NeuroRegulation

Transcranial Direct Current Stimulation of Dorsolateral Prefrontal Cortex in Major Depression: Improving Visual Working Memory, Reducing Depressive Symptoms

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Abstract

Recent studies on major depression (MD) have used noninvasive brain stimulation techniques such as transcranial direct current stimulation (tDCS) to improve impaired emotion and cognition in MD. However, such experiments have yielded mixed results, specifically with respect to cognition in MD. This study aimed to investigate whether anodal and cathodal tDCS applied over the dorsolateral prefrontal cortex (DLPFC) would significantly improve visual working memory and reduce depressive symptoms in patients with MD. Thirty patients with major depression (n = 30) were randomly assigned to receive either experimental (active) or control (sham) tDCS. To measure cognitive functions, the participants underwent a series of visual memory neuropsychological tasks; and to measure depression symptoms, the Beck Depression Inventory (BDI) and Hamilton Depression Scale (HDRS) were used. The parameters of active tDCS included 2 mA for 20 min per day for 10 consecutive days, anode over the left DLPFC (F3), cathode over the right DLPFC (F4) region. After 10 sessions of anodal and cathodal tDCS, patients showed significantly improved performance in visual working memory tasks. The same results were observed for depression symptoms. This study showed that anodal tDCS over left DLPFC, concurrently with cathodal tDCS over right DLPFC, improved cognitive impairment (specifically visual working memory), as well as reduced depressive symptoms in patients with MD. This finding provides evidence that supports effectiveness of a specific montage of tDCS to improve impaired cognition in MD, specifically in visual working memory.

Keywords: major depression; memory; tDCS; visual memory

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Background

With a lifetime prevalence estimated at 16%, major depression (MD) is a serious public health issue (Gohier et al., 2009). Previous studies have shown MD to be associated with a variety of cognitive correlates such as the ability to think, concentrate, make decisions, formulate ideas, reason, and remember (Marazziti, Consoli, Picchetti, Carlini, & Faravelli, 2010). It unquestionably affects specific cognitive domains including executive functions (Marazziti et al., 2010; McDermott & Ebmeier, 2009), different types of memory (e.g., episodic memory, semantic memory, visuospatial memory), and information processing speed (McDermott & Ebmeier, 2009).

MD is usually accompanied by alterations of cortical activity, especially in prefrontal areas (Nitsche, Boggio, Fregni, & Pascual-Leone, 2009). The prefrontal cortex (PFC) consists of regions including the dorsolateral PFC (DLPFC) and ventromedial PFC (VMPFC) that are involved in depression psychopathology in terms of cognition and emotion,

respectively. Functional imaging, lesion and brain stimulation studies, suggest that the DLPFC is primarily associated with “cognitive” or “executive” functions, whereas VMPFC is largely associated with “emotional” or “affective” functions (Koenigs & Grafman, 2009), suggesting that cognition and emotion, which are seriously malfunctioned in MD, are associated with altered cortical activity in the PFC. It is beyond the scope of this paper to review how the PFC is involved in cognitive, executive, and emotional processes. However, we can briefly outline that the PFC is a collection of interconnected cortical regions, in which diverse information converge; and that these areas have interconnections with virtually all sensory systems, with cortical and subcortical motor system structures, and with limbic and midbrain structures involved in affect, as well as memory (Miller & Cohen, 2001).

It is indicated that the activity of the PFC is pathologically altered in MD, mostly in the direction of decreased bilateral or predominantly left-sided activation (Davidson, Pizzagalli, Nitschke, & Putnam, 2002). Some studies suggest an imbalance of function between right and left DLPFC activity as an important causal factor in MD psychopathology (Grimm et al., 2008; Nitsche et al., 2009), suggesting a causal relationship between hemispheric imbalances of function (especially in the PFC) and depressive cognitive and emotional symptoms. More specifically, a decrement of cortical activity exists in the left DLPFC, whereas an increment of cortical activity is seen in the right DLPFC (Davidson et al., 2002; Nitsche et al., 2009; Speer et al., 2000).

