Underpinning The Neurological Source of Executive Function Following Cross Hemispheric tDCS Stimulation

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Highlights

- Bilateral tDCS (F3/F4) influenced cortical regions responsible for executive functions, including working memory and interference control or attention
- Multiple sessions of bilateral tDCS stimulation resulted in increases in theta, alpha, and beta-band activity in the DLPFC, cingulate and parietal cortex respectively
- Findings provide evidence for the use of tDCS to augment executive functions.

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Abstract

Transcranial direct current stimulation (tDCS) is a promising technique for enhancement of executive functions in healthy as well as neurologically disturbed patients. However, the evidence regarding the neuropsychological and behavioral change with neurophysiological shifts as well as the mechanism of tDCS action as evidenced by activation of neuronal sources important for executive functions have remained unaddressed. The study thereby endeavors to (1) determine the neuropsychological, behavioral, and neurophysiological change induced with five sessions of bilateral tDCS stimulation and (2) identify putative neuronal sources related to the executive functions responsible for neuropsychological and behavioral change. For this single blinded study, a total of 40 healthy participants, randomly allocated to active active (n = 19) or sham (n = 21) groups completed five sessions of 2mA tDCS stimulation administered over Dorso-Lateral Prefrontal Cortex (DLPFC) (F3 as anode, F4 as cathode). Repeated measure analysis was performed on neuropsychological (Everyday Memory Questionnaire and Mindful Attention Awareness Scale), and behavioral assessment (n-Back and Stroop tests) to investigate within and between group differences. Pre and post neurophysiological (Electroencephalogram) results showed that bilateral tDCS stimulation activates cortical regions responsible for executive functions including updation (working memory) and inhibition (interference control or attention). Multiple sessions of bilateral tDCS stimulation results in a significant increase in theta, alpha, and beta-band activity in the DLPFC, cingulate and parietal cortex. This study provides evidence that tDCS can be used for performance enhancement of executive functions in able-bodied people.

Keywords

tDCS, executive function, working memory, inhibition control, sLORETA, EEG, EMQ-R, MAAS

1. Introduction

Executive functions are defined as a set of higher-order cognitive skills that are engaged in directing and coordinating numerous cognitive processes for the purpose of achieving a complex cognitive task (Diamond, 2013a; Huo et al., 2018). Three distinctive core cognitive constructs of executive functions include (i) updating (also called working memory), (ii) interference processing (also called inhibition and sometimes referred to as attention) and (iii) cognitive flexibility (Gunzenhauser and Nückles, 2021; Huo et al., 2018; Miyake et al., 2000a; Pascual et al., 2019). Several cortical regions are involved in the processing and execution of cognitive functions (Bettcher et al., 2016). The frontal region and its interaction with the parietal area are considered vital for executive functions (Nowrangi et al., 2014).

Transcranial Direct Current Stimulation (tDCS) is an effective neuromodulation tool to improve executive functions in both healthy as well as patient populations (Boggio et al., 2012; Bystad et al., 2020; Manenti et al., 2013; Siegert et al., 2021). It delivers low-intensity short duration direct current to induce cortical changes represented by excitation or inhibition of cortical neurons (Batsikadze et al., 2013; Been et al., 2007). Results from the literature suggest that the effect of tDCS varies with polarity, montage, duration, and intensity of stimulation (Nasseri et al., 2015; Nitsche et al., 2003; Nitsche and Paulus, 2000). Anodal tDCS stimulation augments cortical excitation by altering a membrane-resting potential in contrast to cathodal stimulation which inhibits the neuronal excitation (Galea et al., 2009; Lang et al., 2005; Nitsche and Paulus, 2000).

With respect to tDCS montage, both uni- and bilateral montages have been widely used to modulate brain activity. Unilateral tDCS modulates the cortical activity of the Dorso-Lateral Prefrontal Cortex (DLPFC) thereby increasing cognitive performance (Andrews et al., 2011; Baumert et al., 2020; Fregni et al., 2005; Imburgio and Orr, 2018; Karthikeyan et al., 2021). Previous studies demonstrated increased working memory (Idova et al., 2017; Nikolin et al., 2015; Schwippel et al., 2018), inhibition control (Angius et al., 2019; Soltaninejad et al., 2019), and cognitive switching (Nejati et al., 2020) in response to unilateral anodal tDCS stimulation.

In bilateral (cross-hemispheric) tDCS stimulation, the anode positioned on one hemisphere and cathode over the contralateral hemisphere modulate neuronal functionality (stimulate and inhibit) of the underlying region (Nasseri et al., 2015). Published literature showed that bilateral tDCS produces more profound and long-lasting effect compared to unilateral configuration because of the circulation of electric current in a transverse manner (Caesley et al., 2021; Lindenberg et al., 2016; Sehm et al., 2013; Vines et al., 2008; Waters-Metenier et al., 2014). Previous studies on bilateral tDCS have reported improvement in executive functions, including updating task (Jeon and Han, 2012), interference processing (Andrea M Loftus et al., 2015), task switching (Leite et al., 2013) and risk taking (Boggio et al., 2010; Fecteau et al., 2007). Moreover, bilateral administration of tDCS have been observed to improve updating i.e. working memory of healthy as well as neuropsychiatric patients with digit-span, n-back, and go-no-go tasks (Grigorescu et al., 2020; Hoy et al., 2014; Jeon and Han, 2012). Furthermore, bilateral tDCS stimulation over DLPFC increase inhibitory control (also called interference processing) with Stroop test (Jeon and Han, 2012; Andrea M. Loftus et al., 2015). Analogously, cognitive flexibility assessed with task switching has also been reported to improve with bilateral DLPFC tDCS (Mostafavi et al., 2021).

