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Effects of transcranial direct current stimulation (tDCS) on cognition, symptoms, and smoking in schizophrenia: A randomized controlled study

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ABSTRACT

Schizophrenia is characterized by cognitive deficits which persist after acute symptoms have been treated or resolved. Transcranial direct current stimulation (tDCS) has been reported to improve cognition and reduce smoking craving in healthy subjects but has not been as carefully evaluated in a randomized controlled study for these effects in schizophrenia. We conducted a randomized double-blind, sham-controlled study of the effects of 5 sessions of tDCS (2 milliamps for 20 minutes) on cognition, psychiatric symptoms, and smoking and cigarette craving in 37 outpatients with schizophrenia or schizoaffective disorder who were current smokers. Thirty subjects provided evaluable data on the MATRICS Consensus Cognitive Battery (MCCB), with the primary outcome measure, the MCCB Composite score. Active compared to sham tDCS subjects showed significant improvements after the fifth tDCS session in MCCB *Composite* score ($p = 0.008$) and on the MCCB *Working Memory* ($p = 0.002$) and *Attention-Vigilance* ($p = 0.027$) domain scores, with large effect sizes. MCCB *Composite* and *Working Memory* domain scores remained significant at Benjamini–Hochberg corrected significance levels ($\alpha = 0.05$). There were no statistically significant effects on secondary outcome measures of psychiatric symptoms (PANSS scores), hallucinations, cigarette craving, or cigarettes smoked. The positive effects of tDCS on cognitive performance suggest a potential efficacious treatment for cognitive deficits in partially recovered chronic schizophrenia outpatients that should be further investigated.

1. Introduction

The persistent cognitive deficits, which can be appreciated across the course of schizophrenia, from prodromal to chronic schizophrenia (SZ) (Green, 1998; Kurtz, 2005; Kremen et al., 2010; Meier et al., 2014), may be the most important underlying dysfunction in preventing functional, occupational, and social recovery in SZ compared to other symptom domains. SZ patients show significant cognitive deficits across all domains with the greatest deficits in speed of processing, working memory, and verbal learning (Saykin et al., 1991, 1994; Kern et al., 2011). There is no generally accepted effective treatment for these cognitive deficits. Brain stimulation is a potential alternative or adjunctive approach to improve cognitive function in SZ. Transcranial direct current stimulation (tDCS) applies weak electrical current to the brain surface by battery powered electrical stimulation; it is an easily available, safe, and relatively inexpensive brain stimulation technique that has been shown to improve some aspects of working memory and general cognitive performance in healthy controls, stroke patients, and older adults (Park et al., 2013, 2014; Brunoni and Vanderhasselt, 2014). Several studies in healthy controls reported improvements in working memory with anodal tDCS delivered over the left dorsal prefrontal cortex (LDLPFC)(Fregni et al., 2005; Jeon and Han, 2012; Berryhill et al., 2014). Although tDCS has not been extensively investigated for cognitive deficits in schizophrenia, a few studies have reported positive effects of tDCS on isolated cognitive tests (Vercammen et al.,

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2011; Palm et al., 2013; Schretlen et al., 2014; Hoy et al., 2015). One study, which did not investigate cognitive effects, reported that tDCS reduced psychiatric symptoms and hallucinations in schizophrenia (Brunelin et al., 2012). Furthermore, none of these studies used the MATRICS Consensus Cognitive Battery (MCCB; (Nuechterlein et al., 2008), which was designed to stimulate research to treat cognitive deficits in SZ and has been accepted as the international standard for assessing cognition-enhancing interventions in SZ.

SZ patients have a high rate of smoking (Dalack et al., 1998), and deficits in the number or functioning of nicotinic receptors in SZ may be related to some of the cognitive deficits in this disorder (Freedman et al., 1995; Adler et al., 1998; Smith et al., 2002). Schizophrenic smokers may be more prone to the cognitive deficits associated with the disorder (Wing et al., 2011; Zhang et al., 2012) possibly because of a greater dysregulation in their neuronal nicotinic system, and the administration of cigarettes or nicotinic agonists have been used to improve some aspects of cognitive function in schizophrenia (Smith et al., 2002, 2006; Sacco et al., 2005). A recent study also provided evidence that smoking in SZ may partially restore neuronal long-term potentiation (LTD) neuroplasticity which is deficient in SZ (Strube et al., 2015). Studies of tDCS in non-psychotic smokers have shown that tDCS stimulation reduced cigarette craving and, in some studies, number of cigarettes smoked (Fregni et al., 2006; Boggio et al., 2009; Fraser and Rosen, 2012; Fecteau et al., 2014) but whether tDCS is effective for reducing smoking or smoking urges in smokers with SZ has not been assessed.