A similar imbalance of function is shown in the activity of the PFC that affects memory processing in MD (Nitschke, Heller, Etienne, & Miller, 2004). Numerous electroencephalography (EEG) and neuroimaging studies have reported more right than left PFC activity in depression, indicating hypoactivity in the left DLPFC and hyperactivity in the right DLPFC (Grimm et al., 2008; Nitschke et al., 2004). This imbalance of function is suggested to be associated with memory impairment in MD (Nitschke et al., 2004). The importance of the PFC for visual and spatial working memory is also well documented (Dockery, Liebetanz, Birbaumer, Malinowska, & Wesierska, 2011; Petrides, 2000; Schecklmann et al., 2011). A number of studies have demonstrated that impaired working memory in patients with MD is related to the PFC; however, the relationship between the underlying brain activity and working memory function in MD, and their clinical characteristics, is not yet clear (Pu et al., 2012).

DLPFC imbalance of function is not only associated with cognitive impairment in MD, but also is suggested to be involved in emotional processing in MD (Davidson & Irwin, 1999; Grimm et al., 2008; Phan, Wager, Taylor, & Liberzon, 2002). This would imply that the PFC region is engaged in cognition-emotion interaction (Phan et al., 2002). Studies suggest that the PFC, specifically the medial PFC, is actively engaged during cognitively bound emotional processing of stimuli. For example, it is shown that the PFC plays a crucial role in affective working memory (Davidson & Irwin, 1999). But studies are needed to investigate how the PFC is associated with both cognition and emotion—to address specific questions, such as, “Which subregions of the PFC are mostly responsible for cognition-emotion interaction?”

Recent studies have highlighted the importance of noninvasive brain stimulation as a means of modulating 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 aftereffects of tDCS up to 90 min in the human motor cortex (Utz, Dimova, Oppenländer, & Kerkhoff, 2010).

Neuromodulation studies have shown that an increase of 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 showed 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) and also could have clinical implications (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).

Although a number of neuropsychological studies suggest an association between the PFC and working memory function in MD, the results are mixed (Pu et al., 2012). In addition, the neuropsychological characterization of the left DLPFC hypoactivity and right DLPFC hyperactivity, and its association with negative emotional processing in MD, remains poorly understood (Grimm et al., 2008). Studies with specific designs based on neuropsychological characterizations of MD would be more useful and less likely to produce mixed results. Such studies are more facilitative when it comes to the study of the PFC as an interconnected brain region that sends and receives projections from many subcortical areas (Miller & Cohen, 2001), although studying such a region with its many neural connections and networks is very difficult.

Based on neuroimaging studies that suggest an asymmetry of function in bilateral DLPFC in depression, which is associated with cognitive impairments in MD, we suggested a specific tDCS montage. Therefore, this study aims primarily to investigate whether applying tDCS with a specific montage of anodal tDCS over the left DLPFC and cathodal tDCS over the right DLPFC would result in cognitive improvement, especially in visual working memory, which is the most impaired neuropsychological domain in MD (Egerhazi et al., 2013). We are also interested to see if this tDCS montage could reduce depressive symptoms in MD. The left DLPFC was selected as the main site of anodal stimulation, which is hypothesized to increase cortical activity in left DLPFC; and the right DLPFC was selected as the main site of cathodal stimulation, which is hypothesized to decrease cortical activity in right DLPFC. We suggest this specific design to be 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. Also, we used a series of cognitive assessment measures that are sensitive to cortical functions and are designed with a focus on neuropsychological functions of frontal lobe regions in depression (Egerhazi et al., 2013; Sahakian et al., 1990). Finally, this study aims to examine visual aspects of memory, which is one of the most impaired cognitive domains in MD (Egerhazi et al., 2013; Sahakian et al., 1990); yet to date no tDCS studies have investigated effects of brain stimulation on visual memory in MD.

Materials and Methods

Participants

Thirty participants, aged 18–44, with a MD diagnosis, who were administered the Beck Depression Inventory (BDI; Beck, Ward, & Mendelson, 1961) and the Hamilton Rating Depression Scale (HDRS; Hamilton, 1960), took part in this study. The subjects were recruited from the Atieh Clinic at Tehran, Iran. Demographic characteristics are shown in Table 1 and 2. Inclusion criteria were: (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 depression scores on the BDI (scores close to 29 and higher); (4) HDRS scores of at least 20 (scored by an experienced psychiatrist); and (5) MD 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. The study was performed according to the Declaration of Helsinki ethical standards and approved by the local Institutional Review Board and the Ethical Committee of the University of Tehran. Patients gave their informed consent before participation.