Although published literature provides evidence that tDCS effectively modulates performance of executive functions, most studies were based on unilateral configuration administering tDCS stimulation to the targeted site only, which limits the effectiveness of tDCS. In addition, most studies, whether single site or bilateral, employed a 10-20 min single session strategy which in turns questions the reliability and efficacy of tDCS treatment (Baumert et al., 2020; Jeon and Han, 2012; Andrea M.

Loftus et al., 2015; Mostafavi et al., 2021; Wang et al., 2021). Some of the studies have employed bilateral tDCS stimulation administered over DLPFC to improve executive functions (Boggio et al., 2010; Fecteau et al., 2007; Grigorescu et al., 2020; Hoy et al., 2014; Jeon and Han, 2012; Leite et al., 2013; Andrea M Loftus et al., 2015; Andrea M. Loftus et al., 2015; Mostafavi et al., 2021) but the neuronal sources responsible for inducing changes for improving the performance of the core components of executive functions have not been reported.

The current study therefore aims to (i) identify the neuropsychological, behavioral and neurophysiological effect of multi session bilateral tDCS administration over DLPFC on the core components of executive function including working memory and interference processing (ii) to identify the putative brain sources responsible for executive functions of working memory and inhibition.

2. Methodology

2.1 Participants

A total of forty healthy volunteers (22 males and 18 females; min 20, max 30 years; mean ±std 22±1.5) were recruited for this single blinded study. The recruited participants were randomly allocated to active (n = 19) and sham (n = 21) group. Participants with self-reported history of neurological illness and psychiatric disorders were excluded from the study. Participants under the effect of analgesics, and antihypertensives were also excluded. The study was approved by the Ethical Review Committee of NED University of Engineering and Technology. All participants signed the informed consent prior to taking part in the study. All the participants completed the experimental protocol indicating no drop-out.

2.2 Procedure

In order to evaluate the efficacy of tDCS treatment on executive functions on attention and working memory, participants completed pre and post intervention neuropsychological, behavioral, and neurophysiological assessments as illustrated in Figure1. A 30 min long tDCS sessions were performed over five consecutive days. A stimulation intensity of 2mA was administered over the DLPFC to the active group, whereas for the sham group the tDCS device was turned on for the initial 30 seconds only. The participants were pseudo-randomly assigned to one of the two groups and were blinded to the stimulation condition. EEG was recorded prior to the first tDCS session and at the end of the last tDCS session in addition to the neuropsychological and behavioral assessments. Participants completed the following task in the listed order (Figure 1) (i) Pre intervention test (1) Baseline EEG (2) Neuropsychological Assessment (Everyday Memory Questionnaire (EMQ-R) and Mindful Attention Awareness Scale (MAAS)) (3) Behavioral Assessment (n-back and Stroop test) (ii) tDCS stimulation (active or sham) (iii) Post intervention test (1) EEG (2) Neuropsychological Assessment (EMQ-R and MAAS) (3) Behavioral Assessment (n-back and Stroop test)

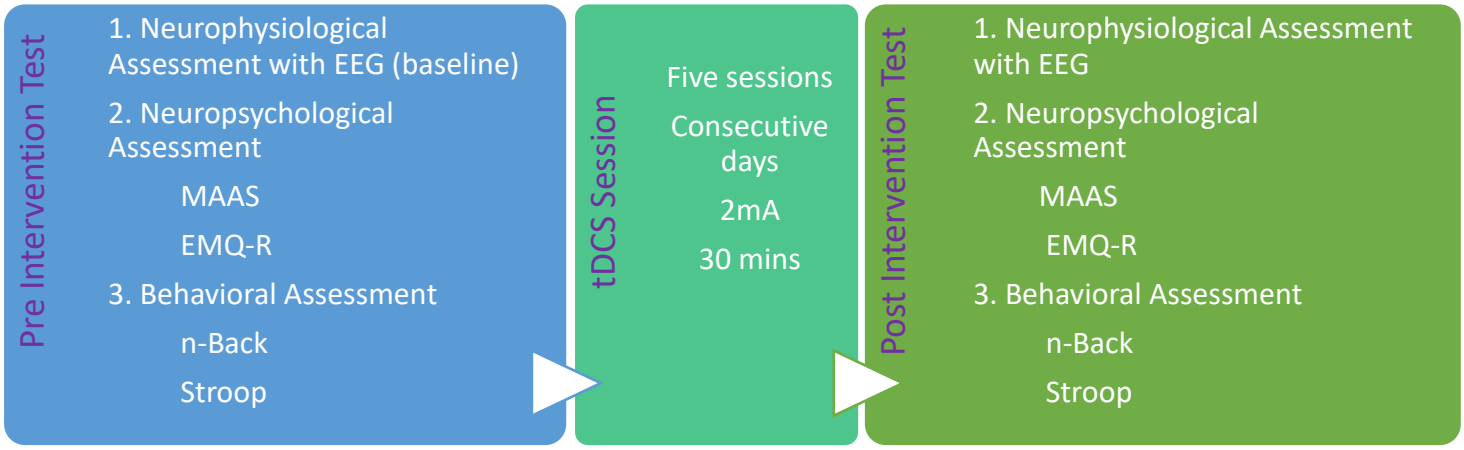


Fig 1: Experimental protocol for the active and sham groups. Acronyms: electroencephalogram (EEG), Mindful Attention Awareness Scale (MAAS), Everyday memory questionnaire (EMQ-R), Transcranial Direct Current Stimulation (tDCS)

2.3 Neuropsychological Assessment

2.3.1 Mindful Attention Awareness:

A widely used self-reported generic measure of mindfulness, the 15-item MAAS questionnaire, was employed to evaluate mindfulness as present-centered attention-awareness in daily life, a state that differs from person to person and a feature that can be fostered via practice (Brown and Ryan, 2003). The MAAS questionnaire evaluates mindfulness by focusing on the attention and awareness of the current events. Each item of the MAAS questionnaire is rated on a six-point Likert scale. Higher scores reflect a higher level of mindfulness.

