Case Report

Neural Effects of Transcranial Direct Current Stimulation in Schizophrenia: A Case Study using Functional Near-infrared Spectroscopy

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ABSTRACT

Schizophrenia is a severe neuropsychiatric disorder characterized by delusions, hallucinations, behavioral symptoms, and cognitive deficits. Roughly, 70%–80% of schizophrenia patients experience auditory verbal hallucinations (AVHs), with 25%–30% demonstrating resistance to conventional antipsychotic medications. Studies suggest a promising role for add-on transcranial direct current stimulation (tDCS) in the treatment of medication-refractory AVHs. The mechanisms through which tDCS could be therapeutic in such cases are unclear, but possibly involve neuroplastic effects. In recent years, functional near-infrared spectroscopy (fNIRS) has been used successfully to study tDCS-induced neuroplastic changes. In a double-blind, sham-controlled design, we applied fNIRS to measure task-dependent cerebral blood flow (CBF) changes as a surrogate outcome of single session tDCS-induced effects on neuroplasticity in a schizophrenia patient with persistent auditory hallucinations. The observations are discussed in this case report.

Key words: *Auditory signal detection, functional near-infrared spectroscopy, schizophrenia, transcranial direct current stimulation*

INTRODUCTION

Schizophrenia is a severe neuropsychiatric disorder characterized by delusions, hallucinations, behavioral symptoms, and cognitive deficits. Roughly, 70%–80% of schizophrenia patients experience auditory verbal hallucinations (AVHs), with 25%–30% of these cases demonstrating resistance to conventional antipsychotic medications.[1] To address this challenge, a great deal of attention has been focused on the development

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of new therapies for persistent AVHs in refractory schizophrenia, including the use of transcranial direct current stimulation (tDCS).[1-3] tDCS is a safe, noninvasive form of continuous low current neurostimulation that can be used to reduce the severity of AVHs with long-lasting effects.[1,3-5] Although many potential mechanisms may underpin the effects of tDCS on AVHs, current evidence suggests the primary effect results from neuromodulation of cortical excitability at the left temporoparietal junction (TPJ) and left dorsolateral prefrontal cortex (DLPFC).[1,6,7] However, assessing the effects of tDCS on neuroplasticity in these distinct brain regions during task performances has proven to be difficult.[8,9]

In recent years, functional near-infrared spectroscopy (fNIRS) has been used successfully to study tDCS-induced neuroplastic changes. Similar to functional magnetic resonance imaging, fNIRS is blood oxygen level dependent and based on the principle of "neurovascular coupling."[10] It has been reported that fNIRS efficiently captures tDCS-induced hemodynamic changes in online, offline, rest, and task conditions.[11-13] During tDCS, anodal current increased oxyhemoglobin (HbO_2) concentrations in the resting state, an effect that persisted for 25–42 min post-tDCS;[11] cathodal current increased HbO_2 concentrations during tDCS, but decreased post-tDCS. Similar results were reported in four chronic ischemic stroke survivors where anodal tDCS administration was associated with an initial dip in HbO_2 followed by increased regional changes in HbO_2 and deoxyhemoglobin concentrations.[12]

In this case report, we have used fNIRS to measure task dependent cerebral blood flow (CBF) changes associated with tDCS administration. Using a double-blind, sham-controlled design, this case study applied fNIRS to measure task-dependent CBF changes as a surrogate outcome of single session tDCS-induced effects on neuroplasticity in a schizophrenia patient with persistent auditory hallucinations.

PATIENT DESCRIPTION AND METHODS

Ms. G was an unemployed right-handed 24-year-old single female with a postsecondary education level. She was admitted to the National Institute of Mental Health and Neurosciences psychiatry wards in 2013. She presented at the age of 21 with 3-year history of an early acute onset of symptoms consisting of AVHs, made phenomena, and delusions of persecution. The patient was diagnosed with schizophrenia according to International Classification of Diseases, Tenth Edition criteria and demonstrated a treatment-refractory continuous course with persistent AVHs. She had failed trials of oral medications such as olanzapine 15 mg/day, risperidone 18 mg/day, penfluridol 20 mg/week, aripiprazole 20 mg/day, asenapine 10 mg/day, iloperidone 16 mg/day, and depot drugs such as flupenthixol decanoate 40 mg/month and olanzapine 405 mg/month. Each regimen was attempted for at least 3 months and elicited negligible or only partial responses. She was started on clozapine 20 days before the study, and the dosage was gradually increased to 125 mg/day. Pre-tDCS Scale for the Assessment of Negative Symptoms and Scale for Assessment of Positive Symptoms scores were 29 and 22, respectively, and the pre-tDCS Auditory Hallucination Rating Scale[14] score was 22. Informed consent was obtained from the patient and the patient's family using a recommended consent form for single case studies. The experiment was designed as a sham-controlled double-blind case study with sessions 48 h apart.

