Transcranial Direct Current Stimulation of Dorsolateral Prefrontal Cortex in Patients with Obsessive Compulsive Disorder to Improve Decision Making and Reduce Obsession Symptoms

Mehrnaz Yekta [1*], Reza Rostami [1], Elham Fayyaz [2]

1. Department of Psychology, Faculty of Psychology and Education, University of Tehran, Tehran, Iran.
2. Department of Psychology, Faculty of Education and Psychology, Shahid Beheshti University, Tehran, Iran.

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ABSTRACT

Objective: Recent studies on treating obsessive compulsive disorder (OCD) have investigated noninvasive brain stimulation techniques such as transcranial direct current stimulation (tDCS) to improve patients' impaired emotion and cognition. However, such experiments have yielded mixed results, especially with respect to cognition. This study aimed to investigate whether anodal and cathodal tDCS applied over the dorsolateral prefrontal cortex (DLPFC) would improve decision making and reduce obsession symptoms in patients with OCD.

Methods: the current study is analysis of variance. In this regard, 20 patients with obsessive compulsive disorder (n=20) were randomly assigned to receive either experimental (active) or control (sham) tDCS. To measure cognitive functions, the participants underwent a series of decision making neuropsychological tasks; to measure obsession symptoms, the Yale-brown obsessive compulsive and Beck anxiety scale (BAI) were used. The parameters of active tDCS included administration of 2 mA for 20 minutes per day for 15 consecutive days, anode electrode over the right DLPFC (F4), and cathode electrode over the left DLPFC (F3) region.

Results: After 10 sessions of anodal and cathodal tDCS, patients showed significant improvement in decision making tasks. The same results were observed for obsession symptoms.

Conclusion: The data were analyzed by SPSS 18.0.0 software, using analysis of variance methods.This study demonstrated that anodal tDCS over left DLPFC, concurrent with cathodal tDCS over right DLPFC, improved cognitive impairment and reduced obsession symptoms in patients with OCD.

1. Introduction

With a lifetime prevalence of 2%-3%, obsessive compulsive disorder (OCD) is a public health problem (Marazzati, et al 2002). Previous studies have shown that OCD is associated with a variety of cognitive correlates such as ability to think, concentration, making decisions, response inhibition, and cognitive flexibility (Dittrich, 2010; Rubies, 2001; Watkins, 2005). OCD is usually accompanied by alterations of cortical activity, especially in prefrontal areas (Nitsche, Boggio, Fregni, & Pascual-Leone, 2009). The prefrontal cortex (PFC) consisting dorsolateral PFC (DLPFC) and orbitofrontal (OFC) area is involved in obsession psychopathology in terms of cognition and emotion, respectively. Functional imaging as well as lesion and brain stimulation studies, suggest that the DLPFC and OFC are primarily associated with "cognitive" or "executive" functions,

*** Corresponding Author:**
Mehrnaz Yekta, PhD
Address: *No. 5, East Sharifi Alley, Sharifi Sq., Ostad Hasan Bana St., Tehran, Iran.*
Tel: *+98 (912) 6985725*
E-mail: *mehrnaz.yekta@gmail.com*

whereas ventromedial prefrontal cortex (VMPFC) is largely associated with "emotional" or "affective" functions (Page, 2009; Dittrich, 2010), suggesting that cognition and emotion, which are seriously malfunctioned in OCD, are associated with altered cortical activity in the prefrontal cortex.

Evidently, the activity of PFC is pathologically altered in OCD, mostly in the direction of decreased bilateral or predominantly right-sided activity (Matiax-Cols, 2004; Lacerda et al., 2003). Some studies suggest a functional imbalance between right and left DLPFC activities as an important cause of OCD psychopathology (Huijser et al., 2011 et al; Nitsche et al., 2009). It denotes a causal relationship between hemispheric imbalances of function (especially in the PFC) and obsession cognitive and emotional symptoms. In particular, a decrement of cortical activity exists in the right DLPFC, whereas an increment of cortical activity is seen in the left DLPFC (Ruch et al., 1994; MacMaster et al., 2008).

A similar imbalance of function is shown in the activity of the PFC that affects decision making in patients with OCD (Nitsche, Heller, Etienne, & Miller, 2004). Numerous electroencephalography (EEG) and neuroimaging studies have reported lower activity in right PFC compared to left PFC in patients with OCD, indicating hypoactivity in the right DLPFC and hyperactivity in the left DLPFC (Mcmaster et al., 2011). Evidently, this functional imbalance is associated with decision making impairment in patients with OCD (Huijser et al., 2011).