It is notable that, although the BDI baseline scores of both control and experimental groups showed a moderate to severe level of depression, the BDI baseline scores of the control group were lower than the experimental group, which may bring to question whether both groups are different. For this reason, we used the HDRS, in addition to the BDI, to ensure participants met the inclusion criterion of MD severity.

Table 1
Demographic data of patients

Patient	Gender	Age	Antidepressant Use	Onset Age	Baseline BDI/HDRS
1	F	28	Yes	24	41/26
2	M	28	Yes	27	30/27
3	M	26	Yes	24	34/24
4	M	27	Yes	26	25/22
5	M	22	No	22	29/20
6	F	33	Yes	33	27/29
7	F	29	Yes	26	39/25
8	F	37	Yes	34	46/22
9	F	25	Yes	24	35/27
10	M	22	Yes	20	28/23
11	M	29	Yes	28	31/24
12	F	32	Yes	29	39/26
13	F	24	Yes	23	40/21
14	F	44	Yes	40	38/28
15	M	25	Yes	22	31/27
16	F	24	No	23	31/ 21
17	F	31	Yes	30	26/22
18	F	36	Yes	35	32/21
19	M	21	Yes	20	29/23
20	M	28	Yes	26	27/24
21	M	41	Yes	37	25/22
22	F	18	No	17	27/21
23	F	32	Yes	30	31/27
24	F	27	Yes	27	29/20
25	M	26	Yes	25	33/24
26	M	28	Yes	26	27/22
27	F	30	Yes	28	26/24
28	F	25	Yes	20	29/26
29	F	29	Yes	28	27/25
30	M	22	Yes	21	26/21

Table 2
Descriptive statistics of demographic data

	Experimental Group	Control Group
Sample size (*n*)	15	15
Antidepressant medication use	14	13
Age in years – Mean (*SD*)	28.7 (28.73)	27.9 (27.86)
Onset age in years – Mean (*SD*)	26.8 (26.80)	26.2 (26.20)
Baseline BDI score – Mean (*SD*)	34.2 (6.09)	28.3 (2.46)
Baseline HDRS score – Mean (*SD*)	24.7 (3.05)	22.8 (2.06)

Experimental Protocol

Participants were randomly assigned in two groups (experimental or active tDCS, *n* = 15; control or sham tDCS, *n* = 15). Participants in the active group received one 20-min stimulation session per day, for 10 consecutive days. Participants in the control group received sham stimulation, but the stimulator was turned off after 30 s 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 once before the first tDCS session as baseline, and once after the tenth tDCS session for each condition (active and sham). Subjects in the sham stimulation condition were recruited for other therapeutic protocols by the end of the study.

tDCS

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 min once a day for 10 consecutive days. The anodal electrode was positioned over area F3 (left DLPFC) according to the 10–20 EEG international system, and the cathode electrode was positioned over F4 (right DLPFC). The electrodes were thick (0.3 cm), and were placed in rectangular saline-soaked synthetic sponges (surface area of 35 cm^2). All patients were blind to the type of tDCS delivered in each session.

Cognitive Assessment

Cognitive functions were assessed using the Cambridge Neuropsychological Test Automated Battery (CANTAB; CeNeS, Cambridge, UK). The CANTAB is designed with a significant focus on neuropsychological functions, subserved by frontal lobe regions, such as frontostriatal circuitry that mediate motor, cognitive and behavioral functions within the brain (Fray, Robbins, & Sahakian, 1996). It has been extensively validated for assessing brain–behavior relationships 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, the CANTAB has been used in cognitive studies of both neurodegenerative disorders, such as dementia and Huntington's disease (Rahman, Sahakian, Hodges, Rogers, & Robbins, 1999; Sahakian et al., 1990), and psychiatric disorders, such as schizophrenia, MD, and bipolar disorder (Egerhazi et al., 2013; Levaux et al., 2007; Porter, Gallagher, Thompson, & Young, 2003; Roiser & Sahakian, 2013). It has also been used successfully to detect deficits in visuospatial short-term memory in neurosurgical patients with temporal or frontal lobe excision (Owen et al., 1995). Specifically, Falconer et al. (2010), in a study involving Electroconvulsive Therapy (ECT), showed that the CANTAB can assess the cognitive impact of ECT on visual working memory.