2.3.2 Everyday Memory Questionnaire:

A reliable subjective measure of memory failure in activities of daily living was accessed using a 13-item EMQ-R (Royle and Lincoln, 2008). Each item is rated on a scale of 0-4. All the 13-items are summed up to determine everyday memory failure. The 13 item of EMQ-R scored on a scale of 0 - 4 indicated that the score can range from 0(min) - 52(max). Higher scores reflect a greater presence of everyday memory problems.

2.4 Behavioral Assessment

2.4.1 n-Back Test:

The 3-back task served as a behavioral measure to evaluate the working memory. The set of stimulus for 3-back task comprised of 15 letters (A,B,C,D,E,H,I,K,L,M,O,P,R,S, and T). Each of the letter stimuli was randomly presented in the center of the screen on a black background in Arial font size 24. Each participant was presented with 20 trials. The interval between the trials was 2000ms in which participants were asked to enter the response of M representing “Memory” if the letter was presented 3 trials back and N indicating “No” in case the appeared letter does not match with the stimuli presented prior to the 3 trials. Each correct and incorrect response was marked as “1” and “0” respectively. The scores of each trial were summed up to provide the total score. The maximum score that could be obtained was 20. The working memory performance was expressed as a percentage by dividing the score of correct responses with the maximum score and multiplying by 100.

2.4.2 Stroop Test:

Behavioral measure of Stroop task was administered for the purpose of evaluating interference processing. A string of a consistent and inconsistent color word was presented on the screen as a stimulus. The stimuli for the Stroop task comprise of four-color words (red, blue, green, and yellow) presented in different print colors in Arial font of size 24. The participants were asked to press the initial of the print color instead of the word meaning. A total of 40 stimuli were presented to participants. The stimuli stayed on the computer screen for 1000ms, and the participants were then allowed to respond within 2000ms. Each correct and incorrect response was marked as "1" and "0" respectively. The scores of each trial were summed up to provide the total score. The maximum score that could be obtained was 40. The Stroop test performance was expressed as a percentage by dividing the score of correct responses with the maximum score and multiplying by 100.

2.5 Transcranial Direct Current Stimulation

Stimulation current was applied using a constant current stimulator (The Brain Driver, Chicago, IL, USA). The tDCS device used in this study is The Brain Driver v2.1 Chicago, IL, USA. It has been extensively used for research purposes (Hwa Oh and Sang Lee, 2019; J.-E. Kim et al., 2021; S.-H. Kim, 2020; S. H. Kim, 2020; Kim, 2021; Lee, 2021; Sunho, 2020) and have capability to continuously monitor the impedance (The Brain Driver, 2022). A pair of surface electrodes with a surface area of 20 cm2 was employed for the administration of direct current. The surface electrodes were soaked in saline solution to enhance conductivity. The electrodes were placed over DLPFC, which is the preferred brain area for inducing electrical stimulations for executive function enhancement. tDCS stimulation of 2mA was delivered for 30 minutes for the active group and 30 seconds for the sham group with anode positioned over F3 and cathode placed over the F4. The location of F3 and F4 was determined using EEG cap where the distance between nasion-inion and ears comply with a standard 10-20 international EEG electrode placement system. The tDCS device was placed on the table positioned at the back of the participant where they could not see the operating condition (on or off) of the device thereby ensuring their blindness to the condition.

2.6 EEG Acquisition

Brain activity was acquired using Mitsar NVX 52 (Mitsar, Russia) from 31 cortical locations (Fp1, Fpz, Fp2, F7, F3, Fz, F4, F8, FT7, FC3, FCz, FC4, FT8, T3, C3, Cz, C4, T4, TP7, CP3, CPz, CP4, TP8, T5, P3, Pz, P4, T6, O1, Oz, O2) which are in accordance with the standard 10-20 international EEG electrode placement system. The reference electrodes were linked ear reference whereas the ground electrode was positioned at AFz. EEG data was recorded in a well-ventilated and quiet room in both pre and post-states in eyes open condition. The sampling frequency was set at 500 Hz. The impedance of electrodes was kept under 5KΩ. The conductive gel was applied to obtain good conductivity.

2.7 EEG Analysis or Data processing

The acquired EEG data was processed offline using MATLAB (MATLAB 2018). A second order Butterworth bandpass IIR filter was employed to eliminate 50 Hz artifact. Eye blinks and EMG artifacts were discarded manually. The eyes open EEG data was split into 4s long epochs providing a maximum of 30 epochs for 2 min EEG recording of each participant. Epochs contaminated by noise (muscle activity, blinking, eye rolling and other artifacts) were eliminated resulting in a minimum of 25 epochs for each participant. The active group's EEG thereby comprised of a maximum of 1140 epochs (19 participants * 30 epoch = 570, 570 * 2 (in pre and post states) and a minimum of 950 epochs (19 participants * 25 epoch = 475, 475 * 2 (in pre and post states). Whereas the sham group's EEG comprises of a maximum of 1260 epochs (21 participants * 30 epoch = 630 epochs, 630 (in pre and post states) and a minimum of 1050 epochs (21 participants * 25 epoch = 525 epochs, 525 * 2 (in pre and post states). In order to achieve a homogenous baseline, pre tDCS EEG of both active and sham groups were merged resulting in a maximum of 1050 and a minimum of 875 epochs. Following this,

the source localization technique was applied, where epoched EEG of active and of sham group were compared with joined epoched baseline EEG to identify the deep cortical regions affected by tDCS stimulation.

2.8 Source localization using sLORETA

sLORETA software package (R. D. Pascual-Marqui, The KEY Institute for Brain-Mind Research, Zurich, Switzerland) (Pascual-Marqui, 2002) was used to compute the current density for each epoch of the recorded scalp EEG based on 3-D Montreal Neurological Institute (MNI) model. It approximates the electrical activity generated by the intracerebral electrical sources in terms of current source density irrespective of the predefined active sources. The computation of current density expressed in terms of amplitude reflects the standardized electrical activity of each voxel mapped on a realistic head model in 3-D MNI space. These MNI space coordinates is also used to report anatomical locations labelled as Broadman areas (BA).