Thus, OCD involves failures in two main inhibitory processes, namely cognitive (responsible for the obsessions) and behavioral (responsible for the compulsions) ones (Chamberlain, 2005). Recent research has supported two cortical–subcortical pathways in OCD pathogenesis: (a) the frontostriatal loop (dorsolateral-caudate–striatum–thalamus) responsible for impairments of behavioral inhibition and (b) the orbitofrontal loop (orbitofrontal, medial prefrontal, and cingulate) responsible for impairments with cognitive inhibitory processes. Several studies suggested certain inter-hemisphere effects. An EEG study (Kuskowski et al., 1993) demonstrated that OCD show lower right hemispheric activation patients compared to healthy control.

Functional neuroimaging studies have focused on the circuit starting from the prefrontal region and continuing through the basal ganglia, particularly the caudate nucleus and thalamus, and ending in the vicinity of the prefrontal region again (Insel, 1992). In structural brain investigations, same neuroanatomical structures associated with this circuit have drawn attention. Consequently, in these imaging investigations, some regions have been established as key brain areas, including the orbitofrontal cortex (OFC), thalamus, caudate nucleus, and anterior cingulate cortex. However, to date, the role of dorsolateral prefrontal cortex (DLPFC) volume has not been evaluated in OCD. The DLPFC is an important section of the prefrontal cortex, associated with executive functions, attention, nonverbal memory, and visuospatial skills, which have been reported to be disabled in OCD.

For example, some investigations have shown that patients with OCD had impaired measures of executive functions (Flor-Henry et al., 1979; Savage et al., 1999), whereas others have demonstrated nonverbal memory deficits (Christensin, 1999; Dirson et al., 1995). Moreover, Russell et al. (2003) examined prefrontal cortex neurochemistry in pediatric patients with OCD and found a significant increase (21% higher) in N-acetylaspartate (NAA) in their left but not right DLPFC compared to control subjects, without any significant differences in choline (Cho) or creatine (Cr) levels. This investigation suggests a neurochemical alteration in the DLPFC in patients with OCD. However, no volumetric study has evaluated that region; hence, we conducted the present study to examine DLPFC volumes in patients with OCD.

Recent studies have highlighted the importance of noninvasive brain stimulation to modulate cortical excitability (Brunoni et al., 2012; Nitsche et al., 2009). The development of noninvasive brain stimulation techniques made it possible to modulate cognitive functions in both healthy subjects and clinical populations (Brunoni et al., 2012; Pereira et al., 2013). Transcranial direct current stimulation (tDCS) is a neurostimulation technique in which a weak direct current, applied on the scalp, reaches the brain and induces shifts in membrane resting potentials (Nitsche et al., 2009), thus modulating cortical excitability. Anodal stimulation increases cortical excitability, whereas cathodal stimulation has the reverse effect (Nitsche & Paulus, 2001). Studies have also demonstrated prolonged after effects of tDCS up to 90 minutes in the human motor cortex (Utz, Dimova, Oppenländer, & Kerkhoff, 2010).

Neuromodulation studies have shown that an increase in excitability of left DLPFC modulates working memory (Boggio, Ferrucci, et al., 2006; Fregni et al., 2005), declarative memory (Javadi & Walsh, 2012), verbal memory and word recognition (Cerruti & Schlaug,

2009; Ferrucci, Mameli, et al., 2008), digit span (Fregni, Boggio, Nitsche, Rigonatti, & Pascual-Leone, 2006), and visual recognition memory (Boggio et al., 2009). Several studies as well as clinical implications have shown that tDCS might modulate cortical excitability in the human motor cortex (Boggio, Castro, et al., 2006; Boggio et al., 2007; Boros, Poreisz, Münchau, Paulus, & Nitsche, 2008), visual cortex (Accornero, Li Voti, La Riccia, & Gregori, 2007; Antal et al., 2004), and parietal cortex (Sparing et al., 2009; Stone & Tesche, 2009; Brunoni et al., 2012). In addition to motor and visual learning tasks, tDCS has been effectively used in memory studies, especially working memory (Boggio, Ferrucci, et al., 2006; Ferrucci, Marceglia, et al., 2008; Fregni et al., 2005; Jo et al., 2009), episodic memory, and declarative memory (Javadi & Walsh, 2012; Marshall, Mölle, Hallschmid, & Born, 2004).