Since the 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, it is believed that performance on the CANTAB is dependent on change in cortical activity, our particular tDCS montage is supposed to modulate prefrontal activity, and the CANTAB is precisely sensitive to cortical activity changes. In addition, the CANTAB is shown to be correlated with traditional and well-validated neuropsychological testing instruments. For example, the CANTAB memory tests are associated with performance on traditional measures assessing visual memory and working memory, such as the "Green Story Recall Test Immediate and Delayed Recall" and the "Digit Span Forwards and Backwards" (Smith, Need, Cirulli, Chiba-Falek, & Attix, 2013).

Moreover, the CANTAB has a specific battery called the CANTAB Depression Battery, which is an accurate assessment system for measuring cognitive functions in MD (Egerhazi et al., 2013; Papakostas, 2014; Roiser & Sahakian, 2013). Studies show that the CANTAB Depression Battery can discriminate the cognitive profile of depression from other disorders and is uniquely sensitive to MD; also, some tests such as the Delayed Matching to Sample (DMS) and Pattern Recognition Memory (PRM) can specifically detect visual memory deficits in MD (Egerhazi et al., 2013). Finally, the CANTAB has been specifically developed to assess the nature of memory deficits (Falconer et al., 2010), especially visual memory, which makes it an efficient measure to assess memory deficits. From an administration standpoint, the CANTAB has highly standardized administrations, with automated response recording and millisecond precision.

In this study, a two-test CANTAB battery was used (15–20 min duration), selected from the CANTAB Depression battery and CANTAB Memory tests: DMS and PRM. This battery was selected to evaluate visual aspects of memory in MD, including visual working memory and visual recognition memory (Rock, Roiser, Riedel, & Blackwell, 2014). The DMS test assesses visual recognition memory by presenting a target pattern and requiring the subjects to pick out the target pattern from an array of four patterns in immediate, 4- and 12-s delay conditions (Robbins et al., 1994). This test is proposed to be primarily sensitive to damage in the medial temporal lobe area, with some input from the frontal lobes (Egerhazi et al., 2013). It lasts about ten 10 minutes and the outputs include the number and percentage of correct responses and response latency.

The PRM is a test of visual recognition memory following a two-choice forced discrimination paradigm. The participant is presented with a series of 12 visual patterns, one at a time, in the center of the screen. These patterns are designed so that they cannot easily be given verbal labels. In the first recognition phase, the participant is required to choose between a pattern they have already seen and a novel pattern. The second recognition phase can be administered either immediately or after a 20-min delay. The tasks last about 5 minutes. The outputs for the PRM include number and percentages of correct and incorrect responses, and response latency.

Mood Measurement

Depressive symptoms and mood were evaluated using two well-known depression inventories and scales: the BDI and the HRSD. The evaluation was made once before the tDCS sessions, and once after 10 sessions. The original form of the BDI, which is used in this study, is a self-reported 21 questions inventory about how the subject has been feeling in the last week, where each question has four answers ranging in intensity. The HRSD is a multiple items questionnaire designed for measuring adult depression and is administrated by a health care professional. HDRS is currently the most common depression measure used worldwide (Marijnissen, Tuinier, Sijben, & Verhoeven, 2002). Both measures are designed to indicate the presence of depressive symptoms in a past number of days.

Statistical Analysis

We used PASW Statistics 18.0 for data analysis. Baseline demographic and clinical data were compared using the Fisher's exact test for categorical variables and a paired-samples *t*-test for continuous variables. This study adopted a 2 x 2 mixed factorial design. The effect of tDCS was assessed with a stimulation condition (pre-stimulation/post-stimulation) as a within-subject factor, group (active/sham) as a between-subject factor, and scores on the CANTAB (cognitive performance) as the dependent variable. A similar 2 x 2 mixed factorial design was used for measuring the effects of tDCS on mood. Our analyses of variance (ANOVA) met linear assumptions and the Leven's test was used to examine homogeneity of variances. A significance level of $p < .05$ was used for all statistical comparisons.