The sLORETA analysis was performed to estimate the electrical current source in of theta, alpha, and beta frequency bands (theta = 6.5-8 Hz, lower-alpha = 8.5-10 Hz, upper alpha = 10.5-12 Hz, lower beta = 12.5-18 Hz, mid beta = 18.5-21 Hz, and upper beta = 21.5-30 Hz). The alpha band was divided into two and the beta band was divided in three frequency ranges. Previous research reported that modulation of theta, lower alpha and mid beta is linked to attentional processing and interference processing (Braithwaite et al., 2020; Gomez-Pilar et al., 2016; Tafuro et al., 2019; Tseng, 2021; Viviani and Vallesi, 2021). To compute the approximated current source density, all of the epochs of each participant in the pre and post-states of the active and sham tDCS group were exported to sLORETA. Group analysis was performed by averaging current source density across epochs and participants. Baseline EEG of both the active and sham groups was aggregated to serve as a reference with respect to which post EEG changes separately in the active and sham groups were compared.

2.9 sLORETA analysis on BAs corresponding to executive functions

The sLORETA analysis was conducted to determine the effect of 5 days tDCS stimulation on the cortical areas involved in the processing of the two core components of executive functions including working memory and interference control. These cortical regions included the Dorsolateral Prefrontal Cortex (DLPFC), Anterior Prefrontal Cortex (APFC), Ventrolateral Prefrontal Cortex (VLPFC), Cingulate cortex (CC), Posterior Parietal cortex (PPC), Inferior Parietal Cortex (IPC), and Insular Cortex (IC). Moreover, the cortical regions of the Premotor cortex (PMC), Primary motor cortex (M1), and Pre-Supplementary motor cortex (SMC) are also involved in the neuropsychological and behavioral tasks. The corresponding BA of these cortical regions include DLPFC [9, 42], APFC [10, 11], IC [13], VLPFC [44, 45, 47], Cingulate Cortex [23, 24, 25, 29, 30, 31, 32, 33], Posterior Parietal Cortex [5, 7], Inferior Parietal Cortex [39, 40].

2.10 Statistical Analysis

Repeated measures analyses (ANOVA) with assessment times (pre and post) as within subjects variable and stimulation group (active and sham) as between subject variable was performed on SPSS V21 (IBM, 2013) to investigate the main effects of group and assessment time for neuropsychological and behavioral measures. An interaction effect between group and assessment time was also obtained. The F-statistics and p-value from the ANOVA were corrected for multiple comparisons using the Holm–Bonferroni procedure. Effect sizes (eta-squared η2) were calculated, from ANOVA results, as the ratio between effect's sum of squares and the total sum of squares. Moreover, pairwise comparison was also performed to examine within and between group difference for neuropsychological measure of MAAS and EMQ-R and behavioral measures of Stroop and 3-Back.

Unpaired t-tests were used to compare voxel by voxel sLORETA images. It was applied on the pre EEG of both active and sham group to compare for the difference in the baseline EEG prior to the tDCS stimulation. Moreover, to investigate frequency-dependent short-term effects of tDCS treatment on executive functions of working memory and attention or interference processing, the following conditions were compared: (i) Post state of Active group vs Baseline (Pre EEG of Active and Sham) and (ii) Post state of Sham group vs Baseline (Pre EEG of Active and Sham). Correction for multiple comparisons was performed via non-parametric single-threshold test based on randomization and permutation test. The omnibus null hypothesis, (there was no activation anywhere in the brain) was rejected if any voxel value (t-value) exceeds the critical threshold, as determined by 5,000 randomizations (Eugene and Masiak, 2014; Nichols and Holmes, 2001).

The significance level of $p < 0.05$ was set for all statistical tests.

3. Results

3.1 Neuropsychological Assessment

The result of the repeated measure analysis for both the neuropsychological measures of MAAS and EMQ-R indicated that the main effect of groups (MAAS: F= 6.28, p = 0.02, η2= 0.07, EMQ-R: F= 6.74, p = 0.01, η2= 0.07) and assessment times (MAAS: F= 4.95, p = 0.02, η2= 0.06, EMQ-R: F= 5.55, p = 0.02, η2= 0.07) as well as the interaction effect of Group x Assessment time (MAAS: F= 5.68, p = 0.05, η2= 0.07, EMQ-R: F= 5.67, p = 0.05, η2= 0.07) is significant. The effect sizes show a medium effect of Groups, Assessment time, and Groups x Assessment time interaction for MAAS as well as for EMQ-R.

Figure 2 illustrates the tDCS-induced psychometric changes evaluated with EMQ-R and MAAS scales. Between groups analysis revealed a significant effect (p-value = 0.00) in the MAAS and EMQ-R score for the post intervention state. However, no significant effect was observed between groups for the pre intervention state. Within group analysis revealed that the MAAS and EMQ-R score indicated a significant effect (p-value = 0.00) for the active group only. Whereas, no significant effect was found for the sham group.

