Effects of Transcranial Direct Current Stimulation (tDCS) on Performance Monitoring and Learning Rate in Schizophrenia

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Abstract

A reliable and valid neurophysiological index of error-monitoring ability is an event-related potential (ERP) known as "error-related negativity" (ERN), which is evoked following an error response. Individuals with schizophrenia show error monitoring deficits accompanied by reduced ERN. Error monitoring is mediated in part by the medial-frontal cortex, which has been shown to be abnormal in schizophrenia. Transcranial direct current stimulation (tDCS) is a noninvasive tool for transient modulation of cortical function, which delivers low current to brain areas through small electrodes. In this study, we sought to improve performance monitoring in schizophrenia by delivering tDCS to the medial-frontal area. Ten patients and 10 demographically matched controls participated in a difficult choice target color discrimination task with stop trials that were designed to elicit errors while ERPs were recorded. TDCS was delivered before the cognitive task. After anodal tDCS stimulation, performance monitoring and learning rates were improved in the patients and ERN was increased to measures comparable to healthy controls during the sham condition. These results suggest that tDCS could be used to treat cognitive deficits in schizophrenia, and other neuropsychiatric illnesses with widespread cognitive impairments.

Introduction

Schizophrenia is a disorder characterized by severe behavioral, cognitive and emotional symptoms, which can be disruptive to the daily functioning of the patient. Due to these deficits, many schizophrenia patients are usually unable to continue with an education or obtain jobs, leading to occupational and social problems. One of the most prominent cognitive deficits includes impairments in performance monitoring (e.g. Thakkar et al, 2011). Patients with schizophrenia show an attenuated corrective response to their errors and thus are less able to learn from their mistakes, either because they do not register the fact that a mistake was made, or due to an inability to apply corrective actions (Kerns et al., 2005). Defective monitoring can account for the misattribution of thoughts and actions leading to positive symptoms such as auditory hallucinations, and delusions of alien control (Frith, 1987). This suggests that supporting and improving error monitoring and error correction could be extremely helpful for those who suffer from schizophrenia. However, very little research has been conducted to determine what methods might be effective.

Antipsychotic medications can be effective in alleviating some of the symptoms of schizophrenia such as hallucination and delusions but one problem is non-compliance rate, which can often be as high as 40%, often due to side effects such as anxiety, and lack of motivation (Lacro et al., 2002). Many patients have also cited ineffectiveness of medication as a reason for nonadherence rather than negative side effects (Lieberman et al., 2005). Moreover, many cognitive and social deficits are medication-resistant and need other interventions such as cognitive behavior therapy (CBT) (Rector & Beck, 2001; Morrison, 2009). CBT has been shown to be effective but it requires intensive treatment with a highly skilled therapist over the course of several months and as such requires the commitment and compliance of the patient (Kumari et

al., 2009). Importantly, in the U.S., most patients with schizophrenia have no access to CBT because of the lack of trained therapists who can deliver CBT to psychotic patients as well as the high cost (i.e., health insurances do not cover CBT).

Recently, non-invasive and safe brain stimulation techniques for cognitive enhancement have been introduced into the neuropsychiatric literature. Transcranial direct current stimulation (tDCS), a noninvasive neurostimulation method that involves application of low-intensity direct current to the scalp, which modulates cerebral excitability, is safer than transcranial magnetic stimulation (TMS) and may be just as effective in affecting brain functions. Studies have shown that tDCS is able to provide causal control over electrophysiological responses of the human brain to errors (Utz et al., 2010; Reinhart & Woodman, 2014).

The goal of the present study is to use tDCS to causally control the processing of errors and learning in schizophrenia patients. Previous research has shown that anodal tDCS excites cortical activity (Utz et al., 2010). By applying anodal tDCS to the medial-frontal cortex, we hypothesize that it would enhance performance monitoring, improve behavioral adjustments following an error, and increase the rate of learning in schizophrenia patients.

The Role of Anterior Cingulate Cortex in Performance Monitoring

Performance monitoring deficits can be demonstrated through reduced error-related negativity (ERN), a response-locked error-related potential (ERP) component associated with errors. ERN potentials are generated in the medial-frontal cortex, particularly the anterior cingulate cortex (ACC), that aid in error detection and support learning (Gehring et al., 1993; Schall et al., 2002). Typically, in healthy people, ERN peaks when they make an incorrect response relative to a correct response (Scheffers & Cole, 2000). Kopp and Rist (1999) and Mathalon and associates (2002) studied the output-associated ERN in schizophrenia. They found

that the amplitude of the ERN in schizophrenia patients was reduced compared to that of healthy controls, thus indicating reduced error-detection abilities. Patients with schizophrenia also showed reduced functional activity in the anterior cingulate cortex during performances of cognitive tasks, and in tasks requiring error detection (Kerns et al., 2005). Conflict theory indicates that the anterior cingulate cortex is involved with the monitoring of response conflict. Due to anterior cingulate dysfunction, patients with schizophrenia show both decreased conflict- and error-related activity.

Bates and his collaborators (2002) examined error-related negativity and correct-related negativity (CRN) in schizophrenia, and found attenuated potentials for both correct and error responses (Bates et al., 2002). They recorded event-related potentials in schizophrenic patients and healthy participants who performed a simple go/no-go task. Participants were instructed to respond every time a white 'X' appeared, and not to respond to the white 'K'. ERN and CRN were measured during the task. Bates et al.'s study confirmed the findings of Kopp and Rist (1999) and Mathalon et al. (2002) in that the amplitude of the ERN is weakened in schizophrenia when responding to a false alarm, and that the CRN observed during correct responses during the simple go/no-go task is also reduced. Thus, showing that not only are schizophrenic patients less receptive and adaptive to their errors, but also may be less responsive to their correct responses. The "reward" associated with a correct response does not retain with patients. Bates and associates attributed the deficits of ERN and CRN to abnormalities in the anterior cingulate cortex.