Results

All subjects tolerated the tDCS treatment well and no adverse effects were reported. The effects of tDCS on the DMS were investigated. For correct responses, the ANOVA results showed that the effect of tDCS on DMS scores depends on group, indicated by a significant interaction effect, $F(1, 28) = 8.270$, $p < .008$. A significant main effect of stimulation condition was also observed, $F(1, 28) = 5.120$, $p < .032$; however, no significant main effect of group was observed, $F(1, 28) = 0.471$, $p < .498$. Regarding latency time, ANOVA results indicated a significant main effect of stimulation condition, $F(1, 28) = 17.571$, $p < .001$; no significant main effect of group, $F(1, 28) = 0.192$, $p < .664$; and a significant interaction between the two factors, $F(1, 28) = 6.790$, $p < .014$. These results show that anodal stimulation of left DLPFC and cathode stimulation of right DLPFC, significantly improved visual recognition memory, as assessed by the DMS and effect of stimulation condition (pre/post) depends on group factor (active/sham).

Table 3
F and P values of ANOVAs for cognitive functions

Cognitive Functions	Degree of Freedom	*F*	*p*
DMS (correct)			
Stimulation	1.28	5.120	**.032**
Group	1.28	0.471	.498
Stimulation*group	1.28	8.270	**.008**
DMS (latency)			
Stimulation	1.28	17.571	**.001**
Group	1.28	0.192	.664
Stimulation*group	1.28	6.790	**.014**
PRM immediate phase (corrects)			
Stimulation	1.28	28.255	**.001**
Group	1.28	3.319	.079
Stimulation*group	1.28	3.469	.073
PRM immediate phase (latency)			
Stimulation	1.28	7.038	**.013**
Group	1.28	3.990	.056
Stimulation*group	1.28	3.499	.072
PRM delay phase (corrects)			
Stimulation	1.28	25.779	**.001**
Group	1.28	3.066	.091
Stimulation*group	1.28	0.818	.373
PRM delay phase (latency)			
Stimulation	1.28	0.006	.940
Group	1.28	2.507	.125
Stimulation*group	1.28	0.050	.826

$p < .05$; DMS = Delayed Matching to Sample; PRM = Pattern Recognition Memory.

Table 4
Performance on DMS and PRM

Cognitive Functions	Mean	Standard Deviation	SEM
DMS (correct)			
Pre-stimulation (PG)	60.33 (54.93)	13.88 (17.26)	3.58 (4.45)
Post-stimulation (PG)	66.43 (57.80)	12.04 (13.71)	3.11 (3.54)
DMS (latency)			
Pre-stimulation (PG)	5167.8* (5267.40)	1734.6 (1598.40)	447.8 (412.70)
Post-stimulation (PG)	4551.3 (4848.40)	1527.8 (1301.41)	394.4 (336.15)
PRM immediate phase (corrects)			
Pre-stimulation (PG)	62.55 (55.17)	11.51 (10.32)	2.97 (2.66)
Post-stimulation (PG)	75.53 (63.68)	17.46 (16.68)	4.50 (4.30)
PRM immediate phase (latency)			
Pre-stimulation (PG)	4316.6* (5000.20)	1753.5 (1789. 30)	452.7 (461.90)
Post-stimulation (PG)	2925.1 (3946.50)	1318.5 (1348.40)	340.4 (348.10)
PRM delay phase (corrects)			
Pre-stimulation (PG)	37.22 (36.11)	10.01 (8.02)	2.58 (2.07)
Post-stimulation (PG)	60.75 (48.24)	18.01 (18.49)	4.64 (4.77)
PRM delay phase (latency)			
Pre-stimulation (PG)	2974.7* (3899.21)	1403.4 (1449.10)	362.3 (374.14)
Post-stimulation (PG)	2913.3 (3772.13)	891.7 (960.52)	230.2 (248.11)

PG = Placebo Group; DMS = Delayed Matching to Sample; PRM = Pattern Recognition Memory; * = Values marked by (*) are in ms.

The effect of stimulation on visual recognition memory was again analyzed through PRM using a 2 x 2 mixed factorial design with stimulation condition (pre-performance/post-performance) and group (active/sham) as within-subject factors and between-subject factors, respectively. For the immediate recognition phase, the results showed a significant main effect of stimulation condition, $F(1, 28) = 28.255$, $p < .001$; no significant main effect of group, $F(1, 28) = 3.319$, $p < .079$; and no significant interaction between the two factors, $F(1, 28) = 3.469$, $p < .073$. The same results were noted in the late recognition phase, in which were observed a significant main effect of stimulation condition, $F(1, 28) = 25.779$, $p < .001$; no significant main effect of group factor, $F(1, 28) = 3.066$, $p < .091$; and no significant interaction between the two factors, $F(1, 28) = 0.818$, $p < .373$. This shows that anodal stimulation of the left DLPFC and cathode stimulation of the right DLPFC significantly improved visual recognition memory; however, the effect of the stimulation condition did not depend on group (active/sham). Results for latency output showed a significant main effect of stimulation type in the immediate phase, $F(1, 28) = 7.038$, $p < .013$, but not in the delay phase, $F(1, 28) = 0.006$, $p < .940$; no significant interaction between stimulation condition and group in the immediate and delay phase; and no significant main effect of group (active/sham) in the immediate and delay phase.