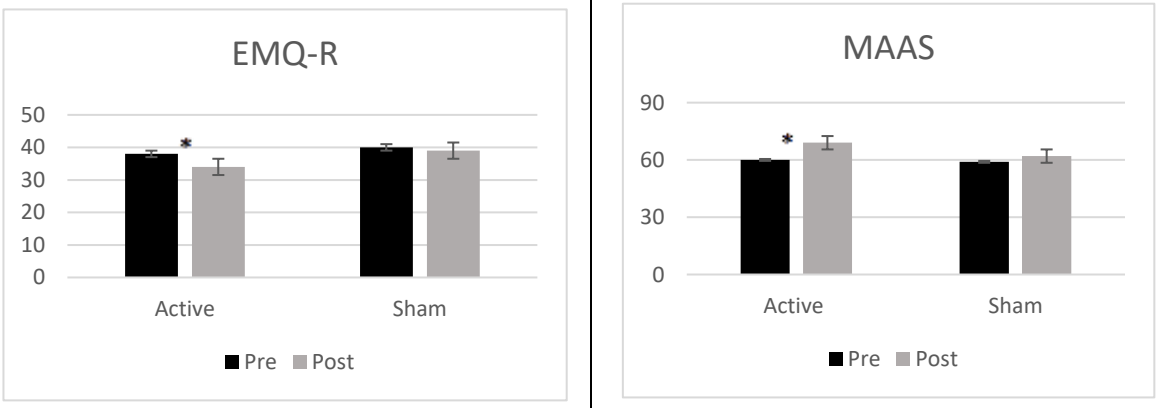


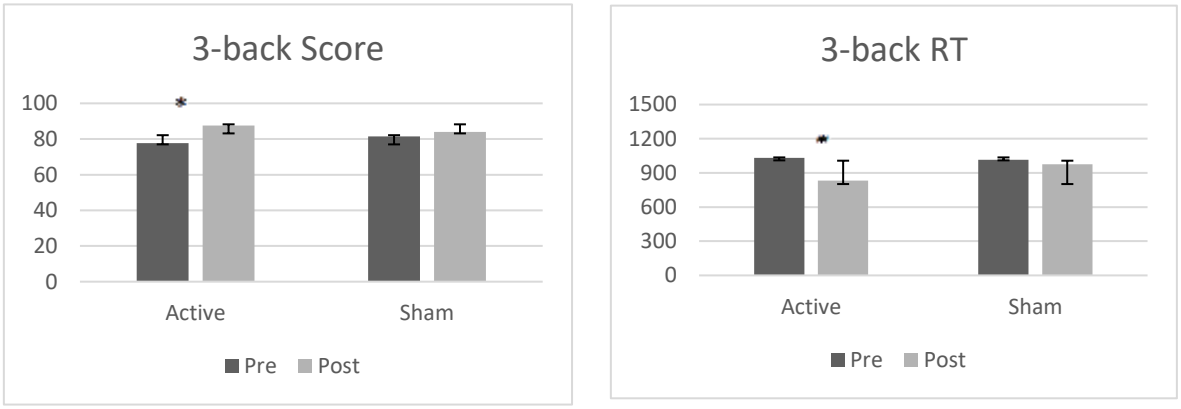
Figure 2 Pre and post comparison of neuropsychological assessment (EMQ-R and MAAS) for active and sham groups.

3.2 Behavioral Assessment

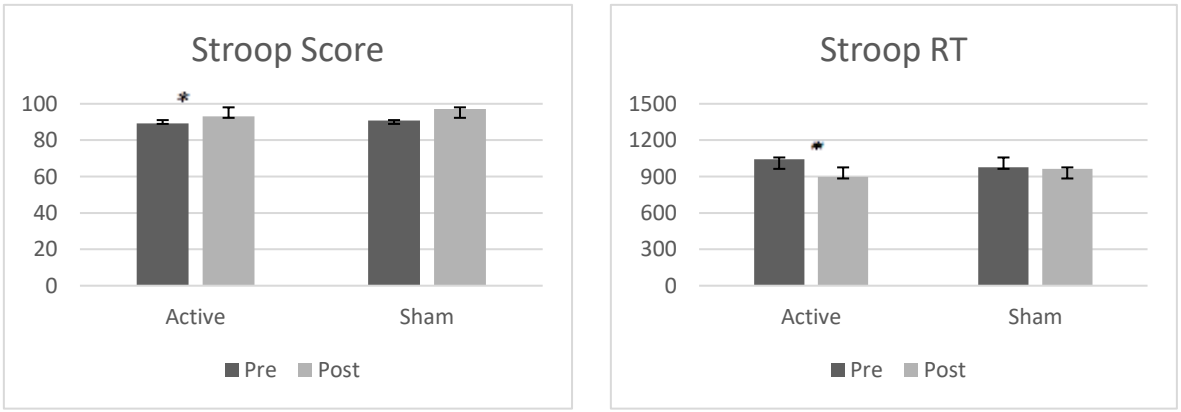
The results of repeated measure analysis for the behavioral measures of the Stroop task and 3-Back task indicated a significant main effect of groups (Stroop Score: F= 4.92, p = 0.02, η^2= 0.06, Stroop Reaction Time: F= 5.93, p = 0.05, η^2= 0.07; 3-Back Score: F= 6.00, p = 0.04, η^2= 0.07, 3-Back Reaction

time: F= 5.80, p = 0.04, η^2= 0.07) and assessment time (Stroop Score: F= 5.69, p = 0.05, η^2= 0.07, Stroop Reaction Time: F= 7.17, p = 0.00, η^2= 0.08; 3-Back Score: F= 6.00, p = 0.04, η^2= 0.07, 3-Back Reaction time: F= 5.30, p = 0.02, η^2= 0.06). In addition to it, a significant interaction effect of Group x Assessment time for both Stroop task (Score: F= 5.93, p = 0.05, η^2= 0.07, Reaction Time: F= 5.83, p = 0.05, η^2= 0.07) and 3-Back (Scores: F= 7.84, p = 0.00, η^2= 0.09, Reaction Time F= 5.48, p = 0.02, η^2= 0.06) was observed. The effect sizes show a medium effect of Groups, Assessment time and Groups x Assessment time interaction for score and reaction time of the Stroop task and 3-Back task.

Figure 3(a) illustrates the working memory performance in terms of accuracy score and reaction time for the 3-back task whereas figure 3(b) depicts the score accuracy and reaction time for the Stroop task. Between group comparison revealed a statistically significant effect on stroop and 3-Back score (p = 0.00) and reaction time (p = 0.00) in post-intervention state. Within group comparison revealed a statistically significant effect on stroop and 3-Back score (p = 0.00) and reaction time (p = 0.00) for the active group only. No significant change was observed for the score and reaction time of stroop and 3-Back task in the pre state for between group comparisons. Furthermore, within group comparison revealed a non-significant effect on score and reaction time of stroop and 3-Back for the sham group.



