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Efficacy of fronto-temporal transcranial direct current stimulation for refractory auditory verbal hallucinations in schizophrenia: A randomized, double-blind, sham-controlled study[☆]

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ABSTRACT

Persistent auditory verbal hallucinations (AVH) that are refractory to antipsychotic medications are reported in about 20–30% of schizophrenia patients. Transcranial Direct Current Stimulation (tDCS), a non-invasive and safe neuromodulatory technique, has attracted significant interest as an add-on treatment for refractory AVH in schizophrenia. Studies examining the efficacy of tDCS for refractory AVH in schizophrenia have reported inconsistent findings. In this study, using a randomized, double-blind, sham-controlled design (RCT), we sought to examine the effect of add-on tDCS [anode corresponding to left dorsolateral prefrontal cortex and cathode to left temporo-parietal junction; 2-mA, twice-daily sessions for 5-days] to treat refractory AVH in schizophrenia patients (N = 25); following this RCT phase, patients that had <30% reduction in AVH severity were offered an open-label extension (OLE) active stimulation to evaluate the effect of cross-over to verum tDCS. In the RCT phase, repeated measures ANOVA with tDCS type [verum (N = 12) vs. sham (N = 13)] as between subjects factor demonstrated a significant tDCS-type X time-point interaction [$F = 21.5$, $p < 0.001$, partial- $\eta^2 = 0.48$] with significantly greater reduction of AVH score in verum tDCS group as compared to sham group. In the OLE phase, sham-to-verum crossed over patients (N = 13) showed significantly greater reduction in AVH severity than their corresponding change during RCT phase ($t = 2.9$; $p = 0.01$). Together, these observations add further support to the beneficial effects of add-on tDCS to treat refractory AVH schizophrenia.

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1. Introduction

Auditory Verbal Hallucination (AVH) is a cardinal symptom of schizophrenia reported by about 70% of patients (Waters, 2012). 25–30% of schizophrenia patients have refractory AVH that persist despite adequate antipsychotic treatment (Shergill et al., 1998). Non-invasive brain stimulation techniques offer immense potential as an add-on treatment for persistent symptoms schizophrenia (Koops et al., 2015; Rajji et al., 2013). Among various non-invasive brain stimulation

techniques, in recent years, transcranial Direct Current Stimulation (tDCS) has attracted significant interest as an add-on treatment for medication-resistant symptoms in schizophrenia (Kekic et al., 2016; Kuo et al., 2017).

tDCS is a non-invasive, neuromodulatory intervention which is well-tolerated and safe; this technique involves application of low intensity, direct current (2 mA) through electrodes placed on the scalp resulting in polarity-specific neuromodulation of focal brain regions (Nitsche et al., 2008). Recent research studies as well as case reports have suggested beneficial effects of tDCS in various clinical components of schizophrenia that are non-responsive to antipsychotic medications; these include hallucinations (Mondino et al., 2015a; Ponde et al., 2017), negative symptoms (Kurimori et al., 2015; Palm et al., 2016), insight (Bose et al., 2014), cognitive deficits (Nienow et al., 2016; Orlov et al., 2017; Schretlen et al., 2014; Smith et al., 2015) catatonia (Shiozawa et al., 2013) and several others (Agarwal et al., 2013; Mervis et al., 2017).

Recently, there have been few randomized, sham-controlled trials (RCTs) examining the efficacy of tDCS for refractory AVH in schizophrenia with inconsistent findings. The first RCT by Brunelin and co-workers demonstrated a striking ameliorative effect of add-on tDCS on

Abbreviations: AHRS, Auditory Hallucination Rating Scale; AVH, Auditory Verbal Hallucination; CONSORT, Consolidated standards of reporting trials; DLPFC, dorsolateral prefrontal cortex; OLE, Open label extension; RCT, Randomized controlled trial; RMANOVA, Repeated Measures Analysis of Variance; RMANCOVA, Repeated measures analysis of co-variance; tDCS, Transcranial Direct Current Stimulation; TPJ, temporo-parietal junction.

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refractory AVH in schizophrenia (Brunelin et al., 2012). The same researchers demonstrated, in partly overlapping samples, that beneficial effect of tDCS on AVH correlated with a decrease in functional connectivity between anterior insula and left temporo-parietal junction (Mondino et al., 2016) as well as with an improvement in source monitoring deficits (Mondino et al., 2015b). In addition, there were several open label studies that reported similar beneficial effects of tDCS on AVH (Kekic et al., 2016). However, two subsequent RCTs (Fitzgerald et al., 2014; Frohlich et al., 2016) did not observe any significant effect of tDCS on AVH. While Brunelin's study protocol applied twice-daily, 20-min sessions of tDCS for 5-days, the negative studies followed the tDCS protocol of once-daily application for 5-days (Frohlich et al., 2016) and 15-days (Fitzgerald et al., 2014). Given these mixed observations, recent systematic reviews have emphasized the need for further RCTs to examine the effect of tDCS on refractory AVH in schizophrenia (Kekic et al., 2016; Lefaucheur et al., 2017; Ponde et al., 2017).

