Effects of transcranial direct current stimulation on working memory and negative symptoms in schizophrenia: a phase II randomized sham-controlled trial

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A R T I C L E  I N F O

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A B S T R A C T

Background: The lack of efficacy of pharmacological treatments for cognitive and negative symptoms in schizophrenia highlights the need for new interventions. We investigated the effects of tDCS on working memory and negative symptoms in patients with schizophrenia.

Method: Double-blinded, randomized, sham-controlled clinical trial, investigating the effects of 10 sessions of tDCS in schizophrenia subjects. Stimulation used 2 mA, for 20 min, with electrodes of 25 cm\textsuperscript{2} wrapped in cotton material soaked in saline solution. Anode was positioned over the left DLPFC and the cathode in the contralateral area. Twenty-four participants were assessed at baseline, after intervention and in a three-months follow-up. The primary outcome was the working memory score from MATRICS and the secondary outcome the negative score from PANSS. Data were analyzed using generalized estimating equations.

Results: We did not find group × time interaction for the working memory (p = 0.720) score or any other cognitive variable (p > 0.05). We found a significant group × time interaction for PANSS negative (p < 0.001, d = 0.23, CI.95 = –0.59–1.02), general (p = 0.011) and total scores (p < 0.001). Exploratory analysis of PANSS 5 factors suggests tDCS effect on PANSS negative (p = 0.012), cognitive (p = 0.016) and depression factors (p = 0.029).

Conclusion: The results from this trial highlight the therapeutic effects of tDCS for treatment of persistent symptoms in schizophrenia, with reduction of negative symptoms. We were not able to confirm the superiority of active tDCS over sham to improve working memory performance. Larger sample size studies are needed to confirm these findings.

1. Introduction

Schizophrenia is a heterogeneous disorder with symptoms classified into four domains: positive symptoms, negative and affective symptoms and cognitive impairments. One of the most used instrument to verify the intensity of the symptoms in this population is the Positive and Negative Scale (PANSS) and principal component analysis of PANSS suggests that the disorder is better understood through 5 factors: negative, disorganization/cognitive, excitement, positive and depressive/anxiety (Higuchi et al., 2014). Although antipsychotic medications are moderately effective for the treatment of the positive symptoms (Leucht et al., 2009), including disorganization, delusions and hallucinations, they have small-to-no effect for the cognitive and negative symptoms (Fusar-Poli et al., 2015; Green and Harvey, 2014).

The negative symptoms are associated with a reduction of the expected functioning and behavior. Symptoms include flattened affect, poverty of speech, apathy, avolition, anhedonia and asociality (American Psychiatric Association, 2013). Both cognitive and negative
symptoms may persist even after stabilization of the illness (Brissos et al., 2011; Haro et al., 2015). In addition, they are strongly correlated to poor functional outcome and low recovery rates, evidencing the need for alternatives in treatment (Fusar-Poli et al., 2013; Fusar-Poli et al., 2015; Green and Harvey, 2014; Grimes et al., 2017; Haro et al., 2015).

The cognitive impairments can be observed ten years before the first psychotic episode (Goff et al., 2011; Kahn and Keefe, 2013) and have been reported in first-degree relatives (Cella et al., 2015). Among the most impaired abilities, the speed of processing, executive functioning, attention, working memory (WM) and cognitive control deficits have been associated with prefrontal cortex (PFC) dysfunction, which has been described as a consequence of illness (Lewis and Glausier, 2016; Sakurai et al., 2015).

Resting-state and task-related activation of the dorsolateral prefrontal (DLPFC) cortex have been a topic of research in schizophrenia. The DLPFC is crucial for mental representation and abstraction and its dysfunction account for WM deficits (Arnstén, 2013). In schizophrenia, DLPFC shows smaller gray matter volume (Arnstén, 2013) and reduced activation (Hill et al., 2004), which reflects a decrease in resting-state blood flow (Andreasen et al., 1997). These abnormalities account for the impairment in cognition and the pathophysiology of the disorder as well. Regardless of the specificity of the deficits in the DLPFC, PFC dysconnectivity to other brain regions is well documented and associated with both cognitive deficits and psychotic symptoms (Zhou et al., 2015). Recently, orbitofrontal cortex thickness in the left hemisphere was associated with negative symptoms severity (Walton et al., 2017).

The lack of efficacy of pharmacological treatments for the cognitive and negative symptoms, in addition to the recent findings of neurobiological studies, boosted the research on non-invasive brain stimulation techniques (NIBS), such as transcranial direct current stimulation (tDCS) (Hasan et al., 2012, 2013). Following the interesting results from previous studies, we hereby present a double-blinded, randomized, sham-controlled clinical trial investigating the effects of 10 sessions of tDCS over the DLPFC in schizophrenia subjects. We hypothesize that anodal tDCS applied over the left DLPFC, with the cathode at the right contralateral area, will improve both working memory and negative symptoms. Despite their differences regarding clinical characteristic, they have been associated in the literature, and share similar brainsubstracts. In this context, we believe that increasing excitability of the left DLPFC may lead to an improvement of both issues.