In addition to visual working memory, the effect of stimulation on mood was also measured. Using a 2 x 2 mixed factorial design with stimulation condition (pre-performance/post-performance) and group (active/sham) as within-subject factors and between-subject factors, respectively, results showed a significant interaction effect of stimulation condition and group on BDI scores, $F(1, 28) = 118.849$, $p < .001$. This indicates our stimulation significantly reduced depressive symptoms and that the effect of stimulation condition depends on group. In addition to the interaction effect, also of significance are the main effect of the stimulation condition, $F(1, 28) = 159.201$, $p < .001$; and group, $F(1, 28) = 18.834$, $p < .001$. Results of the HDRS also show the same pattern with significant interaction effect, $F(1, 28) = 35.973$, $p < .001$; which means, depending on group, stimulation condition significantly reduces HDRS scores. Also of note from the results shown in Table 5 are the main effect of stimulation condition, $F(1, 28) = 131.822$, $p < .001$; and group, $F(1, 28) = 21.971$, $p < .001$.

As Figure 1 clearly depicts, the effect of stimulation condition depends on the group (active/sham). In other words, tDCS effects on mood and depressive symptoms of patients depend on receiving active or sham stimulation. We see a significant reduction in depressive scores after 10 sessions of tDSC only in the experimental group. It is also notable that the baseline scores of the BDI are different, which may give rise to a question about group homogeneity in terms of severity of depression in both control and experimental groups. Although both groups' BDI baseline score indicates a moderate to severe level of depression, this baseline difference could be due to the subjective nature of the BDI self-report. To make sure both groups' depression severity is similar, we used the HDRS (completed by an experienced psychiatrist) in addition to BDI to make sure participants met inclusion criterion of MD severity. As left graph in Figure 1 shows, the baseline HDRS scores of both groups indicate that both groups suffered from severe MD.

Table 5
F and P values of ANOVAs for depression scores

Cognitive Functions	Degree of Freedom	*F*	*p*
BDI			
Stimulation	1.28	159.201	.001
Group	1.28	18.834	.001
Stimulation*group	1.28	**118.849**	**.001**
HDRS			
Stimulation	1.28	131.822	.001
Group	1.28	21.971	.001
Stimulation*group	1.28	**35.973**	**.001**