In addition to an attenuated ERN, schizophrenic patients also show minimal behavioral adjustments in response to feedback. Kerns et al. (2005) tested healthy participants and schizophrenia patients using the Stroop task. Healthy participants showed significant behavioral

post-error adjustments such as post-error slowing, while patients lacked post-conflict adjustments. Performance monitoring experiences show that even without instruction, participants will immediately correct an error in the next trial (Rabbitt, 1966). On trials after the error, healthy participants demonstrated significant post-error adjustments as a consequence of the error detection (Rabbitt, 1966). This is not seen in schizophrenic patients (Malenka et al., 1982, 1986). These findings indicate that stimulating the anterior cingulate cortex to improve its functions may be beneficial to patients with schizophrenia not only for cognitive control, but also refractory positive symptoms resulting from abnormal self-monitoring. TDCS, a noninvasive and safe brain stimulation method, may be optimal for enhancing cortical functions because of its ability to increase activity in the targeted brain area—serving as a potential method for improving performance monitoring in patients with schizophrenia.

Current Literature on Transcranial Direct Current Stimulation

Transcranial direct current stimulation is a form of noninvasive brain stimulation in which very low currents are delivered to the brain area of interest, and modulates cortical excitability. It provides three different types of stimulation: anode, cathode, and sham. Anodal stimulation is a positive stimulation that increases neuronal excitability by depolarizing the neurons. Cathodal stimulation decreases neuron excitability through hyperpolarization, while sham is used to measure baseline, and emits current for a brief moment before it is turned off for the rest of the stimulation. After several minutes of stimulation, long-lasting changes have been found in the underlying cerebral regions (Nitsche & Paulus, 2001). In the mid 1900's, several animal studies demonstrated that tDCS had strong effects on brain activity and excitability (Bindman et al., 1964; Purpura and McMurtry, 1965). Using potentials with a current between 0.01-0.05 microamps, Bindman and associates (1964) produced neuronal excitability in the rat

cortex. The change in neuronal excitability lasted for several hours after the current was turned off, and thus sparked renewed interest in modulating neuronal excitability through brain polarization. Although tDCS is an old technique used to stimulate the brain, studies utilizing cortical modulation through tDCS on humans have only recently generated interest.

Since its recent revival, tDCS studies on its application have been twofold. Firstly, tDCS has been used to study cortical functions through stimulating a specific region with anodal or cathodal stimulation, and then conducting neuropsychological tests (Vines et al., 2006). By using tDCS to study specific cortical functions, it has also found important potential as treatment for neurological and psychiatric diseases through anodal and cathodal modulation of excitability of stimulated regions (Fregni et al., 2006; Boggio et al., 2006; Rigonatti et al., 2008).

Many studies have focused on tDCS excitability changes in the human motor cortex, but few have focused on its cognitive effects. Fregni and colleagues (2005) realized this gap and investigated the effects of anodal stimulation of the prefrontal cortex on working memory. They tested fifteen healthy human subjects by applying tDCS to localized areas in the left dorsolateral prefrontal cortex (DLPFC). Participants were tested during sham and active stimulation. During active stimulation, they were either given anodal or cathodal stimulation to the left DLPFC. After the stimulation, participants performed an *n*-back working memory task. Results showed that those who received anodal stimulation of the left DLPFC performed better than those who went through sham stimulation (Fregni et al., 2005). Thus, they concluded that left prefrontal anodal stimulation may enhance working memory, and that the improvement of cognitive function depends on the specific site of the tDCS, and the stimulation polarity (anodal or cathodal).

As research on the effects of tDCS on working memory has increased, focus has now shifted to other cognitive functions, such as performance monitoring—an important ability

required to prevent future errors by adjusting our behavior accordingly. Woodman and Reinhart (2014) demonstrated causal control of the medial-frontal cortex using tDCS to govern electrophysiological and behavioral indices of performance monitoring and rate of learning in healthy participants. They found that different polarities of tDCS were able to up or down regulate the functioning of mechanisms of cognitive control and learning. With anodal stimulation, Woodman and Reinhart found that ERN amplitudes increased to levels twice that of the sham condition. In addition to improvements in ERN, they also found improvements in feedback-related negativity (FRN), and behavioral measures such as reaction time and percentage of trials answered correctly. Woodman and Reinhart's study will prove helpful when developing future interventions and treatments for disorders with widespread cognitive impairments.

Transcranial Direct Current Stimulation in Schizophrenia Patients

TDCS has not been completely or efficiently utilized to improve cognition in schizophrenia, but it has been used, most recently, to reduce hallucinations in patients. Transcranial magnetic stimulation (TMS), a more invasive procedure, has in the past been used to reduce auditory hallucinations (Speer et al., 2000; Lee et al., 2005; Hoffman et al., 2005; Poulet et al., 2005; Chibbaro et al., 2005). These studies are now being replicated using tDCS. Brunelin and associates (2012) tested the possibility of using cathodal tDCS over the left temporo-parietal cortex and anodal stimulation over the left DLPFC to reduce auditory visual hallucinations and negative symptoms. Stimulation lasted for 20 minutes. Auditory verbal hallucinations were greatly reduced, and Brunelin et al. found that this effect lasted up to three months. Additionally, Brunelin and associates found that a number of positive and negative symptoms were greatly reduced. Although the sample size for the study was small, these results

show that tDCS could be very promising in the treatment of psychosis especially in patients who are refractory towards drugs.

Although there have not been many studies regarding the effects of tDCS on cognitive deficits of schizophrenia, there is accumulating evidence from healthy participants to suggest its potential. Defective performance monitoring contributes to the variety of clinical symptoms such as auditory hallucinations (Frith, 1987), delusions of alien control (Frith & Done, 1989), and formal thought disorder (McGrath, 1991). Although studies have already found effects of tDCS on specific positive symptoms such as hallucinations (Brunelin et al., 2012), by focusing on improving performance monitoring, we can target related cognitive issues in the future. In this study, we use anodal and sham stimulations on our participants to test whether anodal stimulation will significantly improve electrophysiological and behavioral indices of performance monitoring in patients. In our patients, we hypothesize that anodal stimulation will improve both electrophysiological and behavioral indices of performance monitoring and increase rates of learning.

