Psychiatry Research 247 (2017) 28–32

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Positive effects of transcranial direct current stimulation in adult patients with attention-deficit/hyperactivity disorder – A pilot randomized controlled study

Carolina Tosetto Cachoeira[a,1,*], Douglas Teixeira Leffa[b,1], Suzana Doneda Mittelstadt[a], Lorenna Sena Teixeira Mendes[a], Andre R. Brunoni[c,d], Jairo Vinicius Pinto[f], Vítor Blazius[f], Vitoria Machado[f], Claiton Henrique Dotto Bau[a,e,g], Luis Augusto Rohde[a,f,g,h], Eugenio Horacio Grevet[a,f,g], Pedro Schestatsky[a,b,i]

[a] Post-Graduation Program of Psychiatry, Universidade Federal do Rio Grande do Sul, Brazil
[b] Post-Graduation Program of Medical Sciences, Universidade Federal do Rio Grande do Sul, Brazil
[c] Interdisciplinary Center for Applied Neuromodulation (CINA), University Hospital, University of São Paulo, São Paulo, Brazil
[d] Service of Interdisciplinary Neuromodulation (SIN), Laboratory of Neurosciences (LIM-27), Department and Institute of Psychiatry, University of São Paulo, São Paulo, Brazil
[e] Department of Genetics, Universidade Federal do Rio Grande do Sul, Brazil
[f] Department of Psychiatry, Universidade Federal do Rio Grande do Sul, Brazil
[g] ADHD Outpatient Program, Hospital de Clínicas de Porto Alegre, Brazil
[h] National Institute of Developmental Psychiatry for Children and Adolescents, Brazil
[i] Service of Neurology, Hospital Moinhos de Vento, Porto Alegre, Brazil

ARTICLE INFO

Keywords:
Attention-deficit/hyperactivity disorder
ADHD treatment
Adult ADHD
Transcranial direct current stimulation (tDCS)
Neurostimulation

ABSTRACT

Almost 30% of adult patients with attention-deficit/hyperactivity disorder (ADHD) do not respond or tolerate standard pharmacological interventions. Few clinical investigations addressed the efficacy and tolerability of transcranial direct current stimulation (tDCS), a non-invasive neuromodulatory technique, in the disorder. We performed a double-blind, sham-controlled randomized clinical trial in 17 patients with ADHD. The set up for tDCS was the following: 2 mA/20 min/day for 5 days with the anode over the right dorsolateral prefrontal cortex and cathode over the left dorsolateral prefrontal cortex. ADHD symptoms were measured by the Adult ADHD Self-Report Scale (ASRS) and impairment with the Sheehan Disability Scale (SDS) in four different time points after stimulation. Participants achieved significant lower ASRS inattention and SDS scores after active tDCS in comparison with sham stimulation group. In addition, we detected a trend for a lower ASRS total score in the active tDCS group. Follow up data analysis revealed a positive interaction between time and treatment in both ASRS inattention, SDS and ASRS total scores. **S**hort-term application of tDCS in adult patients with ADHD improved their symptoms, and this improvement persisted after the end of the stimulation. Future studies with larger sample sizes are needed.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a prevalent disorder characterized by inappropriate age-adjusted levels of inattention, and/or hyperactivity-impulsivity (American Psychiatric Association, 2013). Even though stimulant and non-stimulant medications for ADHD have been reported to be effective in reducing symptoms (Faraone and Glatt, 2010), they have significant drawbacks such as adverse effects that can, in some cases, lead to treatment discontinuation (Castells et al., 2013). In addition, medication alone may not be enough to relieve ADHD symptoms and induce satisfactory functional improvement (Davidson, 2008; Santosh et al., 2011). Therefore, the search for new non-pharmacological interventions for the disorder is justified.

Transcranial direct current stimulation (tDCS) is a technique that consists of applying a weak, constant, low intensity current between

* Correspondence to: Universidade Federal do Rio Grande do Sul, Programa de Pós, Graduação em Psiquiatria e Ciências do Comportamento, Rua Ramiro Barcelos, 2400 – 2° andar – Porto Alegre/RS – Brazil. CEP: 90035-003.
E-mail address: carocachoeira@gmail.com (C.T. Cachoeira).
[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.psychres.2016.11.009
Received 27 May 2016; Received in revised form 2 September 2016; Accepted 6 November 2016
Available online 10 November 2016
0165-1781/

two electrodes over the scalp in order to modulate cortical excitability (Nitsche and Paulus, 2000). Anodal stimulation is able to enhance cortical excitability, while cathodal stimulation is able to reduce it (Nitsche and Paulus, 2000).

Although tDCS has been repeatedly shown to enhance attention and working memory in healthy and neuropsychiatric populations, its possible role in improving clinical measures of symptoms and functionality in ADHD has not been elucidated yet (Fregni et al., 2005; Oliveira et al., 2013; Smith et al., 2015; Zaehle et al., 2011). In animal models of ADHD, Leffa et al. (2015) demonstrated that tDCS was able to improve short-term memory deficits, suggesting a possible role for this technique in the disorder. In addition, there is evidence of increased functional brain connectivity in ADHD patients after tDCS (Cosmo, 2015).

We conducted a pilot randomized double blind, placebo controlled clinical trial. Our primary aim was to evaluate the efficacy of tDCS in reducing symptoms in ADHD patients. We hypothesized that the stimulation would be effective in reducing ADHD symptoms when compared to the sham stimulation.