In this study, using a randomized, double-blind, sham-controlled design, we sought to examine the effect of add-on tDCS [twice-daily sessions for 5-days (Brunelin et al., 2012)] to treat medication-refractory AVH in schizophrenia patients; in addition, following RCT, we also included an open-label extension (OLE) phase [without breaking the allocation-concealment (i.e. blind) till completion of all subjects] with active stimulation to evaluate the effect of cross-over to verum tDCS.

2. Materials & methods

2.1. Patient description

Twenty-five, right-handed schizophrenia patients, in the age range of 18–45 years, attending the special clinical services for schizophrenia at National Institute of Mental Health and Neurosciences (Bengaluru, India) were examined in this study. The DSM-IV diagnosis of schizophrenia was established through Mini International Neuropsychiatric Interview (Sheehan et al., 1998) by trained interviewers with independent confirmation by another experienced psychiatrist (GVS/JCN). Right-handedness was ascertained by Edinburgh Handedness Inventory (Oldfield, 1971). Details regarding illness onset, course and treatment response were collected from the patient as well as at least one first-degree relative (primary care-giver). The patients were recruited if they had refractory Auditory Verbal Hallucinations (AVH), i.e. persistence of AVH without remission despite treatment with at least one

antipsychotic medication at adequate dose for a minimum period of three months as defined earlier (Brunelin et al., 2012). The patients were maintained on the same medications throughout the study period. Also, patients were screened for following exclusion criteria: psychiatric emergency, substance dependence, neurological disease, uncontrolled medical condition, pregnancy/post-partum status and contraindication for tDCS (e.g. local lesion, metal in head). The research protocol was approved by the institute ethics committee and registered in Clinical Trials Registry India. (<http://ctri.nic.in/Clinicaltrials/login.php>; Registration Number: CTRI/2014/12/005307); patients were recruited with written informed consent.

2.2. Study design

The study design had two phases (Fig. 1) implemented as per CONSORT guidelines (Moher et al., 2010) (please refer to Supplementary Fig. 1 for trial flow chart). In the first phase, a double-blind, randomized, parallel-arm, sham-controlled design was implemented (RCT phase). Randomized allocation was implemented using a computer-generated list of randomization sequence. The allocation concealment was ensured by administration of tDCS using “study mode” in which a five-digit numerical code unique to each patient was fed into the device that resulted in either sham or verum (active) stimulation; thus, tDCS administrator, patients and raters were blind to tDCS stimulation type (verum or sham).

Each patient was re-assessed after five days of twice-daily (10 sessions) tDCS administration; if reduction in AVH severity is <30% (as assessed by Auditory Hallucinations Rating Scale (Hoffman et al., 2003), the patient was given the option to receive additional tDCS sessions in the second phase of the study. Reduction severity of 30% was chosen based on mean severity reduction with active tDCS in earlier study (Brunelin et al., 2012).

In the second phase (open-label extension (OLE) phase), irrespective of the type of tDCS (i.e. verum or sham) received during the RCT phase, patient received verum tDCS for additional 5 days of twice-daily sessions. Importantly, the randomized allocation concealment was maintained till the completion of the all the study subjects (i.e. patients, raters and tDCS administrators were unaware of tDCS type received by the patient during the RCT phase; this blind was maintained till completion of recruitment).

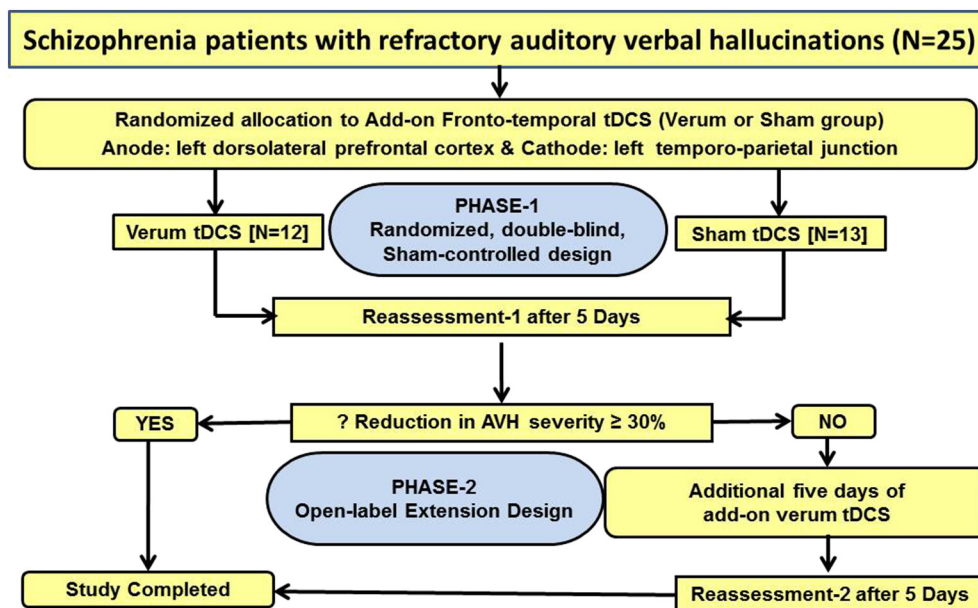


Fig. 1. Overview of the study design depicting the RCT and OLE phases.

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