Method

Subjects

Ten outpatients with schizophrenia were recruited from a psychiatric facility in Nashville, TN. Diagnoses of patients were confirmed according to the Diagnostics and Statistical Manual of Mental Disorders, Fourth Edition Text Revised (DSM-IV-TR). Ten healthy controls with no history of DSM-IV Axis I as confirmed by the SCID-IV in themselves or their families were recruited from the same city. Both groups were matched for age, and sex. All subjects reported normal color vision, and normal or corrected-to-normal visual acuity. Exclusion criteria are

substance abuse/dependence history within 6 months, or lifetime history of significant head injury or neurological illness. All patients were clinically stable and on medication.

Current symptom ratings for schizophrenia patients were assessed within two weeks of the experiments using the Brief Psychiatric Rating Scale (BPRS, Overall and Gorham, 1962), the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984), and the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1983). All healthy controls completed the Schizotypal Personality Questionnaire (SPQ; Raine, 1991), a 74-item self-report questionnaire assessing schizotypal personality. The demographics and clinical characteristics of participants are outlined in Table 1.

Participants gave informed consent prior to procedures approved by the Vanderbilt University Institutional Review Board and were paid for their participation.

Materials

For tDCS, a pair of conductive rubber electrodes placed in saline-soaked synthetic sponges was used. A stretchy headband was used to keep the sponges and rubber electrodes in place. TDCS was administered using a battery driven, constant current stimulator (Mind Alive Inc, Alberta, Canada) for 20 minutes before the start of the behavioral experiments.

Design

The experiment was a 2-day, single-blind, sham-controlled, within-subject tDCS/ERP experiment with patients with schizophrenia and healthy controls. Subjects were told that they would be participating in a working memory study and that tDCS would be applied before the cognitive experiment. Patients underwent anodal stimulation on the first day, and sham stimulation on the second day, but were unaware of the type of stimulation they were receiving.

Stop-Signal Task

Error-related negativity was gauged using the stop-signal task with explicit feedback. All trials began with a central fixation point (0.37˚ square, 30 cd/m^2, 800-1200 ms). On no-stop trials (66% of all trials), a peripheral target (1˚ x 1˚, 10˚ from the center of screen along the horizontal meridian, 700ms) appeared to either the left or right of the fixation point. On stop trials (33% of all trials), subjects had to withhold their response when they saw the stop signal (a central square 0.66˚, with 0.08˚ line width, 30 cd/m^2). Six stop signal delays (SSDs, the stimulus-onset asynchrony between the onset of the target and the onset of the stop signal) were sampled with equal probability: 60, 120, 180, 240, 300, 360 ms. After presentation of the stop signal, the stimuli remained on the screen until 700 ms had elapsed from the presentation of the target. The inter-trial interval was 100-1200 ms. Each participant performed 720 trials in each session.

The stop-signal task required participants to learn which of two buttons (2 or 4, which were the up and down buttons) on a handheld gamepad corresponded to which target color. Both buttons were pressed with the thumb of the right hand. Target colors changed across the two sessions so that subjects would have to relearn the stimulus-response mapping for each session. Target stimuli could appear in 1 of 3 pairs of colors (red, $x = 0.612$, $y = 0.333$, 15.1 cd/m^2 and blue, $x = 0.146$, $y = 0.720$, 6.41 cd/m^2; magenta, x = 0.295 y = 0.153, 19.3 cd/m^2 and green, $x = 0.281$, $y = 0.593$, 45.3 cd/m^2; purple, x = 0.245 y = 0.126, 9.3 cd/m^2; yellow: $x = 0.408$, $y = 0.505$, 54.1 cd/m^2). The stimulus-response mapping assignments (the three color pairs, and the mapping of each color to the appropriate button) were randomized across the two days with the order of each color-to-button set randomized across participants. Participants were told that one button only corresponded with one color, but were not told which button responded to which color. Participants had to learn through trial and error which button was mapped to which color.

This was made more challenging by the implementation of a 700 ms deadline for any button press.

To establish stimulus-response mappings, patients received performance-based feedback (presented for 1000 ms at the end of each trial) in the form of either a centrally presented outline of a circle (0.88˚ diameter, 0.13˚ thick) or a cross (0.88˚ length, 0.13˚ thick). Depending on the trial, the plus and the circle could either mean an incorrect or correct response. The meaning of these symbols was randomized. Feedback assignments were different in both sessions, and participants were told before the task which signs corresponded with a correct or incorrect response. A schematic representation of the change detection task can be seen in Figure 1.

Transcranial direct current stimulation

TDCS was administered using a battery driven, constant current stimulator and a pair of conductive rubber electrodes (active: 19.25 cm^2 reference: 52cm^2) placed in saline-soaked sponges, which were held in place by a headband (Mind Alive Inc., Alberta, Canada). The reference electrode was placed on the center of the right cheek 3 cm diagonally from the lip to avoid any confounding effects from other brain regions (Berryhill et al., 2010; Hsu et al., 2011; Tseng et al., 2012). Current was applied for 20 minutes at 2.0 mA intensity over the medial-frontal cortex (site FCz, from the International 10-20 System), which created an excitatory (anodal) current for up to 90 minutes (Nitsche & Paulus, 2001). A sham tDCS condition was administered following an identical procedure, but the stimulation only lasted one minute before tDCS was turned off without the patient's knowledge. Patients were blind to the polarity of stimulation.

ERP Procedure

The error-related negativity (ERN) was recorded to observe error monitoring. The electroencephalogram (EEG) was acquired (250 Hz sampling rate, 0.01 to 100-Hz bandpass filter) using an SA Instrumentation Amplifier from 21 tin electrodes, including 7 lateral pairs (F3/F4, C3/C4, P3/P4, PO3/PO4, T3/T4, T5/T6, O1/O2), 3 midline (Fz, Cz, Pz), and 2 nonstandard sites (OL, midway between O1 and T5; and OR, midway between O2 and T6), aligned according to the International 10-20 System and embedded into an elastic cap (Electrocap International, Eaton, OH). Signals were referenced to the right mastoid electrode. Vertical and horizontal eye movements were recorded from electrodes placed lateral to both eyes, and below the left eye (Woodman & Luck, 2003). Trials tainted by ocular contaminations (e.g. blinks and lateral movements) or excessive peak-to-peak deflections were automatically rejected before averaging. Electrode impedances were kept under 4 kΩ. The EEG was recorded in an electrically shielded chamber to eliminate electrical noise.