Based on neuroimaging studies suggesting functional asymmetry in bilateral DLPFC in depression and cognitive impairments in OCD, we proposed a specific tDCS montage. Therefore, this study aimed primarily to investigate the effect of tDCS with a specific montage of anodal and cathodal tDCS respectively over the right and left DLPFC, on cognitive improvement, especially decision making, which is the most impaired neuropsychological domain in OCD. We were also interested to see if this tDCS montage could reduce obsession symptoms. The right DLPFC was selected as the main site of anodal stimulation, which is supposed to increase cortical activity in right DLPFC; and the left DLPFC as the main site of cathodal stimulation, to decrease cortical activity in left DLPFC. We propose that this specific design is more helpful in interpreting results, as it is based on a research hypothesis derived from neuropsychological and neuroimaging findings of the PFC, and considers both the left and right DLFPC. Finally, this study aimed to examine decision making aspects, one of the most impaired cognitive domains in OCD; yet to date, no tDCS studies have investigated the effects of brain stimulation on decision making in patients with OCD.

2. Methods

A total of 20 participants, aged 20-45 years, with OCD diagnosis recruited through accidental sampling. The target population was all OCD patients referring at Atieh Clinic in Tehran, Iran and the results will generalized to obsessive compulsive patients. The results were analyses by SPSS 18.0.0 analysis, using analysis of variance. Demographic characteristics are shown in Table 1. Inclusion criteria were as follows: (1) failure in response to antidepressant pharmacotherapy for at least 2 weeks before tDCS sessions; (2) not on antidepressant or other psychotropic medications during the study; (3) moderate to severe obsession compulsion scores on the Yale-brown obsessive compulsive Scale (YBOC); (4) BAI scores of at least 20 (scored by an experienced psychiatrist); and (5) OCD diagnosis based on a clinical interview by an experienced psychiatrist, according to DSM-IV criteria. Patients with schizophrenia, substance use disorders, personality disorders, mental retardation, and other severe medical conditions were excluded. Patients gave their informed consent before participation. Then, they were administered the Yale-brown obsessive compulsive Scale (YBOC) and the Beck anxiety inventory (BAI) test (Beck et al., 1988).

Participants were randomly assigned in two groups (experimental or active tDCS, n=10; control or sham tDCS, n=10). Participants in the active group received one session of 20-minute stimulation per day, for 15 consecutive days. Participants in the control group received sham stimulation, but the stimulator was turned off after 30 seconds of stimulation. Therefore, participants in the control group felt the initial itching sensation but received no current for the rest of the stimulation period. Cognitive functions and mood were assessed before the first tDCS session as baseline, and after the 15th tDCS session for each condition. Subjects in the sham stimulation condition were recruited for other therapeutic protocols by the end of the study.

Direct current generated by an electrical stimulator was bilaterally delivered through a pair of saline soaked surface sponge electrodes. We used the tDCS stimulator Model 101 (TCT Research Limited, Hong Kong, China). Stimulation was applied at an intensity of 2 mA for 20 minutes once a day for 15 consecutive days. The anodal electrode was positioned over area F4 (right DLPFC) according to the 10–20 EEG international system, and the cathode electrode was positioned over F3 (left DLPFC). The electrodes were thick (0.3cm) and placed in rectangular saline-soaked synthetic sponges (surface area of 35cm^2). All patients were blind to the type of tDCS delivered in each session.

Cognitive functions were assessed using the Cambridge neuropsychological test automated battery (CANTAB; CeNeS, Cambridge, UK). CANTAB was designed with a special focus on neuropsychological functions, subserved by frontal lobe regions, such as frontostriatal circuitry, which mediates motor, cognitive, and behavioral functions within the brain (Fray, Robbins, & Sahakian, 1996). This test has been extensively validated for assessing brain–behavior relation-

Table 1. Descriptive statistics of demographic data.

Group	Sample size	Age, Y (mean)	Onset age, Y (mean)	Baseline BAI score (mean)	Baseline YBOC score (mean)
Experimental	10	27.5	19.6	33.20	19.5
Control	10	26.5	23.2	33.80	18.60

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ships and is sensitive to detect brain dysfunctions in the frontal, temporal, and amygdalo-hippocampal regions (Clark, Chamberlain, & Sahakian, 2009; Owen, Sahakian, Semple, Polkey, & Robbins, 1995; Sahakian et al., 1990).

Over the last decade, CANTAB has been used in cognitive studies of both neurodegenerative disorders, such as dementia, Huntington disease (Rahman, Sahakian, Hodges, Rogers, & Robbins, 1999; Sahakian et al., 1990), and psychiatric disorders such as schizophrenia, and bipolar disorder (Egerházi et al., 2013; Levaux et al., 2007; Porter, Gallagher, Thompson, & Young, 2003; Roiser & Sahakian, 2013).

