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The effect of transcranial direct current stimulation on psychotic symptoms of schizophrenia is associated with oxy-hemoglobin concentrations in the brain as measured by near-infrared spectroscopy: A pilot study

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ABSTRACT

Transcranial direct current stimulation (tDCS) has been shown to be effective in treating some of the symptoms of schizophrenia. In the current study, we sought to determine whether oxy-hemoglobin ([oxy-Hb]), measured by near-infrared spectroscopy (NIRS), is associated with effects of transcranial direct current stimulation (tDCS) on psychotic symptoms of schizophrenia. Twenty-six patients underwent tDCS (2 mA × 20 min) two times per day for five consecutive days. The anodal electrode was placed over the left dorsolateral prefrontal cortex while the cathodal electrode was placed over the right supraorbital region. One month after the last administration of tDCS, positive, but not negative symptoms, evaluated by the Positive and Negative Syndrome Scale (PANSS), were significantly improved. At baseline, regional [oxy-Hb] concentrations in the brain were measured by a 52-channel NIRS instrument. Significant negative correlation was demonstrated between [oxy-Hb] concentrations of left temporoparietal regions throughout verbal fluency tasks vs. changes of PANSS Positive and Negative subscale scores. This is the first study to demonstrate the correlation between the response of neural activity to cognitive tasks at baseline and the ability of tDCS to improve positive and negative psychotic symptoms. Our observations suggest that NIRS provides a marker to predict the response to treatment with tDCS in schizophrenia.

1. Introduction

Schizophrenia is a psychiatric disorder characterized by psychotic symptoms, mood symptoms, and cognitive impairments (Kremen et al., 2010; Kurtz, 2005; Micallef et al., 2006). Although its pathogenesis has not been fully elucidated, several types of intervention, such as antipsychotic treatments and electroconvulsive therapy, have been used. However, they are not always effective and some symptoms often remain treatment-resistant (Englisch and Zink, 2012), indicating a need for the development of novel therapeutics.

Neuromodulation is defined as alterations of neural activity with targeted delivery of a stimulus to the brain. Methods of neuromodulation include non-invasive approaches, e.g. transcranial magnetic stimulation, as well as invasive (implanted) devices, e.g. spinal cord stimulation and deep brain stimulation. Among them, transcranial direct current stimulation (tDCS) is feasible and safe, using weak and direct electrical current to the brain through electrodes (Yokoi et al., 2017; Yokoi and Sumiyoshi, 2015). tDCS changes cortical excitability (Schretlen et al., 2014; Stagg and Nitsche, 2011), and has been suggested to modulate cortico-subcortical/cortico-cortical pathways (Lorenz et al., 2003; Stagg et al., 2013).

In schizophrenia, connectivity in the frontoparietal and interhemispheric networks is decreased (Baker et al., 2014; Guo et al., 2014; Hoptman et al., 2012), providing a rationale for beneficial effects of tDCS on some of the symptoms of the illness, particularly, psychotic symptoms. For example, as Yokoi et al. (2017) reviewed, most of the studies to investigate the benefits of tDCS in the treatment of schizophrenia have focused on psychotic symptoms, such as positive and negative symptoms (Brunelin et al., 2012; Gomes et al., 2015; Mondino et al., 2016; Palm et al., 2016; Yokoi et al., 2017). Also, we have reported the beneficial effects of tDCS on psychotic symptoms in patients with schizophrenia (Narita et al., 2017). Overall, psychotic symptoms of schizophrenia have been suggested to be alleviated by tDCS.

Since there is little knowledge on objective methods to predict whether an intervention will be successful, search for objective indices, such as biomarkers, is desirable (Ferrarelli, 2013). Near-infrared

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spectroscopy (NIRS) is a non-invasive tool to evaluate brain function which offers several advantages; it is easy to set up, requires minimal constrains, and does not occupy a large space (Pu et al., 2014). NIRS estimates oxy-hemoglobin ([oxy-Hb]) and deoxy-hemoglobin ([doxy-Hb]) concentrations, which reflect changes of regional cerebral blood volume (Sato et al., 2013). Several studies have evaluated the relationship between brain activities, measured by NIRS, and symptoms of schizophrenia. Thus, Chou et al. (2014) et al. reported that longer duration of untreated psychosis is associated with decreased cortical activities over the fronto-temporal regions (Chou et al., 2014). In addition, Noda et al. (2017) et al. found an aberrant re-increase in [oxy-Hb] concentrations in prefrontal and temporal regions of patients with schizophrenia performing verbal fluency tasks, and concluded that NIRS may provide a potential biomarker of working memory deficits in chronic schizophrenia (Noda et al., 2017). Furthermore, Lee et al. (2008) et al. observed that increased frontal activity was correlated with accuracy of working memory in patients with schizophrenia. Taken together, NIRS may provide a measure of brain functions based on regional blood flows, as in the case with functional magnetic resonance imaging (fMRI) (Lee et al., 2008).