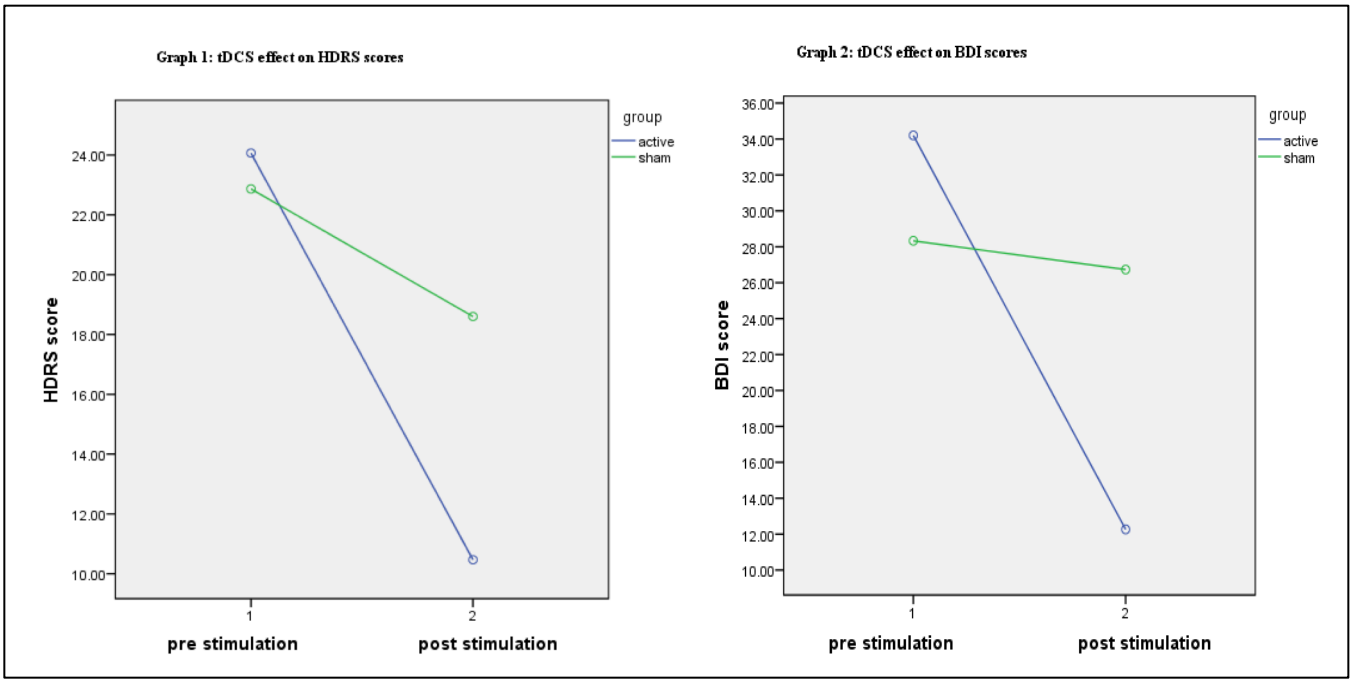

Figure 1. Interaction effect of stimulation condition and group (active/sham) on HDRS scores (left) and BDI scores (right).

Discussion

This study primarily showed that anodal tDCS over DLPFC for 10 consecutive days improved visual working memory in patients with MD. Visuospatial memory, in which its function is associated with prefrontal cortex function (Church, Petersen, & Schlaggar, 2010; Dockery et al., 2011; Fregni et al., 2005), is impaired in patients with MD, and some recent studies suggest that visual memory is the most impaired cognitive domain in MD (Smith et al., 2013). This is proposed to be the result of large alterations in cortical activity of the PFC in major depression (Nitsche et al., 2009). Therefore, we can expect to observe improving effect on visual memory if we modulate cortical activity of the PFC in MD. To modulate cortical activity of the PFC, we applied anodal tDCS of the left DLPFC concurrently with cathodal stimulation of the right DLPFC. We applied this specific treatment montage according to pathological cortical activity of PFC in MD. This study also indicated that our specific stimulation montage significantly reduced depressive symptoms.

There is an imbalance of function between the right and left DLPFC in MD (Grimm et al., 2008; Nitsche et al., 2009; Nitschke et al., 2004). It is suggested that there is a higher than normal cortical activity in the right DLPFC and a lower than normal activity in the left DLPFC in MD, which is responsible for impaired visual memory deficits in depression. A similar imbalance of function is suggested to be associated with negative emotional processing in MD (Grimm et al., 2008). We modulated this imbalanced activity in the left and right PFC by applying anodal tDCS on the left DLPFC and cathodal tDCS on the right, and we observed improved performance in visual spatial memory tasks after a 10-session tDCS protocol using this montage. In other words, we tried to alter pathologic cortical activity in depression to normal cortical activity using this specific stimulation montage.

What our study claims to find is considerable from several points. First of all, visual memory impairment is one of the most impaired cognitive function in MD (Smith et al., 2013); although numerous studies showed effectiveness of tDCS on memory, specifically working memory (Boggio, Ferrucci, et al., 2006; Ferrucci, Mameli, et al., 2008; Fregni et al., 2006; Jo et al., 2009), few studies have evaluated visual aspects of memory using tDCS; and no study has investigated these aspects of memory in MD specifically. However, an animal study conducted by Dockery et al. (2011) found anodal and cathodal tDCS of the frontal cortex improved visuospatial working memory in rats.