Data Analyses

Behavioral Data

We adopted the Logan and Cowan (1984) method to estimate stop-signal reaction time (SSRT). Post-error slowing calculations accounted for the effects of nonstationarity on RT estimates (Nelson et al., 2010). For this correction, post-error slowing was calculated as the RT on no-stop trial n + 1 minus RT on no-stop trial n - 1, in which n is an error following a stop signal or on a no-stop trial.

Error-Related Potentials (ERPs)

For ERN analyses, the continuous EEG recording was baseline corrected to the interval from 200 to 50 ms prior to response and time-locked to the button-press onset. The baseline

interval ended 50 ms before the time-locking event to allow these analyses to reveal error-related activity starting before response onset (Gehring et al., 2012). For the analysis of the responses to the stop signals, EEG was locked to stop-signal stimuli on correct stop trials and baseline corrected from 200 to 0 ms prior to stop-signal onset. Stop trials in which subjects responded before the stop signals were presented were not included in ERN analyses because subjects did not have the necessary information to understand an error was committed.

The ERN amplitudes were measured from the central midline electrode (Cz) using a time window from -50 to 150 ms relative to the response onset. We calculated amplitude of the voltages as the average area under the curve of the difference wave subtracting incorrect stop and no-stop trials from correct no-stop trials (Gehring et al., 2012). The P1, a visually evoked potential (VEP) typically modulated by attention, N1, also a VEP influenced by selective attention, and N2, an ERP that peaks during uncertain responses, amplitudes quantified as mean values during the time windows (Luck and Hillyard, 1990; Pliszka et al., 2000; Schmajuk et al., 2006). Latency was measured using peak amplitude in each measurement window for each of the components.

ERN amplitudes were entered into analyses of variance (ANOVAs) with the factors of condition (anodal vs. sham), group (patients vs. controls), and trial bin (bin 1 vs. bin 2 vs. bin 3 vs. bin 4 vs. bin 5) for the learning analyses. Additionally, we used preplanned two-tailed t-tests for simple comparisons between anodal versus sham and between the two subject groups. Separate analyses were performed for each dependent variable of accuracy (in percent correct), RT and ERN values averaged into 5 bins of 10 trials each (i.e., bin 1 contained trials 1 - 10, bin 2 contained trials 11 - 20, etc.). We focused learning analyses on the first five trial bins from both

anodal and sham conditions, as this is the period in which behavior improved during the baseline sham condition.

Results

At baseline, there was no statistically significant difference between groups in age or gender. TDCS was well tolerated by all participants. All participants felt a tingling sensation during the beginning of anodal and sham stimulations.

We found that anodal stimulation to the medial-frontal cortex was able to up regulate the neurological indices of performance monitoring in schizophrenia patients. As seen in Figure 2, in the sham condition, ERN for patients was absent (error versus correct waveforms $t_9 = 0.980$, $p = 0.353$), and was significantly reduced compared to the sham condition ERN of healthy controls ($t_9 = 3.181$, $p = 0.011$). However, after 20 minutes of anodal stimulation, patients showed a significant improvement in ERN. There was a significant difference between the negative potential elicited from error versus correct trials in the anode condition ($t_9 = 3.588$, $p = 0.006$), in addition to significant improvement within the same patients ($t_9 = 4.700$, $p = 0.001$). Anodal tDCS was able to improve patient ERN to a level comparable to the healthy control ERN in the sham stimulation ($t_9 = 0.779$, $p = 0.456$). This suggests that tDCS was able to boost the abnormally low ERN of schizophrenia patients so that it was indistinguishable from the ERN of healthy subjects without any stimulation.

The improvement in the electrophysiological index of performance monitoring is coupled with improvements in the behavioral index. In Figure 3, during the sham condition, patients show significant impairment with correctly mapping the stimulus color to a button-press response compared to healthy controls ($t_9 = 2.570$, $p = 0.030$). Through anodal stimulation, we were able to improve accuracy of responses of patients comparable to that of healthy controls in

the sham condition, such that there was a negligible difference between the two ($t_9 = 0.366$, $p = 0.723$). However, RT for correct responses between the two stimulations for patients showed no significant difference ($t_9 = 0.917$, $p = 0.383$) indicating that the improvement in accuracy was not a trade-off with response times. Thus, by increasing the ERN amplitudes through anodal, patients were able to increase response accuracy without slowing down their behavior.

Improvements in both behavioral and electrophysiological indices of performance monitoring after anodal tDCS should then be apparent on trials following errors. Two important markers of cognitive control: post-error RT slowing and accuracy showed improvement after anodal tDCS. In the sham condition, patients display large cognitive control impairments such as significant reduction in post-error slowing ($t_9 = 2.292$, $p = 0.048$), and accuracy ($t_9 = 2.256$, $p = 0.050$) compared to healthy controls. After 20 minutes of anodal stimulation, patients exhibited significant improvements in post-error slowing ($t_9 = 3.330$, $p = 0.009$) and accuracy ($t_9 = 2.645$, $p = 0.027$), which did not significantly differ from those of healthy controls during the sham condition (post-error slowing $t_9 = 0.238$, $p = 0.817$, accuracy $t_9 = 0.050$, $p = 0.961$).

In addition to improved performance monitoring, medial-frontal anodal stimulation could temporarily repair magnitude of ERN, reaction time, and learning rates. Figure 5 shows that in the sham condition ERNs from patients are severely attenuated compared to those of controls. Learning behaviors were reduced in patients compared to controls as shown by a significant interaction of subject group x trial bin on accuracy ($F_{4,36} = 3.725$, $p = 0.045$), and on no-stop RT ($F_{4,36} = 3.845$, $p = 0.020$). Anodal stimulation to the medial-frontal cortex was able to temporarily improve learning in schizophrenia patients by improving learning rates and ERN. Figure 5 shows that patients receiving anodal stimulation had increased ERN during learning, and they were able to match learning rates to those of healthy controls in the sham condition.