An auditory signal detection task was administered concurrently with fNIRS acquisition pre-and post-administration of coded tDCS on both days. tDCS was administered using standard equipment (neuroConn DC-STIMULATOR PLUS, http://www.neuroconn.de/dc-stimulator_plus_en/) as previously described with strict safety measures.[1,3] During tDCS, the anode was placed with the electrode centered over a midpoint between F3 and FP1 (left DLPFC), and the cathode was centered over a midpoint between T3 and P3 (left TPJ). The electrode size was 35-cm.[2] The tDCS parameters for true and sham tDCS were identical to those administered by Brunelin *et al*.[1] During true tDCS, 2 mA of current was administered for 20 min with a ramp up and down of 20 s each. During sham tDCS, 2 mA of current was passed for the first 40 s of stimulation, followed by small current pulses every 550 ms (110 μA over 15 ms). The two sessions were conducted 48 h apart, and both sessions were coded to blind the subject and the investigators to the authenticity of treatment. Potential adverse effects of tDCS were assessed using a previously validated questionnaire.[3]

The patient performed a signal detection task during the administration of fNIRS. The signal detection task was constructed as previously described[15-18] and was validated for use in the Indian population.[18] The subject was asked to detect a voice stimulus embedded in white noise. Stimuli were presented using Bose noise cancelling earphones (QuietComfort® 20 Acoustic Noise Cancelling® Headphones) and played using a desktop at 65 sound pressure level (SPL). Four different versions of the auditory signal detection task were used to minimize the influence of a practice effect. On the basis of hits and false alarms incurred by the patient, discriminability index (d') and response decision bias

were calculated.[15] Response bias is the measure of decision-making bias the patient accepted to report the ambiguous noise as meaningful stimuli. d' recorded the sensitivity with which the patient distinguished voiced trials (signals) from the white noise (noises).

fNIRS optical data were acquired with a continuous wave fNIRS system (NIRScout, NIRx Medical Technologies, LLC, CA, USA) operating at 2 wavelengths (760 nm and 850 nm). Eight sources and four detectors were used for acquisition in a unilateral montage with a sampling frequency of 7.812 Hz yielding a total of 12 active channels (source-detector pairs). Based on the international electroencephalography 10–20 system, the optodes were placed using a tight fitting cap in a band-like configuration on the scalp, covering the DLPFC anteriorly and extending to the TPJ laterally. fNIRS data were processed using the SPM for NIRS software.[19] Activation contrasts were generated, and the beta values were extracted for repeated measure ANOVA analysis.

RESULTS

There was no observed difference in the clinical profile of the subject between days 1 and 2. During both true and sham tDCS, the subject reported no discomfort except "mild itching and burning" during tDCS initiation. No significant changes were reported on the auditory signal detection task, and the scores were unaffected by tDCS on both days; however, the subject demonstrated a clear lenient response bias on both days 1 and 2. The repeated measure ANOVA was performed on fNIRS beta values with tDCS type (true/sham) and time point (pre/post) for voice versus noise contrast results. The post- and pre-change in HbO_2 concentration during true tDCS was found to be greater than that of sham tDCS [Figure 1]. However, this interaction effect (time X tDCS type) was not found to be significant at α level of 0.05 ($F = 0.46$, $P = 0.52$).

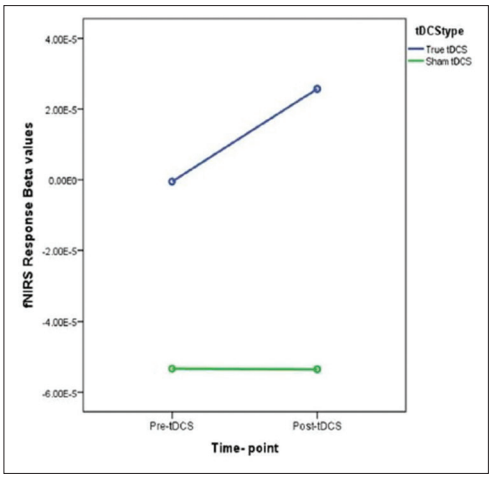

Figure 1: Effect of pre- and post-true versus sham transcranial direct current stimulation on estimated functional near-infrared spectroscopy activation mean beta values of voice minus noise contrast during auditory signal detection task

DISCUSSION

This case study evaluated the neural effects of single-session tDCS in a schizophrenia patient with refractory auditory hallucination using a double-blind, sham-controlled design. Although there were no significant changes observed in behavioral performance on the Auditory Signal detection (ASD) task, the patient demonstrated a clear external bias on both days 1 and 2, which has been routinely observed in schizophrenia patients when compared to healthy controls.[20,21] The patient also reported belief of receiving sham tDCS on both days, providing validity for the blinded experimental design and minimizing the potential for placebo effects of tDCS administration in the findings presented. Although interaction effects between tDCS time point X tDCS type were not observed, there was a clear change in cortical activation post true tDCS. The result is consistent with previous studies reporting that single-session tDCS can cause significant changes in neuroplasticity in the area under electrodes.[22,23]

Despite the abundance of limitations associated with single-subject experiments, particularly their lack of generalizability, three impressions can be drawn from this case study that may help guide future more rigorous studies on related topics. First, the feasibility of conducting this series of experimental paradigms in a refractory schizophrenia patient was established. Second, single-session tDCS under the previously described parameters was not sufficient to elicit detectable behavioral changes in ASD task performance in this subject. However, the lack of findings in the ASD task results may reflect unique psychopathology in the subject. Third, we showed that fNIRS can be used effectively to measure the modulatory effects of tDCS on cortical excitability, highlighting viability of an alternative low-cost, portable neuroimaging method in this setting. With these results, our hope is to encourage further investigation of fNIRS and its utility in the characterization of tDCS-induced effects on AVHs and neuroplasticity.

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Conflicts of interest
There are no conflicts of interest.

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