2. Methods

2.1. Trial design

This study was a randomized double blind, placebo controlled clinical trial. Trial design and its reporting followed the Consolidated Standards of Reporting Trials (CONSORT) group recommendations (Schulz et al., 2010). It was conducted at the Hospital de Clínicas de Porto Alegre (HCPA), Brazil. Patients were recruited from September 1, 2014, to October 4, 2015. The local Ethics Committee approved this study. All participants provided written informed consent. This trial was submitted to ClinicalTrials.gov under the identifier NCT02580890.

2.2. Participants

Participants were adults who were referred to the ADHD outpatient clinic in the HCPA and meeting our inclusion criteria. The inclusion criteria for this study were: 1) adults aged between 18–45 years; (2) met criteria for ADHD according to the DSM-5; (3) be without any ADHD pharmacological treatment at least one month; (4) able to read, write, and speak Portuguese. Exclusion criteria were the following: current depressive episode with Beck Depression Inventory-II greater than 9; current anxiety disorder with Beck Anxiety Inventory greater than 15; Bipolar disorder with maniac or depressive episode in the last year; Schizophrenia or other psychosis; substance use disorder; Autism; intelligence quotient lower than 70; Dementia. Participants with contraindication for tDCS application, such as those with metallic implants in the head or history of seizure, were also excluded. In addition, patients were excluded if they started any psychopharmacotherapy or changed dose in usual medication in the last three months.

2.3. Interventions

Commercial tDCS devices (TCT Research Limited, CR1781195, Hong Kong) were used. Participants received tDCS active stimulation with the anode over the right DLPFC and the cathode over the left DLPFC (corresponding to F4 and F3, respectively, according to the International 10–20 electroencephalography system). Anodal stimulation was over the right DLPFC since this region has been shown to be hypoactive in ADHD patients (Hart et al., 2013). Rubber electrodes were inserted in 35 cm^2 (7 cmx5 cm) saline-soaked sponges and fixed with a headband. We applied a direct current of 2 mA for 20 min/d for 5 consecutive days. For the sham stimulation the same approach was used, but the device was turned off after 1 min of active stimulation in order to mimic the mild itching sensation that is commonly reported right after stimulation onset. The procedure was performed preferably in the morning and the subjects were instructed to relax, don't talk, read, listening music or sleep while being stimulated.

Randomization occurred before intervention (active or sham) using the website www.random.org. Participants, investigators, and study staff were blind to allocation and remained blinded until the end of the study (time 4, see below). At the end, patients and physicians were asked to guess in which group patients were allocated.

2.4. Outcomes

The primary outcome measure (efficacy assessment) was the Adult ADHD Self-Report Scale Symptom Checklist-v1.1 (ASRS) (Adler and Cohen, 2004). The ASRS is an 18-item self-report scale based on the DSM-IV ADHD criteria. This scale evaluates inattentive and hyperactive/impulsive symptoms by presenting questions like "how often do you have problems remembering appointments or obligations? " and "how often do your leave your seat in meetings or others situations in which you are expected to remain seated? ". Items are scored on a 5 points scale [from 0=never (i.e., absence of a symptom), 1=rarely, 2=sometimes, 3= often, 4= very often]. The psychometric properties and clinical utility of the ASRS have been demonstrated in several clinical studies (Adler et al., 2006; Kessler et al., 2005). The ASRS v1.1 Symptom Checklist has shown high internal consistency and concurrent validity with the clinician-administered ADHD-RS in community and clinic-based samples of adults with ADHD (Adler et al., 2006; Kessler et al., 2005) and as a measure of treatment response (Adler et al., 2009). The intra-class correlation coefficients between scales (ASRS versus ADHD RS) for total scores was high (0.84) and for subset symptom scores were also high (both 0.83) (Adler et al., 2006). Students' ratings of their ADHD symptoms on the 18-item ASRS were highly correlated with self-ratings of executive functioning impairment and everyday cognitive failures (Gray et al., 2014). We also analyzed difference in inattentive and hyperactive/impulsive scores from the ASRS separately over time.

With regard to secondary outcome measures, we used the Sheehan Disability Scale (SDS), which was developed to assess functional impairment in three domains: work, school and family life (Sheehan et al., 1996). Patients have to give a grade from 0 to 10 to each domain, with a higher number indicating increased impairment. The sum of values in three domains was used.

Participants were assessed before the first stimulation (time 0), right after the last stimulation (time 1), and one (time 2), two (time 3) and 4 weeks (time 4) after the last stimulation.

2.5. Statistical analyses

Differences in total ASRS, ASRS inattention, ASRS hyperactivity/impulsivity and SDS scores between time 0 and time 1 were compared between active and sham stimulation groups. Comparisons were done using a Mann-Whitney U test for non-normally distributed variables. A generalized estimation equation (GEE) followed by Bonferroni *post-hoc* test was used to analyze the follow up data. A p-value < 0.05 was considered a statistically significant result, a p-value < 0.07 was considered a trend.

3. Results

3.1. Participants

Of 29 patients that were accessed for eligibility, 12 were not included. One was excluded due to a titanium plate in the brain, four had depression with BDI greater than 9, three did not met criteria for ADHD, and four could not commit to the treatment protocol. Seventeen patients were randomized as previously described, 8 to the sham group and 9 to the active group. One subject from the active