This improvement between the anodal and sham sessions was demonstrated through an interaction of stimulation condition x trial bin on ERN amplitude ($F_{4,36} = 5.858$, $p = 0.004$), no-stop RT ($F_{4,36} = 6.438$, $p = 0.003$), and accuracy ($F_{4,36} = 8.262$, p=0.001). There were no significant differences between the anodal condition patients and sham condition healthy controls (ERN $F_{4,36} = 0.531$, $p = 0.625$, RT $F_{4,36} = 2.110$, $p = 0.125$, accuracy $F_{4,36} = 0.862$, $p = 0.477$).

There were no significant changes in stop-signal reaction time (SSRT), an index of how quickly a preplanned response can be stopped. Patients show impaired SSRT compared to healthy controls ($t_9 = 2.271$, $p = 0.049$), but there is no change in SSRT after the anodal stimulation for either groups (patients $t_9 = 0.146$, $p = 0.887$, controls $t_9 = 1.027$, $p = 0.33$). These findings indicate that medial-frontal tDCS stimulation was able to selectively regulate post-error behavioral adjustments suggesting a causal link between medial-frontal cognitive deficits and cognitive control deficits in schizophrenia.

Although general improvements were found in both performance monitoring and learning, there were individual patient differences in the ERN changes between sham and anodal conditions. Figure 6 shows the individual patient response locked ERPs from both correct and error no-stop trials. The individual differences in improvement may indicate correlations with specific clinical symptoms. Table 2 shows the correlational analyses between the mean ERN amplitudes across both stimulations against illness duration and each measure of clinical symptoms. Figure 7 shows that delusions have a significant negative correlation with tDCS-induced ERN changes between sham and anodal stimulations. The patients with the largest ERN improvements had the lowest delusion scores as indicated by the Scale of Assessment for Positive Symptoms ($t_9 = -0.719$, $p = 0.019$). This finding reveals an important relationship

between positive clinical symptoms and patients who receive more cognitive benefits from medial-frontal cortex stimulation.

Discussion

Cognitive deficits in schizophrenia include significant abnormalities in performance monitoring (Carter et al., 2001; Thakkar et al, 2011) and learning (Saykin et al., 1991), especially compared to healthy controls (Kopp & Rist, 1999, Mathalon et al., 2002). These deficits often cause schizophrenia patients to fail to respond to and learn from their errors. An inability to monitor performance can contribute to a number of positive and negative symptoms such as hallucinations (Bentall, 1990), delusions of alien control (Frith & Done, 1989), and formal thought disorder (McGrath, 1991). Studies have shown that these specific deficits can be attributed to abnormalities in the medial-frontal cortex (Kerns et al., 2005, Sanders et al., 2002). An ability to up regulate ERN in the medial-frontal cortex could eliminate these attenuations.

Anodal stimulation to the medial-frontal cortex improved electrophysiological and behavioral indices of performance monitoring, and learning rates. At first, patients showed a large number of errors, no post-error corrective behaviors and an inability to adapt to their errors compared to healthy controls in sham. After the 20 minutes of anodal stimulation, schizophrenia patients reached cognitive control levels comparable to those of healthy controls in the sham condition, such that no significant differences were found. Although performance monitoring and learning did not show exemplary improvements as initially thought (comparable to anodal condition healthy controls), the improvements demonstrated that tDCS is able to optimally enhance cognitive control. In line with our hypothesis, we were able to temporarily improve ERN after anodal tDCS relative to sham tDCS.

There were individual differences in the benefits of tDCS for patients. Seven out of ten of the patients showed significantly more negative potential after anodal stimulation compared to sham. By correlating clinical symptoms with the improvements in ERN, we found that patients with higher delusions scores had lower levels of ERN improvement after anodal stimulation. No other clinical symptoms correlated with induced ERN changes from sham to anodal, thus noting that specific aspects of delusions were blocking patients from ERP and behavioral gains after medial-frontal stimulation. One explanation for this phenomenon could be that delusions and suspiciousness are typically denoted by paranoia, and Drake et al. (2004) noted that depression in schizophrenia was highly predicted by paranoia. There is already dysfunctional dopamine processing in schizophrenia affecting cognitive activation of the anterior cingulate cortex (Corlett et al., 2007; Dolan et al., 1995). Dopamine lowering processes during depression could then exacerbate performance monitoring and learning deficits (Meyer et al., 2001) causing patients with high delusion scores to respond weakly or less efficiently to the anodal stimulation and thus are not effectively responding to the feedback provided after each trial.

The improvements in learning rates could have implications for working memory. Working memory is a cardinal cognitive deficit in schizophrenia (Silver et al., 2003; Lee & Park, 2005). Working memory is an active, short-term memory system with limited capacity (Baddeley, 1992). Information is temporarily held in the central executive to be manipulated and maintained by the visuospatial and phonological buffers. As we do not inform the participants which color square corresponds with which button, it is dependent on the participants' response to the feedback given at the end of each trial. Upon receiving the feedback, participants must hold the image (of either a cross or a circle) in their visual working memory, and apply the feedback onto the next trial (through post-error behaviors). If patients are unable to hold the

feedback image in working memory before it is replaced by the fixation point, then it becomes much harder for them to learn and improve in subsequent trials. Additionally, this could affect long-term memory, as it becomes harder to explicitly learn which color corresponds with which button if feedback is not properly processed. By improving indexes of learning such as ERN, RT, and accuracy, it implies that working memory and long-term memory may be subsequently improved through medial-frontal cortex anodal stimulation. TDCS's potential to directly control and enhance working memory in schizophrenia patients could lead to better treatments and therapy interventions (Fregni et al., 2005; Hoy et al., 2013).