We report the results of a randomized, sham-controlled study of the effects of tDCS on cognition and cigarette craving, in schizophrenic smokers. We hypothesized that tDCS would improve cognition and decrease smoking urges. The MCCB Composite score was the primary outcome measure for cognition and the response to the QSU smoking urges scale and differential craving responses to neural vs. smoking images were the main carving measures. Changes in psychiatric symptoms were explored as accessory outcome measures because some previous studies had reported that tDCS improves hallucinations and overall psychiatric symptoms.

2. Methods

2.1. Subjects

Thirty–seven outpatients with a DSM-IV diagnosis of schizophrenia or schizoaffective psychosis, who were regular cigarette smokers and living in community residences, were enrolled, and 33 (24 male/9 female) were available for analysis on at least one outcome measure. A CONSORT diagram of subject recruitment and retention is shown in Fig. 1. Subjects did not have to have a current desire to quit smoking. Subjects provided written informed consent on forms from a protocol approved by the NKI IRB.

2.2. Procedures

2.2.1. Overall design

This was a randomized, sham-controlled, parallel group study of the effects of 5 tDCS sessions on cognition, smoking, and psychiatric symptoms. (The timeline of the experimental procedures, which are detailed below, is outlined in supplementary data Table 4).

2.2.2. tDCS administration

tDCS stimulation was performed using a Chattanooga Ionto System stimulator delivering direct current through 2 surface electrodes (through 2 in^2 [5.08 cm^2] saline-soaked sponges attached by non-conducting Velcro). Placement of electrodes for tDCS had the anode placed over LDLPFC (F3) and the cathode over the contralateral supraorbital ridge (Fp2). Electrode placements were determined by the 10/20 placement method using EEG cap. Subjects had 5 tDCS sessions on consecutive days (weekends and holidays excluded); an occasional subject had to have a tDCS session day rescheduled because of scheduling conflicts, inclement weather, or travel problems. Actual days to completion of 5 tDCS sessions was (mean ± S.D.) 8.7 ± 2.7 days and there was no significant difference between the active (7.2 ± 1.9) and sham (8.2 ± 3.1) groups. The active tDCS group was stimulated with a 2 mA current

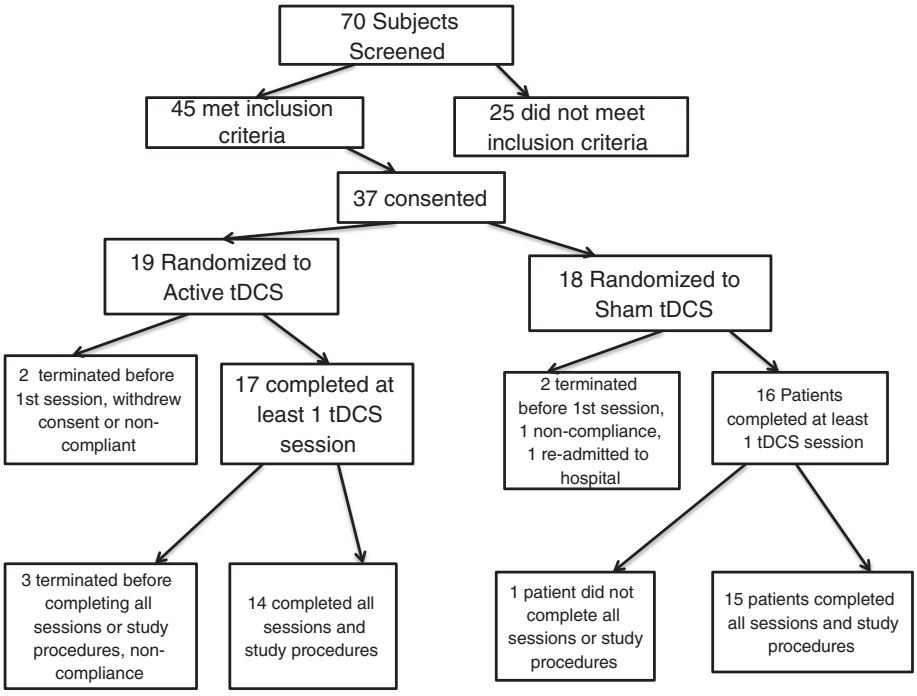

Fig. 1. CONSORT diagram of patient flow though study. Number of subjects completing sufficient evaluations to be included in statistical analysis of specific measures: 1) MCCB N = 30 active = 14, sham = 16; 2) Symptom ratings PANSS N = 30, active = 15, sham = 15; 3) Cigarette and breathalyzer CO N = 32 active = 16, sham = 16; 4) Smoking urges (QSU scale) N = 31, active = 15, sham = 16; 5) Side effects N = 31 active = 15, sham = 16.