(a)



(b)

Fig.3 Pre and post comparison of behavioral assessment (3-back and Stroop) for active and sham groups. (a) Comparison of 3-back test score and reaction time in pre and post intervention of active and sham group. (b) Comparison of Stroop test score and reaction time in pre and post intervention of active and sham group. Black bar indicates pre state while grey bar represents post intervention state.

3.3 Neurophysiological Analysis

Theta and lower alpha frequency bands were chosen for this study based on their association with executive function and attentional demands (Braithwaite et al., 2020; Tseng, 2021). Beta is correlated with concentration ("Niedermeyer, Lopes da Silva - Electroencephalography 5th ed - 2005," n.d.) and serves as supporting evidence for the change in theta and lower alpha frequency band. sLORETA results for unpaired t-test revealed that no significant difference ($p > 0.05$) for pre states of both active and sham group for all the frequency bands and for all brain regions. An absence of a significant difference indicated that no sufficient evidence was found to conclude that the baseline EEG between groups were different. Therefore, pre EEG of both active and sham groups was aggregated to increase the sample size and serve as a reference/baseline to compare changes in EEG over time for active and sham groups separately. Figure 4 shows only the significant change for theta, alpha and beta bands observed at BA 9, BA 40 and BA 11 respectively, evident from the brain tomographic maps. In addition to BA 9, BA 40 and BA 11, there were various other brain regions including DLPFC [9, 42], APFC [10, 11], IC [13], VLPFC [44, 45, 47], Cingulate Cortex [23, 24, 25, 29, 30, 31, 32, 33], Posterior Parietal Cortex [5, 7], Inferior Parietal Cortex [39, 40] and Motor Cortex [4, 6, 8] at which significant change was observed. The numbers of voxels (in percentage) showing significant change in various brain regions for theta and alpha bands is presented in table 1 and 2. This approach has been adopted in previous researches (Goel et al., 2013; Hasan et al., 2021; Hassan et al., 2015)

Figure 4 shows brain tomographic maps in theta, lower alpha and mid beta bands for both active and sham group. The magnitude of current density is reflected with a side colored bar where blue color indicate a decrease and red color reflects an increase in magnitude of current density. Subfigures 'a', 'b' and 'c' show increased activity of theta, alpha, and beta bands in areas BA 9 (t-value = 4.84 and p-value < 0.05), BA 40 (t-value = 5.13 and p-value < 0.05), and BA 11 (t-value = 5.26 and p-value < 0.05) respectively in the active group.

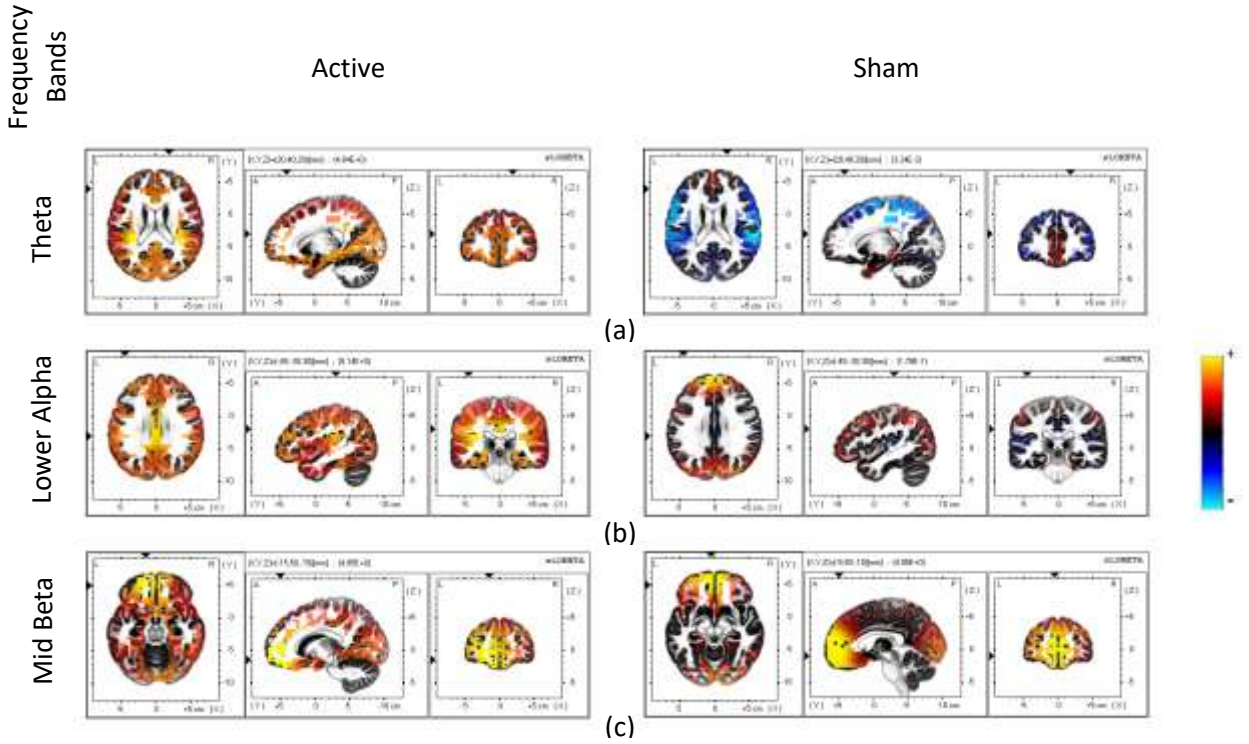


Figure 4 MNI slice view representing modulation of brain activity of active and sham groups. Figure (a) shows Theta activity in BA 9. Figure (b) shows Lower alpha in BA 40. Figure (c) shows Mid beta is reflected in BA 11.