However, there are a couple caveats regarding sample size, medication, and counterbalancing. Our sample size is small. Although we have a small sample size, the two groups were demographically matched and we ran anodal and sham stimulations for both patients and controls. Another potential problem is that all the patients were medicated, but previous studies did not find that medication resulted in working memory or error monitoring deficits (Park et al., 1995; Thakkar et al., 2011). Additionally, during the course of the experiment, we were limited to the amount of time allowed for ERN data collection, as patients could only stay in the booth for 45 minutes before becoming uninterested in the task. Thus, fewer trials were collected than a typical EEG study with a healthy control, which lasts around 3-4 hours. In addition to a fewer number of trials, many trials were unreliable due to contamination from eye blinks and movement during the task. Although the number of trials collected were fewer than expected, there was still a sufficient amount of data to show highly significant differences in ERN data for both patients and healthy controls from sham to anodal stimulation. Lastly, we were unable to counterbalance between anodal and sham sessions due to possible patient attrition. In order to take advantage of the small sample size, all participants had their

anodal session first, and sham session second, and this could have resulted in an order effect. In future studies, we will incorporate a new design, which involves counterbalancing between the two sessions in order to avoid learning and order effects.

During our experiment, symptom interviews were conducted before the experiment or on the first stimulation day. Although no other significant correlations were found between symptoms and ERN changes besides delusions, future experiments could focus on long-term positive and negative symptom changes. In our experiment, most sessions were scheduled days from each other and symptoms do not change over the course of a couple days. Yet, tDCS could have a long-term improvement effect on performance monitoring and learning. Brunelin et al. (2012) found that 20 minutes of anodal tDCS twice a day on five consecutive weekdays over the left dorsolateral prefrontal cortex in schizophrenia patients reduced reports of refractory auditory hallucinations, significantly reduced negative symptoms, and showed medium effect sizes on the positive and depressive symptom dimensions. These improvements lasted for three months. If consistent anodal tDCS is applied to the medial-frontal cortex, instead of improving performance monitoring and learning temporarily, it may be possible to find a long-term solution for the cognitive deficits. An improvement in self-monitoring could subsequently reduce positive symptom ratings. The amount of stimulation and the time course required for such results would require further studies.

Our results suggest that tDCS holds potential as a relatively simple, and low-cost stimulation tool. Twenty minutes of stimulation to the compromised medial-frontal cortex was able to temporarily improve abilities in learning, adaptation and control. If anterior cingulate cortex dysfunction reliably produces debilitating positive and negative symptoms, then there may be higher perceived benefits of employing tDCS into a clinical environment. Not only is tDCS

helpful in terms of cognitive mechanisms, but could also have developmental potential towards treating debilitating, refractory symptoms. TDCS, in the future, may have a more direct application for intervention therapy for patients with psychiatric illnesses and other disorders displaying cognitive abnormalities such as Huntington's (Beste et al., 2008) and Parkinson's disease (Ito and Kitagawa, 2006).

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Table 1. Demographic and Clinical Characteristics of Patient and Control Groups

Characteristics	Patients	Controls	*t*	*P*
Age (Years)	38.90 (6.05)	33.60 (9.70)	1.33	0.22
Gender	4F, 6M	4F, 6M	$\Phi = 0.0$	1.0
Years of Education	12.3 (2.26)	12.6 (1.35)	0.22	0.83
Handedness	68.50 (25.39)			
Duration of Illness (Years)	18.5 (7.11)			
LN Span Score	14.5 (2.51)			
SAPS (total)	20.6 (14.22)			
Hallucinations	2.1 (1.59)			
Bizarre Behavior	0.6 (1.07)			
Delusions	1.5 (1.35)			
Positive Formal TD	0.8 (1.69)			
SANS (total)	37.8 (13.81)			
Affective Flattening	2.4 (1.43)			
Alogia	1.3 (1.25)			
Avolition Apathy	3.2 (0.79)			
Anhedonia Asociality	2.3 (1.49)			
Attention	0.6 (0.70)			
BPRS (total)	21.7 (6.07)			

Note: SAPS, Scale for the Assessment of Positive Symptoms; SANS, Scale for the Assessment of Negative Symptoms; BPRS, Brief Psychiatric Rating Scale. The Φ value is the result of a Fisher exact test.

Table 2. Correlation Analysis

	Sham ERN		**TDCS-induced Δ ERN**	
	r	*P*	*r*	*P*
Illness Duration	-0.097	0.790	-0.296	0.406
SAPS	-0.470	0.171	-0.463	0.178
Hallucinations	0.013	0.972	0.017	0.963
Bizarre Behavior	-0.022	0.952	-0.208	0.565
Delusions	-0.438	0.205	-0.719	0.019*
Positive Formal TD	-0.197	0.585	-0.079	0.829
SANS	0.708	0.022*	0.396	0.257
Affective Flattening	0.543	0.104	0.534	0.112
Alogia	0.611	0.061	-0.158	0.664
Avolition Apathy	0.028	0.938	0.183	0.613
Anhedonia Asociality	0.301	0.398	0.414	0.234
Attention	-0.029	0.937	-0.412	0.237
BPRS	-0.524	0.120	0.210	0.560

Note: The two-tailed Pearson correlations indicate relationships between the clinical symptom scores, illness duration, and the patients ERN amplitudes. The left side of the column is correlations based on ERN amplitudes from the sham condition. The right side of the column is based on ERN amplitude changes from the sham to anodal conditions.

Figure Captions

Figure 1 Schematic representation of transcranial direct current stimulation. Sham sessions did not require any stimulation, while anode sessions contained 20 minutes of anodal stimulation (represented by blue).

The stop-signal task required participants to report one of two color squares (purple versus yellow, red versus blue, or magenta versus green) by pressing either the up or down button on a gamepad. The stop trials required participants to cease responses if a stop signal appeared after the target stimulus.

Figure 2 Response locked grand average event-related potentials from no-stop trials. These are from the correct (solid line) and error (dashed line) trials at the central midline electrode (Cz) across both sham and anodal conditions and subject groups. The gray regions indicate the latency window of the error-related negativity (ERN).

Figure 3 Mean percentage of stimulus response mapping the errors on no-stop trials (black), and mean RT on all no-stop trials (red) across both conditions for patients (dashed) and controls (solid).

Figure 4 Post-error slowing of RT (black) and post-error accuracy (red) after a failure to stop or make a correct response across patients (dashed) and healthy controls (solid).

Figure 5 Mean ERN amplitude, RT, and accuracy from no-stop trials across sham (black) and anodal (blue) for patients (dashed) and controls (solid).