Although previous trials demonstrated the relationship between cortical activity measured by NIRS and symptoms of schizophrenia (Chou et al., 2014; Lee et al., 2008; Noda et al., 2017), no study has been attempted to determine whether neural activity of specific regions, measured by NIRS would predict clinical benefits of tDCS. Considering that longer duration of untreated psychosis is associated with decreased cortical activities of the frontotemporal regions (Chou et al., 2014), we hypothesized that neural activity of some brain areas, e.g. temporal regions, would be related to effects of tDCS on psychosis. In the current study, we sought to determine whether [oxy-Hb] concentrations in specific brain regions measured by NIRS at baseline are correlated with change of psychotic symptoms treated with tDCS in patients with schizophrenia. The dataset used in this study is overlapped with that in our previous study (Narita et al., 2017). Data from 26 patients (who underwent NIRS measurement) out of the full dataset comprising of 28 subjects were used for analyses.

2. Materials and methods

This study was carried out in accordance with the latest version of Declaration of Helsinki, and was approved by Ethical Committee of National Center of Neurology and Psychiatry, Tokyo, Japan. Informed consent of the participants was obtained after the nature of the procedures had been fully explained.

2.1. Participants

Inpatients and outpatients at National Center Hospital, National Center of Neurology and Psychiatry were enrolled. Participants were recruited by referrals of psychiatrists, according to inclusion/exclusion criteria, as follows;

Inclusion criteria:

1) Meeting DSM-5 criteria for schizophrenia
2) Being 20 through 60 years old
3) Being able to sign and give consent

Exclusion criteria:

1) Alcohol or substance disorder
2) Traumatic brain injury
3) Epilepsy

2.2. tDCS

Soterix Medical 1 × 1 Transcranial Direct Current Low-Intensity Stimulator Model 1300A was used. For each session, the tDCS montage comprised placement of the anode over the left dorsolateral prefrontal cortex (DLPFC) and the cathode over the right supraorbital area (corresponding to F3 and FP2, according to the International 10–20 electroencephalography system), as previously described (Boggio et al., 2008; Narita et al., 2017). Rubber electrodes were inserted in 35-cm^2 saline-soaked sponges and fixed with headband. We applied direct current of 2 mA for 20 min for each session. Participants underwent ten tDCS sessions (twice per day for five consecutive days). tDCS was performed approximately at 10 a.m. and 2 p.m (Narita et al., 2017).

tDCS was administered by trained psychiatrists. In order to improve adherence, we provided all patients and their study partners with costs of transportation, and reminded and rescheduled all visits if necessary.

Criteria for discontinuing interventions were as below:

1) In case patients withdraw informed consent to participate
2) In case severe adverse effects are observed
3) In case patients fail to undergo three consecutive sessions of tDCS

2.3. Outcome measures

2.3.1. NIRS

Hemoglobin concentrations throughout verbal fluency tasks were measured by a 52-channel NIRS instrument (ETG-4000; Hitachi Medical Co., Tokyo, Japan), as previously reported (Noda et al., 2017).

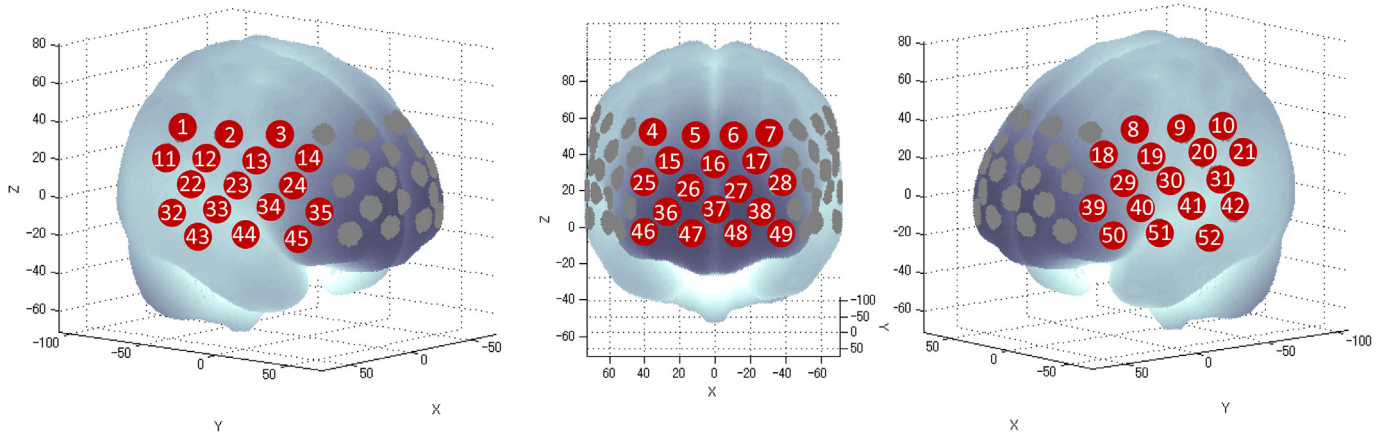

Fig. 1. Measurement points of 52 channels for near-infrared spectroscopy (NIRS). The 52 measuring positions are labeled from ch1 to ch52, i.e. from the right-posterior to the left-posterior regions.