tDCS. Conventional tDCS has much lower current density than HD-tDCS which likely limited its effectiveness. A recent phase II, multicenter clinical trial found that increasing the dosage to 4 mA and 30 min stimulation in the conventional tDCS did not improve its effectiveness as compared to 2 mA stimulation, as well as sham stimulation (Schlaug et al., 2025). This is likely because that a conventional tDCS uses a large size sponge electrode which results in a low current density (0.114 mA/cm²). It has been suggested to increase current density by reducing the electrode size, which is exactly what we did in this study using the HD-tDCS. With the 2-mA dosage in our proposed HD-tDCS setup, the current density at the central electrode is 20 A/m² and at the surrounding electrodes is 5 A/m². Furthermore, a previous study shows that 20 min of tDCS can effectively change the cortical excitability while 30 min of tDCS did not improve the outcome (Vignaud et al., 2018). Increasing the stimulation time from 20 min to 30 min is not recommended, thus, we used 20 min in this study.

Identifying objective parameters that can measure and predict recovery after stroke is useful in creating individualized rehabilitation. In the case of non-invasive brain stimulation, stimulation location, current, and time can be optimized with an online real-time HD-tDCS-EEG

procedure. qEEG biomarkers, DAR or BSI could be used to guide a tailored intervention to improve outcomes. The use of qEEG metrics as a measure of stroke recovery for HD-tDCS is also important in the assessment of severely impaired post stroke individuals who cannot perform functional movement tasks, as well as in individuals in the acute/subacute phases of recovery from a stroke whose movement ability is still limited or absent. Being able to track recovery without voluntary movement of the paretic arm may also prevent "over-exerting" a more impaired individual or an acute individual while performing motor assessments or strenuous non-targeted rehabilitative interventions.

Study Limitations

This proof-of-concept study involved a few stroke subjects in the sub-acute/chronic phase post stroke. Therefore, future work involves increasing the sample size and including acute stroke participants to observe the effects in this phase. An additional aspect to consider is accounting for infarction volume and location (cortical vs. subcortical) to compare the responses. Furthermore, while others have reported correlations between qEEG metrics and FM-UE scores (Agius Anastasi et al., 2017; Bentes et al., 2018), we did not observe this in our result. Without clear functional relevance, it is difficult to make conclusions for clinical use. It is suggested to increase the sample size to observe if this changes the significance of the correlation.

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Declaration of Conflicting Interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: The authors report that this research was conducted in the absence of any known commercial or financial relationships that could cause potential conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author.

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