Since CANTAB is sensitive to brain dysfunctions in frontal and temporal regions, it is highly appropriate for assessing cognitive functions, especially in studies involving passage of electrical current on the frontal and temporal regions, by means of bilateral electrodes (Falconer, Cleland, Fielding, & Reid, 2010). Considering that our study involves applying direct current stimulation to the brain, we decided to use this battery. Moreover, as performance on the CANTAB depends on the change in cortical activity and our particular tDCS montage is supposed to modulate prefrontal activity, the CANTAB is precisely useful and sensitive to cortical activity changes. In addition, CANTAB is correlated with traditional and well-validated neuropsychological testing instruments. Practically, CANTAB has highly standardized application, with automated response recording and millisecond precision.

In this study, a 2-test CANTAB battery (15–20 minutes duration), selected from the CANTAB decision making tests was used: CGT, IST. This battery was selected to evaluate decision making in patients with OCD (Kim, et al, 2014). The CGT test assesses decision making by presenting a row of 10 boxes across the top of a screen, some of them are red and some blue. At the bottom of the screen, there are rectangles containing the words 'Red' and 'Blue'. The participant must guess whether a yellow token is hidden in a red or a blue box (Deakin et al., 2004). The likely neural substrate for this task is the orbitofrontal prefrontal cortex.

It lasts about ten 30-minute times and the outputs include risk taking, quality of decision making, deliberation time, risk adjustment, delay aversion, and overall proportion bet. The IST test assesses decision making by presenting with a 5x5 array of grey boxes on the screen, and 2 larger colored panels below these boxes. The participants are instructed to play a game for points, which they can win by making a correct decision about which color is in the majority under the grey boxes. They must touch the grey boxes one at a time, which opens up to reveal one of the two colors shown at the bottom of the screen. Once a box was touched, it would

Table 2. Levene's test for CGT Scores.

Variables	df	f	Sig.
CGT quality of decision making	1	0.01	0.89
CGT deliberation time	1	0.41	0.52
CGT risk taking	1	0.41	0.52
CGT risk adjustment	1	0.56	0.46
CGT delay aversion	1	1.09	0.31
CGT overall proportion bet	1	0.18	0.67

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Table 3. ANCOVA after control of pretest scores.

Variables	df	f	Sig.
CGT quality of decision making	1	26.26	0.01
CGT deliberation time	1	0.56	0.78
CGT risk taking	1	0.56	0.01
CGT risk adjustment	1	17.26	0.01
CGT delay aversion	1	5.61	0.03
CGT overall proportion bet	1	11.58	0.01

remain open. When the participants made their decision about which color is in the majority, they must touch the panel of that color at the bottom of the screen to indicate their choice. After the participants indicated their choice, all the remaining grey boxes on the screen would reveal their colors and a message was displayed to inform the participants whether or not they were correct. The colors change from trial to trial. At the end of a trial, the grey boxes were displayed on the screen again at a speed which depends on how fast the trial was completed, so that there is always at least 30 seconds between trials.

The 8 IST outcome measures cover errors, latency, total correct trials, mean number of boxes opened per trial, and probability of the participant's decision being correct based on the available evidence at the time of the decision.

Obsession compulsion symptoms and anxiety were evaluated using 2 well-known inventories and scales: the BAI and YBOC. The evaluation was made once before the tDCS sessions, and once after 15 sessions of stimulations. The original form of BAI, which is used in this study, is a self-reported 21-question inventory about how the subject has felt in the last week, where each question has 4 answers ranging in intensity. The YBOC has 10 scales which measures the obsession compulsion and its intensity. Both measures are designed for indicating the presence of symptoms in the past days.

We used PASW Statistics 18.0 for data analysis. Our analyses of variance (ANCOVA) met linear assumptions and the Levene's test was used to examine homogeneity of variances. A significance level of $P<0.05$ was used for all statistical comparisons.

3. Results

All subjects tolerated the tDCS treatment well and no adverse effects were reported. The effects of tDCS on the CGT were investigated. Regarding deliberation time, the ANCOVA results showed that there was no significant difference ($F=0.56$, $P>0.05$). The effects of tDCS on IST were investigated. With regard to IST mean box opening latency (win condition), no significant difference was observed ($F=0.97$, $P>0.05$).

Table 4. Levene's test for IST scores.

Variables	df	f	Sig.
IST discrimination errors	1	1.30	0.58
IST sampling errors	1	0.17	0.12
IST mean box opening latency	1	4.28	0.06
IST mean color decision latency	1	2.51	0.13
IST mean P (correct)	1	1.63	0.21
IST mean number of boxes opened per trial	1	1.44	0.24
IST total correct	1	0.08	0.08

Table 5. ANCOVA after control of pretest scores.

