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Original article

Exploratory study of once-daily transcranial direct current stimulation (tDCS) as a treatment for auditory hallucinations in schizophrenia

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ABSTRACT

Background: Auditory hallucinations are resistant to pharmacotherapy in about 25% of adults with schizophrenia. Treatment with noninvasive brain stimulation would provide a welcomed additional tool for the clinical management of auditory hallucinations. A recent study found a significant reduction in auditory hallucinations in people with schizophrenia after five days of twice-daily transcranial direct current stimulation (tDCS) that simultaneously targeted left dorsolateral prefrontal cortex and left temporo-parietal cortex.
Hypothesis: We hypothesized that once-daily tDCS with stimulation electrodes over left frontal and temporo-parietal areas reduces auditory hallucinations in patients with schizophrenia.
Methods: We performed a randomized, double-blind, sham-controlled study that evaluated five days of daily tDCS of the same cortical targets in 26 outpatients with schizophrenia and schizoaffective disorder with auditory hallucinations.
Results: We found a significant reduction in auditory hallucinations measured by the Auditory Hallucination Rating Scale ($F_{2,50} = 12.22$, $P < 0.0001$) that was not specific to the treatment group ($F_{2,48} = 0.43$, $P = 0.65$). No significant change of overall schizophrenia symptom severity measured by the Positive and Negative Syndrome Scale was observed.
Conclusions: The lack of efficacy of tDCS for treatment of auditory hallucinations and the pronounced response in the sham-treated group in this study contrasts with the previous finding and demonstrates the need for further optimization and evaluation of noninvasive brain stimulation strategies. In particular, higher cumulative doses and higher treatment frequencies of tDCS together with strategies to reduce placebo responses should be investigated. Additionally, consideration of more targeted stimulation to engage specific deficits in temporal organization of brain activity in patients with auditory hallucinations may be warranted.

1. Introduction

Medication-refractory hallucinations occur in about 25% of all people with schizophrenia and represent a significant cause of impaired quality of life in affected individuals [1]. Noninvasive brain stimulation that targets pathological network dynamics, in particular repetitive transcranial magnetic stimulation (rTMS), has been evaluated with mixed success for the treatment of auditory hallucinations [2–4]. Transcranial direct current stimulation (tDCS) has emerged as a complementary noninvasive brain stimulation modality that modulates cortical activity by applying a weak, constant electric current to the scalp [5]. The resulting weak electric field alters neuronal activity levels in a polarity-specific way and appears to recruit brain-derived neurotrophic factor (BDNF)-dependent plasticity [6]. A recent study successfully employed twice-daily tDCS to treat medication-refractory auditory hallucinations by simultaneously

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targeting hypoactivity in left dorsolateral prefrontal cortex (dl-PFC) and hyperactivity in left temporo-parietal junction [7].

The rationale for this spatial targeting strategy was based on imaging and electrophysiological studies. Specifically, auditory cortical areas in the left temporo-parietal region have been shown to be hyperactive during auditory hallucinations in functional magnetic resonance imaging (fMRI) studies [8,9]. In addition, a diverse set of changes in cortical oscillation patterns and functional connectivity during auditory verbal hallucinations measured by magnetoencephalography (MEG) and electroencephalography (EEG), in particular but not limited to left auditory areas, have been reported [10–14]. Further motivation for simultaneously targeting both dl-PFC and temporo-parietal junction is provided by findings of impaired functional fronto-temporal connectivity that scaled with severity of auditory hallucinations [15].

We performed a double-blind, sham-controlled exploratory clinical trial to examine if once-daily tDCS of the same targets reduce auditory hallucinations in people with schizophrenia as determined by the auditory hallucination rating scale (AHRS).

2. Methods

The study was performed at University of North Carolina - Chapel Hill (Clinical Trials.gov, NCT01963676) and approved by the UNC - Chapel Hill Institutional Review Board. Participants were recruited through referral by mental health care providers in local university clinics. All 26 participants met DSM-IV criteria for schizophrenia or schizoaffective disorder, confirmed by the Structured Clinical Interview for DSM-IV (SCID-IV). The inclusion criteria required that patients had at least three auditory hallucinations per week and were clinically stable (defined by no hospitalization or change in level of care) for a minimum of 12 weeks with no change in antipsychotic medication dose for at least 4 weeks prior to study entry. All participants were verified by chart review and/or discussion with the treating clinician to have treatment-persistent auditory hallucinations, defined as having ongoing auditory hallucinations during trials of at least 2 antipsychotic agents of adequate dose and duration. All participants or their legally authorized representatives provided written informed consent. Exclusion criteria required that subjects did not meet DSM-IV alcohol or substance abuse criteria within the past month or alcohol or substance dependence criteria within the past 6 months (other than nicotine or caffeine), had no history of significant head trauma, and had no comorbid neurological conditions (e.g. seizure disorder) or unstable medical illness.