Figure 6 Individual response locked event-related potentials from correct (solid) and error (dashed) no-stop trials measured at the central midline electrode (Cz) across both transcranial direct current stimulation (tDCS) conditions. The yellow regions indicate the latency window of the error-related negativity (ERN).

Figure 7 A negative correlational relationship between the change in ERN amplitude from sham and anodal conditions for each patient and the patients' delusional score on the Scale for the Assessment of Positive Symptoms (SAPS).

Figure 1

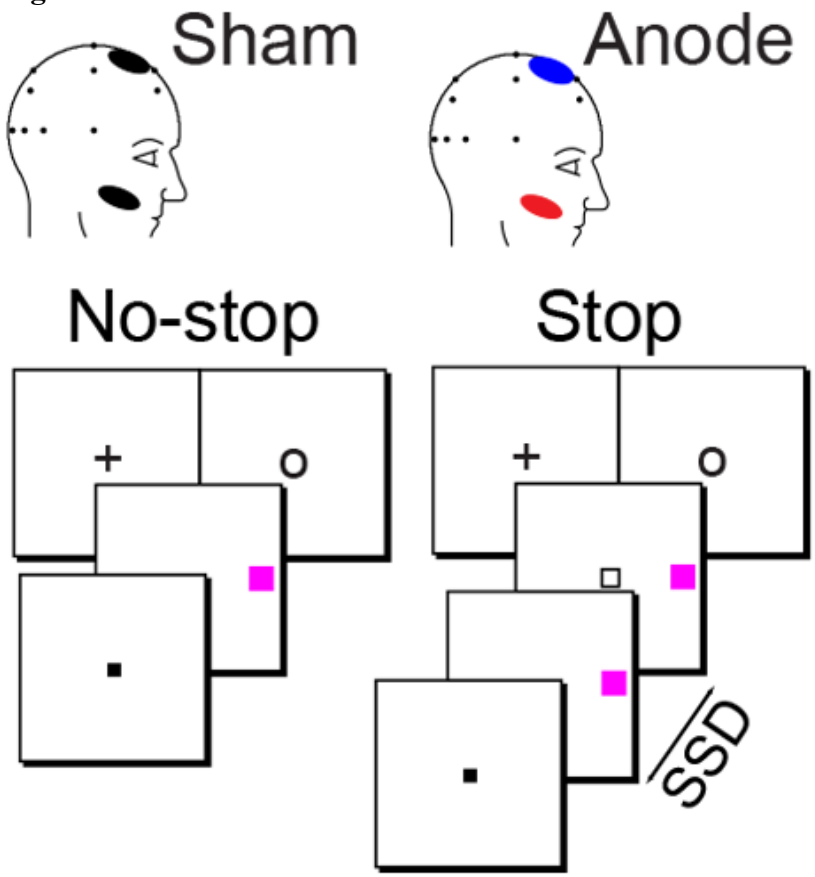

Figure 2

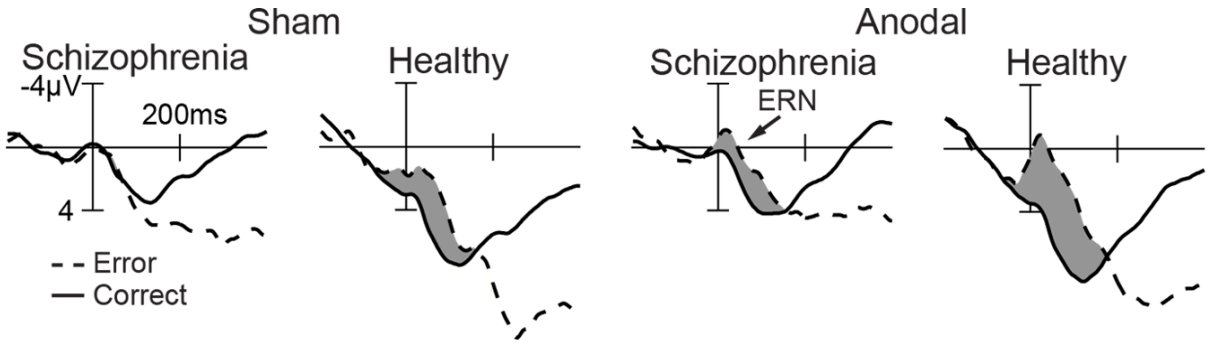
Sham
Anodal
Schizophrenia
Healthy
Schizophrenia
Healthy
-4μV
200ms
4
ERN
Error
Correct