Variables	df	f	Sig.
IST discrimination errors	1	6.37	0.02
IST sampling errors	1	6.16	0.02
IST mean box opening latency	1	0.97	0.33
IST mean color decision latency	1	4.78	0.04
IST mean P (correct)	1	5.12	0.03
IST mean number of boxes opened per trial	1	9.914	0.01
IST total correct	1	11.52	0.01

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4. Discussion

This study primarily showed that administration of anodal tDCS over DLPFC for 15 consecutive days improved decision making in patients with OCD. Decision making, in which its function is associated with prefrontal cortex function (Studer et al., 2015; Chan et al., 2014), is impaired in patients with OCD, and some recent studies suggest that decision making is the most impaired cognitive domain in OCD. Evidently, It is due to large alterations in cortical activity of the PFC in patients with OCD (Banca et al., 2014). Therefore, we can expect to observe the improving effect on decision making if we modulate cortical activity of the PFC in patients with OCD. To modulate cortical activity of the PFC, we applied anodal tDCS of the right DLPFC concurrently with cathodal stimulation of the left DLPFC. We used this specific treatment montage according to pathological cortical activity of PFC in patients with OCD. This study also indicated that our specific stimulation montage significantly reduced obsession compulsion symptoms.

There is a functional imbalance between the right and left DLPFC in patients with OCD (Russell et al, 2003; Nitsche et al., 2009). Seemingly, there is a higher than normal cortical activity in the left DLPFC and a lower than normal activity in the right DLPFC, which is responsible for impaired decision making in patients with OCD. A similar imbalance of function is suggested to be associated with negative emotional processing in OCD (Chamberlain, 2005). We modulated this imbalanced activity in the left and right PFC by applying anodal tDCS on the right DLPFC and cathodal tDCS on the left, and observed improved performance in decision making tasks after a 15-session tDCS protocol. In other words, we tried to alter pathologic cortical activity in patients with OCD into normal cortical activity using this specific stimulation montage.

Our study hypothesis is of importance from several aspects. First of all, decision making impairment is one of the most damaged cognitive functions in OCD (Banca et al., 2014). Although numerous studies showed effectiveness of tDCS on executive functions (Boggio, Ferrucci, et al., 2006; Ferrucci, Mameli, et al., 2008; Fregni et al., 2006; Jo et al., 2009), few studies have evaluated decision making using tDCS; and no study has specifically investigated these function in patients with OCD.

Secondly, and more importantly, our study suggests a specific stimulation montage for OCD tDCS studies, based on findings of neuroanatomical and neuroimaging studies. Results of this study suggest that application of anodal tDCS over the right DLPFC concurrently with cathodal tDCS over the left DLPFC can improve decision making in patients with OCD. Previous brain stimulation studies on various neuropsychological patients, especially depressive patients targeted left DLPFC for anodal stimulation, usually did not apply cathodal stimulation on right DLPFC, as a part of treatment protocol.

Although the main purpose of this study was to investigate the effect of transcranial brain stimulation on decision making in patients with OCD, we also observed reduced obsession compulsion scores, which support previous brain stimulation studies of OCD. Both excitability enhancement of the right DLPFC and excitability reduction of the left DLPFC to treat OCD have been studied; however, mechanism of action is certainly not proven (Chamberline, 2004). It is also known that VLPFC is involved in emotional processing, rather than cognitive processing (Marazziti et al., 2010). One explanation from a brain-stimulation mechanism perspective is that, by applying anodal tDCS, we increase cortical activity in the

right DLPFC which is pathologically low in OCD; and by applying cathodal tDCS, we decrease cortical activity in the left DLPFC which is pathologically high in OCD.

Although the results are encouraging, our study had several limitations too. First of all, we did not evaluate the long-term effects of the intervention in terms of follow-up study. Further studies should evaluate decision making improvement after tDCS treatment in fixed intervals. Secondly, although our sample is theoretically representative for a clinical intervention study, a larger sample size is preferred. Our study is a pilot study that has an exploratory nature using small sample. Pilot studies are not adequate to test the clinical efficacy of tDCS for a particular condition for the first time (Brunoni et al., 2012).

Therefore, in spite of promising results, future studies that compare tDCS effect versus other therapies are needed to validate tDCS as an effective treatment. Finally, even though significant effects of tDCS on decision making was observed in patients with OCD, the mechanisms underlying tDCS-induced decision making enhancement still remain unclear and they should be the focus of future controlled studies. Using neuroimaging measures such as functional magnetic resonance imaging, Positron emission tomography, and some measure of neural changes such as event-related potential and quantitative Electroencephalography, would be more beneficial and yield more accurate results.

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