The study design was double-blind, randomized, and sham-controlled. Blinding of the participants and all study personnel was achieved by using the "study mode" of the Neuroconn DC Plus stimulators (NeuroConn Ltd., Ilmenau, Germany) used in this study. Every participant received a numeric code by randomization performed by a third party with no knowledge or interest in the outcome of the study. Participants were assigned to a code based on entry date into the study. There were no restrictions on randomization such as blocking or stratification. All authors of the study and all other personnel involved therefore did not know which patients received verum and which patients received sham stimulation until completion of the entire study. TDCS was performed with two Neuroconn DC Plus stimulators that were synchronized by an external trigger device (Fig. 1). The montage in this study is functionally equivalent to the one used in [7,16]. However, two stimulators were used since we are preparing a follow-up study that will contrast tDCS with tACS and we did not want the study personnel or the patients to be able to discriminate between these two arms of these planned future studies by the number of devices used. A consistent electrode montage across studies will facilitate future comparisons. Three saline-soaked (0.9% sodium chloride, irrigation, USP) electrodes (7 × 5 cm) were placed between F3/FP1 (anodal, left dorsolateral prefrontal cortex), T3/P3 (cathodal left temporo-parietal junction) and a return electrode placed over Cz (posterior midline). For the tDCS used here, the return electrode has a nominally zero current flow and therefore the montage is equivalent to the ones used on previous studies. However, if theoretically the output of the two stimulators were not matched due to technical imperfections, a small stimulation current could be passed through Cz. We performed electric field simulations for a worst-case scenario of a 10% mismatch between the current output of the two stimulators using the option to simulate standard tDCS electrode pads in the HDExplore software (Soterix, New York, New York). We compared the resulting electric field distribution to the one from the original Brunelin montage and found only minimal differences that are unlikely to drive any of the effects observed in this study (Fig. 2). The location of the stimulation electrodes on the patients was found using the 10–20 placement system. Stimulation was set at +2 mA (at frontal site, anodal) and −2 mA (at temporo-parietal site, cathodal) for 20 minutes for the treatment group. The active sham group only received an initial 40 s of stimulation (same amplitudes as in treatment group) to mimic the skin sensation of tDCS. Stimulation was administered at approximately the same time of day (± 2 hours) for 5 consecutive days (Monday through Friday).

The primary outcome measure was change in auditory hallucinations severity after the 5 days of stimulation assessed

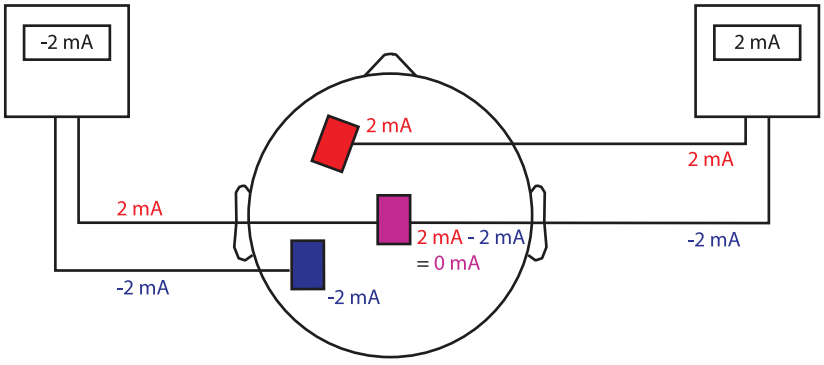

Fig. 1. Symbolic representation of stimulator and electrode configuration. Using two stimulators in the arrangement shown is functionally equivalent to using one stimulator as done in the Brunelin et al.'s study. We used this more complex setup in preparation of a study that requires two devices such that blinding to study condition can be maintained in the future.