2. Method

2.1. Trial design

This is a parallel randomized, double-blinded sham-controlled clinical trial with two arms and 1:1 allocation ratio. The study was conducted following the principles of the Declaration of Helsinki and guidelines of Good Clinical Practice and was approved by the Ethics Committee of the Federal University of Sao Paulo (UNIFESP) and is registered in the Brazilian Clinical Trial platform under number RBR-69g952. It also follows the Consolidated Standards of Reporting Trials (CONSORT) (Turner et al., 2012).

2.2. Participants

Assessments and stimulation sessions were conducted at one of the two recruitment centers enrolled in the study: Schizophrenia Program from the Federal University of Sao Paulo (PROESQ – UNIFESP) or at outpatient unity from Santa Casa School of Medical Sciences. Two trained psychiatrists performed the diagnosis of schizophrenia by using the Structured Clinical Interview of the DSM-IV (SCID-I) (American Psychiatric Association, 1994). Patients eligibility criteria included: (a) Subjects between 18 and 65 years old diagnosed with DSM-IV schizophrenia; (b) No history of substance abuse/dependence, in exception to tobacco and/or caffeine; (c) No diagnosis of any neurological conditions affecting central nervous system(e.g. Parkinson’s disease); (d) No history of seizures; (e) No unexplained loss of consciousness; (f) Stability of pharmacological treatment for at least 6 weeks; (g) No contraindications to tDCS, such as metal in the head or implanted brain medical devices; (h) No pregnancy at enrollment; (i) acceptance to participate in the study and provide the written informed consent, given in the first interview. Dropout was considered after the absence in two consecutive tDCS sessions or declined consent to participate. Sixty patients were initially contacted, 16 did not meet the eligibility criteria, and 20 patients refused to participate. Twenty-four patients were included and randomized to either sham or active tDCS treatment (Fig. 1).

2.3. Interventions

A total of ten sessions of either sham or active tDCS was performed, with the anode placed over the left DLPFC, and the cathode in the contralateral area, following the 10/20 EEG system (Beam et al., 2009; Saletu et al., 2010). The stimulation was performed over two consecutive weeks (Monday to Friday) and was initiated immediately after the baseline assessment. For the active stimulation, the following parameters were used: 2 mA of tDCS applied for 20 min with electrodes of 25 cm² wrapped in cotton material soaked in saline solution. For the sham stimulation, the stimulation procedures were the same, with the exception that the current remained active for the first 30 s of the session only. This is a suitable method of blinding for this technique (Brunoni and Fregni, 2011).

2.4. Outcomes

The primary outcome was the performance on working memory task. As a secondary outcome, we investigated the effects on negative symptomatology, based on PANSS negative subscale score. Other cognitive and clinical measures were analyzed as exploratory outcomes. Measures were obtained at three-time points: baseline (T0), after intervention (T1) and after a 3-month follow up (FU) (T2).

2.4.1. Clinical assessments

Patients were assessed at baseline and after the last session of tDCS using the Positive and Negative Syndrome Scale (Higuchi et al., 2014; Kay et al., 1988), the Calgary Depression Scale (CDS) (Addington et al., 1993) and the Global Assessment of Functioning Scale (GAF) (Endicott et al., 1976).

2.4.2. Cognitive assessments

The Brazilian version of the Measurement and Treatment Research to Improve Cognition in Schizophrenia Consensus Cognitive Battery (MATRICS) (Fonseca et al., 2017) was used to assess changes in cognition. The MATRICS is a standardized cognitive assessment for patients with schizophrenia composed by cognitive tasks with normative data (Green et al., 2004; Lezak et al., 2004; Strauss et al., 2006). Ten tests from the MATRICS were used, in order to evaluate the following domains (Fonseca et al., 2017; Green et al., 2004):

1. Speed of processing: Trail Making Test: Part A (TMTA), Brief Assessment of Cognition in Schizophrenia (BACS): Symbol Coding and Category Fluency Test: Animal naming (Fluency);
2. Attention: Continuous Performance Test—Identical Pairs (CPT-IP);
3. Working memory: Wechsler Memory Scale—Third Edition (WMS-III): Spatial Span (SS) and Letter-Number Span Test (LNS);
4. Verbal learning: Hopkins Verbal Learning Test—Revised (HVLT-R);
5. Visual learning: Brief Visuospatial Memory Test—Revised (BVMT-R);
6. Reasoning and problems solving: Neuropsychological Assessment Battery (NAB): Mazes;
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