3.4 Changes in the Theta Band for Active and Sham Groups

Table 1 presents the percentage of voxels showing significant change for the theta band for the active and sham groups. In addition to it, the coordinates for which maximum significant change is observed in each Brodmann area is provided. Although tDCS stimulation was administered over the DLPFC a statistically significant neural activity was also noticed in other cortical areas involved in cognitive process of attention or interference processing and working memory for active group only whereas no significant neural activity was noted in the sham group. The number of voxels reflecting a significant increase in theta activity was large in the right hemisphere for active group.

Table 1 Percentage of voxels showing significant change in Brodmann areas related to executive functions in theta band

Cortical areas	Brodmann areas	Voxels (%)		Maximum activation		MNI coordinates with maximum values		Left voxel		Right voxel	
		A	S	A	S	A	S	A	S	A	S
M1	4	40.4	-	3.9	-	(40, -20, 40)	-	**50.8**	-	49.1	-
PMC	6	20.0	-	4.0	-	(40, 0, 30)	-	**51.3**	-	48.6	-
SMC	8	19.5	-	3.8	-	(40, 30, 45)	-	**70.5**	-	29.4	-
DLPFC	9, 46	89.2	-	4.8	-	(20, 35, 20)	-	**50.9**	-	49.0	-
APFC	10, 11	98.9	-	5.2	-	(-10, 25, -10)	-	50.4	-	**49.5**	-
IC	13	81.0	-	6.4	-	(-30, -35, 20)	-	49.7	-	**50.2**	-
VLPFC	44, 45, 47	43.0	-	5.1	-	(-15,25, -15)	-	19.9	-	**80**	-
Cingulate cortex	23,24,25,29, 30,31,32,33	97.0	-	6	-	(-20, -45, 25)	-	59.5	-	**40.3**	-
Posterior parietal cortex	5,7	95.7	-	4.8	-	(-15, -50, 40)	-	53.7	-	**46.2**	-
Inferior parietal cortex	39,40	99.3	-	5.3	-	(-35, -45, 35)	-	46.0	-	**53.9**	-

The Active group is represented as A and the Sham group is represented as S. Bold values in left and right voxels indicate maximum activation

3.5 Changes in the Alpha Band of Active and Sham Groups

Table 2 presents the percentage of voxels showing significant change for the alpha band for the active and sham groups. In addition to it, the coordinates for which maximum significant change is observed in each Brodmann area is provided. For the active group, a statistically significant activation is reflected

in various cortical regions involved in the executive function of attention and working memory and is dominant over the right hemisphere. Whereas no significant change was noticed for the sham group.

Table 2 Percentage of voxels showing significant change in Brodmann areas related to executive functions in alpha band.

Cortical areas	Brodmann areas	Voxels (%)		Maximum activation		MNI coordinates with maximum values		Left voxel		Right voxel	
		A	S	A	S	A	S	A	S	A	S
M1	4	67.8	-	4.5	-	(-40, -20, 40)	-	49.4	-	**50.5**	-
PMC	6	44.0	-	4.8	-	(-35, -10, 35)	-	46.3	-	**53.6**	-
SMC	8	35.6	-	4.0	-	(40, 30, 45)	-	**46.7**	-	53.2	-
DLPFC	9, 46	95.0	-	4.9	-	(-20, 35, 20)	-	52.8	-	**47.1**	-
APFC	10, 11	100	-	5.1	-	(-10, 25, -10)	-	50.9	-	**49.0**	-
IC	13	91.5	-	6.0	-	(-30, -30, 20)	-	51.1	-	**48.8**	-
VLPFC	44, 45, 47	63.2	-	5.0	-	(-20, 30, -5)	-	32.6	-	**67.3**	-
Cingulate cortex	23,24,25,29, 30,31,32,33	99.5	-	5.8	-	(-5, -30, 30)	-	59.1	-	**40.7**	-
Posterior parietal cortex	5,7	46.4	-	4.5	-	(-5, -35, 45)	-	53.8	-	**46.1**	-
Inferior parietal cortex	39,40	95.9	-	5.1	-	(-45, -30, 30)	-	45.0	-	**54.9**	-

The Active group is represented as A and the Sham group is represented as S. Bold values in left and right voxels indicates maximum activation.

4. Discussion

The novelty of this study is that it demonstrates the neuropsychological, behavioral, and neurophysiological change induced as a result of multi-session bilateral tDCS stimulation. Neuropsychological scores assessment such as EMQ-R and MAAS is a clinical practice to evaluate the effect of a tDCS stimulation whereas researchers are more inclined towards the neurophysiological analysis for instance, EEG to comprehend the underlying mechanism inducing the change, in response to a tDCS stimulation. It is thereby essential to investigate both the neuropsychological assessment as well as neurophysiological analysis in addition to the behavioral change induced with tDCS stimulation. Although the effect of bilateral tDCS administered over DLPFC on executive functions has been previously assessed with behavioral measures (Ke et al., 2019; Andrea M Loftus et al., 2015), evidence of the accompanying neuropsychological and neurophysiological changes is scarce. The cortical areas affected by tDCS were previously identified via fMRI (K. Kim et al., 2021; Nissim et al., 2019), but here we also analyze the effect of tDCS on the frequency-dependent oscillatory brain activity. We propose the mechanism of tDCS action by identifying the putative frequency-dependent cortical sources affected by tDCS and responsible for inducing behavioral as well as neuropsychological changes.