Secondly, and more importantly, our study suggests a specific stimulation montage for MD tDCS studies, based on findings of neuroanatomical and neuroimaging studies. Results of this study propose that application of anodal tDCS over the left DLPFC concurrently with cathodal tDCS over the right DLPFC can enhance visual working memory and visual recognition memory in MD. Previous brain stimulation studies on depression targeted left DLPFC for anodal stimulation, and usually did not apply cathodal stimulation on right DLPFC, as part of treatment protocol. This could be partly due to the fact that tDCS studies on depression are fairly new, especially when it comes to the study of cognitive functions in MD, and more studies are needed to replicate findings and suggest more accurate treatment protocol. By applying cathodal stimulation of the right DLPFC, we suggest a specific tDCS montage and treatment protocol, especially when we are concerned about improving cognitive impairments of MD.

The PFC and DLPFC are suggested to be engaged in cognitive functions. More specifically they are directly involved in different aspects of memory, including visual-spatial memory (Dockery et al., 2011; Petrides, 2000). Dysfunction of distributed cortico-subcortical, bihemispheric regions in the DLPFC network, with higher activity in the right hemisphere and lower activity in the left hemisphere, has been found central in depression pathology (Brunoni & Vanderhasselt, 2014; Nitsche et al., 2009). Thus modulation of PFC and DLPFC cortical activity is supposed to be accompanied by cognitive improvement in depression. Our study suggests improving effects of tDCS on visual working memory and recognition memory of patients with MD, by targeting left DLPFC for anodal stimulation and right DLPFC for cathodal stimulation. This has important theoretical implications for MD studies too, in terms of how the DLPFC contributes to MD cognitive impairments. As mentioned, the relationship of the PFC and working memory has been supported by previous studies; however, results are still mixed, especially in MD studies (Pu et al., 2012). This study attempted to investigate this relationship in a brain stimulation context.

This proposed mechanism of how our tDCS montage improves cognitive visual memory is a suggestion based on our controlled study. However, it is possible that cognitive improvement is a positive side effect of general improvement in depression severity. Memory deficit in depression is secondary to other cognitive dysfunctions, such as attention deficits and impaired cognitive initiative, rather than the ability of short-term memory storage (Marazziti et al., 2010). Thus, tDCS over the DLPFC, the brain region involved in cognitive functions and emotional processing, is associated with therapeutic effect, and it is reasonable to hypothesize that altering this pathological state could be associated with cognitive improvement. We altered this pathological state in MD patients by modulating cortical activity of the DLPFC through anodal and cathodal tDCS.

Although the main purpose of this study was to investigate the effect of transcranial brain stimulation on visual working memory in MD, we also observed reduced depression scores, which support previous brain stimulation studies of MD. One way we can explain such findings is that the PFC regions, specifically tumors, ischemia and epileptogenic zones of the left hemisphere, are frequently accompanied by depressed mood (Nitsche et al., 2009). Both excitability enhancement of the left DLPFC and excitability reduction of the right DLPFC to treat depression have been studied; however, mechanism of action is certainly not proven (Nitsche et al., 2009). It is also known that the 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 increased cortical activity in the left DLPFC that is pathologically decreased in major depression; and by applying cathodal tDCS, we decreased cortical activity in the right DLPFC that is pathologically increased in major depression.

Although the results are encouraging, our study had several limitations. First of all, we did not evaluate the long-term effects of the intervention in terms of follow-up study. Further studies should evaluate visual-spatial memory 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, despite of promising results, future studies that compare tDCS effect versus another therapy are needed to validate tDCS as an effective treatment. Finally, even though significant effects of tDCS on memory was observed in patients with MD, the mechanisms underlying tDCS-induced visual memory enhancement still remain unclear and they should be the focus of investigation in further controlled studies. Using neuroimaging measures

such as fMRI, PET, and some measure of neural changes such as ERPs and qEEG, would be more beneficial and yield more accurate results.

In conclusion, our study demonstrated that anodal stimulation of the left DLPFC concurrently with cathodal stimulation of the right DLPFC improved visuospatial aspects of memory (visual working memory, visual recognition memory) in MD, after 10 consecutive sessions of tDCS. This effect is suggested to be the result of cortical activity modulation of DLPFC through tDCS. By increasing cortical activity of the left DLPFC and decreasing it in the right DLPFC, we altered pathologic imbalanced activity of the PFC in MD and visual memory performance improved after such a treatment protocol. A mood improvement was also observed after 10 sessions of tDCS treatment. Although further controlled studies with larger sample sizes and longer stimulation periods are needed, our results encourage using this stimulation montage for improving both cognitive and emotional impairment in MD.

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