Figure 3

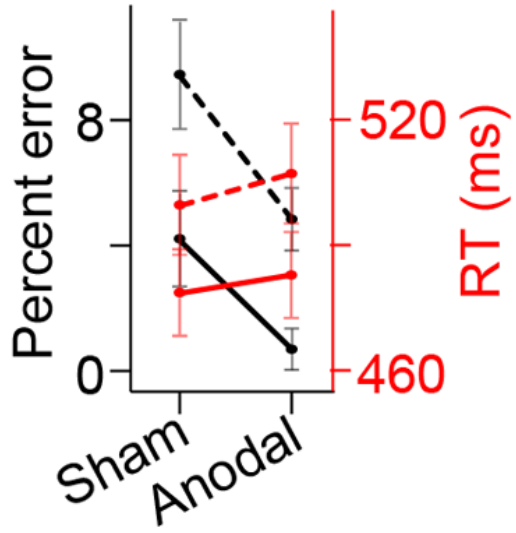

Figure 4

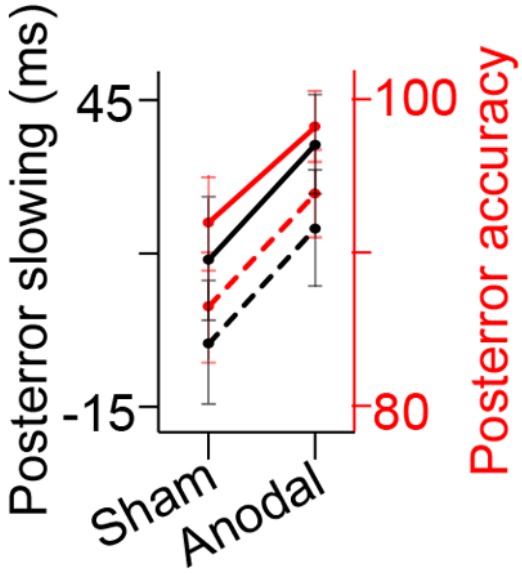

Figure 5

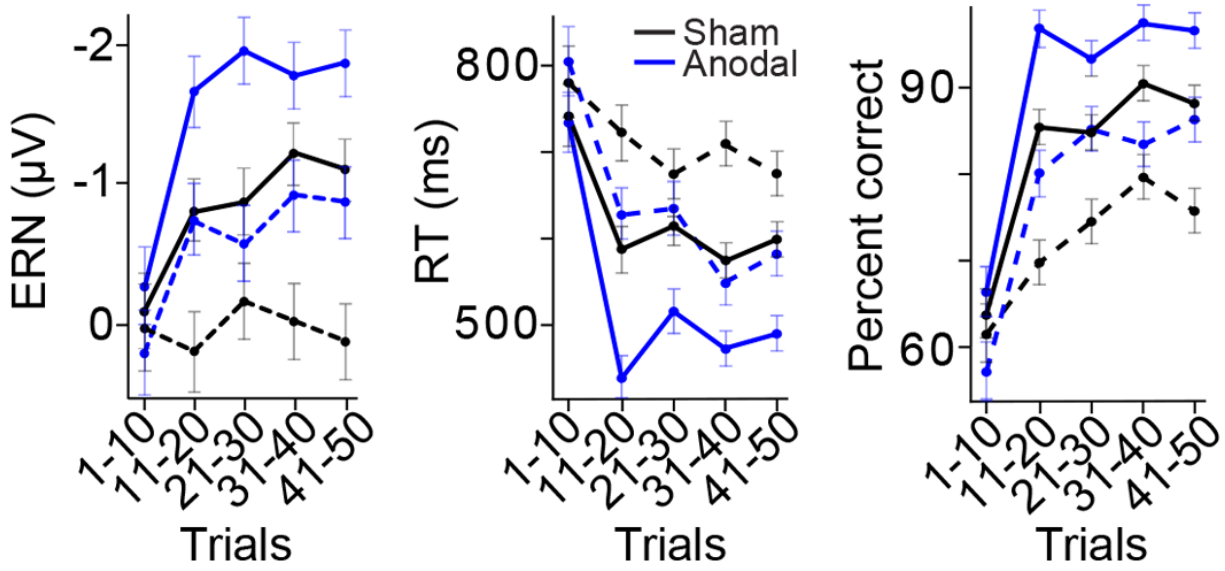
ERN (μV)
-2
-1
0
1-10
11-20
21-30
31-40
41-50
Trials
RT (ms)
800
500
Sham
Anodal
Trials
Percent correct
90
60
Trials

Figure 6

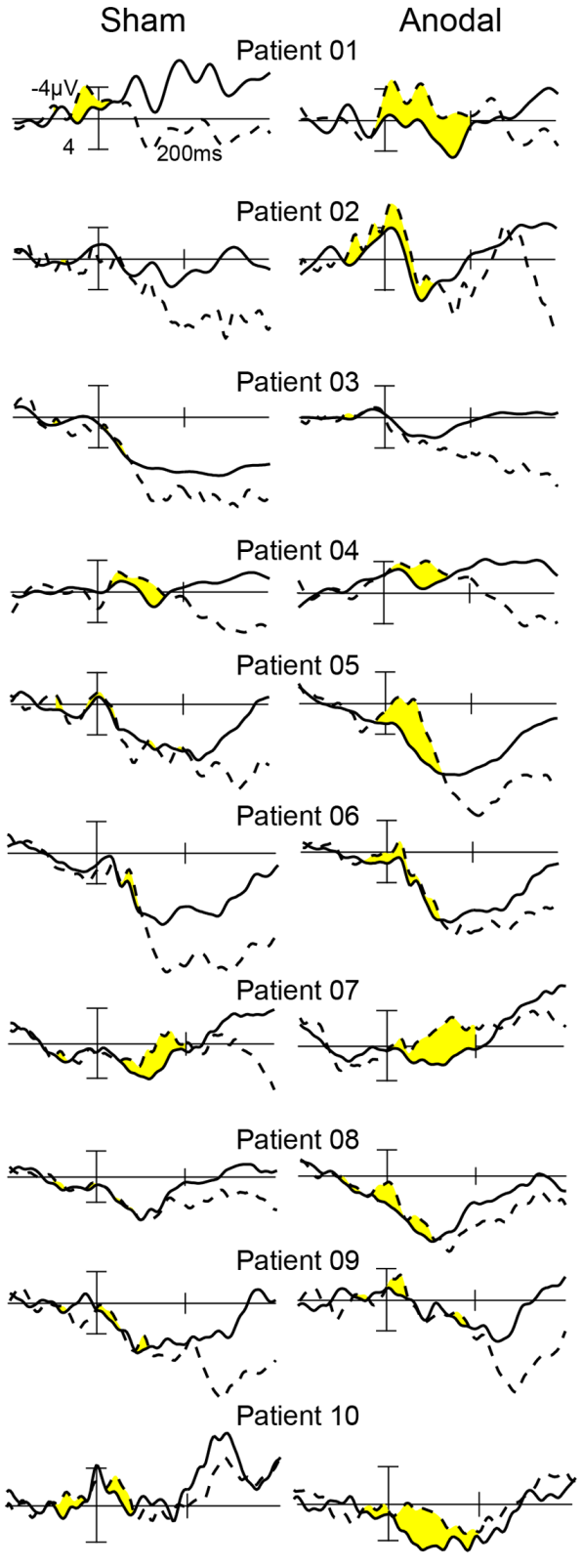
Sham
Anodal
Patient 01
-4μV
4
200ms
Patient 02
Patient 03
Patient 04
Patient 05
Patient 06
Patient 07
Patient 08
Patient 09
Patient 10

Figure 7