Enhancement of executive functions with tDCS has been demonstrated by neurophysiological and behavioral outcomes (Abellaneda-Pérez et al., 2020; Baumert et al., 2020; Ikeda et al., 2019). However, neuropsychological evaluation in addition to behavioral and neuronal change has not been performed with tDCS stimulation. Consistent with previous studies (Ke et al., 2019; Andrea M Loftus et al., 2015), tDCS stimulation in this study caused the reduction of EMQ-R scores and increased MAAS scores for the active tDCS group which is further supported by reduced reaction time along with improved accuracy, measured as a behavioral tasks. Moreover, the increased activation in the frontal and parietal regions further supports the effect of bilateral DLPFC stimulation on executive functions and behavioral self-regulation (Declerck et al., 2006; Hunt et al., 2013). To the best of our knowledge, this is the first study supporting the enhancement of executive functions reflected in neuropsychological, behavioral, and neurophysiological changes following tDCS stimulation.

A further novelty of this study is that it explores dynamic oscillatory changes in the cortical areas related to executive functions following multi-session tDCS. An increase in theta and lower alpha activity observed in this study indicates the improved performance of executive functions with enhanced attention (Dai et al., 2017; Grunwald et al., 2014; Hsieh and Ranganath, 2014; Langer et al., 2013; Sauseng et al., 2010; Tseng, 2021). It is noteworthy that the effect of tDCS is not only evident at the stimulation site but induces a global over-activation of frontal, parietal, and motor cortices. These regions are crucial in cognitive processing and form a "task activation ensemble" for the execution of cognitive tasks (Bettcher et al., 2016; Gonzalez et al., 2014; Hertrich et al., 2021; Levine and Rabbitt, 1999; Moriguchi and Hiraki, 2013; Morton et al., 2009; MW et al., 2013) such as working memory performance and interference processing (AM et al., 2005; Clark et al., 2000a; Diamond, 2013b; Gonzalez et al., 2014; Koechlin et al., 1999; M. et al., 2020; Miyake et al., 2000b; MM et al., 2001; Ramnani and Owen, 2004; Uddin et al., 2017; Y et al., 2003). The effect of tDCS extends beyond the surface of the cortex and activates deeper cortical structures. Increased activation of PFC alongside activation of deeper cortical structures such as VLPFC, CC, and IC reflects the involvement of higher-level cognition and recruitment of centers that control attention, memory retrieval, and response performance (Barbey et al., 2013; Braem et al., 2017; Braver et al., 2001; Carter and van Veen, 2007; Hussey and Novick, 2012; Jalalvandi et al., 2020; Jiang et al., 2015; Leh et al., 2009; M. et al., 2020; Roca et al., 2011; Uddin et al., 2017). Hence, an enhanced PFC activity in response to multi-session tDCS is an indication of improved executive functions performance of working memory and inhibition control for the active group. Moreover, increased activation of PPC and IPC is associated with increased visual attention (Coderre and van Heuven, 2013; V and M, 2009), nonlinguistic representation, and maintenance of working memory (Clark et al., 2000b; EK and JD, 2001; M et al., 1995, 2009) as well as with conflict detection and resolution (M et al., 2009). The increased parietal activity thus resulted in improvement in visual attention and working memory which are required in response to letter-related stimuli involved in the n-back and Stroop test performed in this study.

The executive and motor functions are inextricably linked (Stein et al., 2017). The neuroimaging studies have reported an active involvement of the motor cortex in executive functions (Gonzalez et al., 2014; Hanakawa, 2011; M and T, 2009). In accordance with this, the results of this study revealed the activation of the primary, premotor/supplementary and motor cortices. A consequence of these was a reduced reaction time of n-back and Stroop tests for the active group only.

The current study investigated the working memory and interference control – the two core components of executive functions with neuropsychological, behavioral as well as neurophysiological measures. However, it did not investigate the third dimension of executive function i.e., cognitive flexibility (the flexibility to switch attention between the tasks) to obtain a full-frame comprehension of executive control and the source brain regions involved. Moreover, this manuscript endeavours to

identify the neuropsychological, behavioral and neurophysiological effect of five sessions of bilateral tDCS stimulation and to identify putative neuronal sources related to the executive functions responsible for neuropsychological and behavioral change. Results obtained from this study recommends to compute the correlation among questionnaires, experimental tasks, and EEG power. Furthermore, 31 electrodes used in this study could be argued with low spatial resolution of sLORETA as most of the sLORETA studies employ 64 electrodes or more. These 31 electrodes, however, excluded the ground and reference electrodes, which we have used, making a total of 34 electrodes. Previous sLORETA studies have employed 19 electrodes in total, which might be including the consideration of the reference and ground electrodes (Imperatori et al., 2014; Khosropanah et al., 2018; Koberda et al., 2012; Lehmann et al., 2012; Zarabla et al., 2017; Zwoliński et al., 2010). Therefore, the number of electrodes used in this study comply with that used in the former sLORETA literature. However, future studies should aim to include larger number of scalp electrodes to ensure high spatial resolution.

5. Conclusion

This study examines the effect of bilateral tDCS on working memory and interference control via neuropsychological, behavioral, and neurophysiological measures. It provides evidence that the neuropsychological and behavioral changes are associated with the increase in theta, lower-alpha, and mid beta power with maximum activation within DLPFC, CC, and parietal cortex thereby outlining the mechanism of action of tDCS stimulation. Future research is required to explore the effect of tDCS on cognitive flexibility, another key component of executive function, and also to study the long-term effectiveness of tDCS on executive functions.

Declaration of interest

The authors declare that they have no conflict of interest.

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Availability of data and material

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors Contribution

Muhammad Abul Hasan contributed to the study conceptualization, data processing, investigation, writing, resources, data curation, and supervision. Hira Shahid contributed to the study conceptualization, data collection, data processing, formal analysis, investigation, writing—original draft preparation, and visualization. Saad Ahmed Qazi contributed to the study conceptualization, resources, data curation, project administration and funding. Osama Ejaz and Muhammad Danish Mujib contributed to the data collection, data pre-processing and visualization. Aleksandra Vuckovic contributed to the investigation, writing and supervision.

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