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

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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

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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

Table 1
Demographics.

	tDCS sham	tDCS active	test statistic (p-value)
Number of patients (% male)	8 (50)	9 (44.4)	0.05 (1.0)[a]
Age (SD)	33.75 ± 3.65	31 ± 6.17	3.77 (0.30)[b]
Age of initial symptoms (SD)	7.5 ± 3.46	7.11 ± 2.57	1.53 (0.79)[b]
ADHD type			
Combined type (%)	5 (62.5)	5 (55.6)	0.08 (1.0)[a]
Inattentive type (%)	3 (37.5)	4 (44.4)	0.08 (1.0)[a]
Hyperactive-Impulsive type (%)	0	0	–

tDCS, transcranial direct current stimulation; SD, standard deviation; ADHD, attention-deficit/hyperactivity disorder.

group declined to participate after the beginning of the study. Although clinical measures were not assessed for the patient that dropped out, we performed all the analysis keeping the scores from times 1, 2, 3 and 4 exactly equal to the score in time 0. Thus, analyses followed an intention-to-treat approach. As shown in Table 1, baseline demographic characteristics were similar between groups.

3.2. Primary outcome

Outcome values are expressed in Table 2. The primary outcome was the ASRS score. Since the variables were non-normally distributed, a Mann-Whitney U test was used to determine if there were differences between active and sham stimulation groups. Difference between time 0 and time 1 in the active group (mean rank=11.1) was higher than for sham group (mean rank=6.6), U=55, z=1.83, and almost reached significance (p=0.07).

Table 2
Effect sizes of sham and real tDCS at different time points.

	Time 0	Time 1	Time 2	Time 3	Time 4
ASRS Inattention					
tDCS sham	27.38 (1.68)	26.25 (1.92)	26.88 (2.29)	27.63 (2.17)	26.75 (2.33)
tDCS active	28.33 (1.39)	20.78 (2.19)	21.22 (1.87)	21.56 (1.47)	22.89 (1.76)
Cohen's d	0.19	0.85[b]	0.87[b]	1.06[a]	0.6
ASRS Hyperactivity/impulsivity					
tDCS sham	19.63 (3.1)	20 (3.38)	18.38 (3.45)	19.13 (3.38)	19.13 (2.88)
tDCS active	18.22 (3.02)	14.11 (2.9)	13.78 (2.85)	13.67 (2.66)	14.44 (2.71)
Cohen's d	0.14	0.6	0.47	0.58	0.53
ASRS total					
tDCS sham	47 (3.99)	46.25 (4.16)	45.25 (4.4)	46.75 (4.73)	45.38 (4.26)
tDCS active	45.44 (3.53)	34.89 (4.8)	35 (4.46)	35.22 (3.72)	37.33 (4.21)
Cohen's d	0.13	0.81[b]	0.74	0.8[a]	0.61
SDS					
tDCS sham	17.5 (2.15)	17.75 (1.65)	16.75 (1.73)	17.5 (1.26)	16.37 (1.42)
tDCS active	18.66 (2.47)	12.44 (2.09)	12.55 (2.17)	15.88 (2.35)	16 (2.13)
Cohen's d	0.16	0.9[a]	0.68	0.27	0.06

ASRS, ADHD Self-Report Scale Symptom; **tDCS**, transcranial direct current stimulation; **SDS**, Sheehan Disability Scale; Data is presented as mean and standard error.

[a] Statistically significant difference between groups in a fixed time (Bonferroni *post-hoc* test).

[b] Trend between groups in a fixed time (Bonferroni *post-hoc* test).

3.3. Secondary outcomes

The secondary outcomes were ASRS inattention, ASRS hyperactivity/impulsivity, and SDS scores. All the variables were non-normally distributes, and a Mann-Whitney U test was used. In ASRS inattention, difference between time 0 and time 1 in the active group (mean rank =11.6) was higher than for sham group (mean rank=6), U=59.5, z=2.27, p=0.02. In ASRS hyperactivity/impulsivity, on the other hand, active group (mean rank=10.7) and sham group (mean rank=7) were not different U=52, z=1.55, p=0.13. For SDS, difference between time 0 and time 1 in the active group (mean rank=11.2) was higher than for sham group (mean rank=6.4), U=56.5, z=1.98, p=0.04.

In the follow up data, a GEE revealed an effect for the interaction between time and treatment in the ASRS scores (χ^2=15.984, p=0.003, Fig. 1a), an effect for time (χ^2=18.324, p=0.001) and no effect for treatment (χ^2=2.263, p=0.13). For SDS score, there was an effect for the interaction between time and treatment (χ^2=18.929, p=0.001, Fig. 1b), an effect for time (χ^2=15.295, p=0.004) and no effect for treatment (χ^2=0.637, p=0.42). For the ASRS inattention, there was an effect for the interaction between time and treatment (χ^2=22.156, p=0.0001), an effect for time (χ^2=19.217: p=0.001) and no effect for treatment (χ^2=2.618, p=0.1). For the ASRS hyperactivity/impulsivity, there was an effect for time (χ^2=10.608, p=0.03), and no effect for the interaction between time and treatment (χ^2=7.583, p=0.1) or for treatment (χ^2=1.118, p=0.29). Post-hoc Bonferroni analysis are described in Table 2. When comparing groups in fixed times, pot hoc Bonferroni revealed a trend in time 1 (p=0.07) and a significant difference in time 3 (p=0.05) on ASRS total; a significant difference in time 1 (p=0.04) on SDS; a trend in time 1 (p=0.06) and 2 (p=0.057), and a significant difference in time 3 (p=0.02) on ASRS inattention.

3.4. Adverse effects

Patients were actively asked for adverse effects based on a previous study (Brunoni et al., 2011). Adverse effects during and after stimulation are reported in Table 3. One subject who was assigned to the active group decline to participate after the first stimulation session due to an acute mood change, feeling sad, hypobulia, tension. This negative effect started to develop five hours after stimulation and persisted in a milder form into the next day. No other reason for this worsening was found. Similar side effect was report with high-frequency rTMS stimulation of the right DLPFC (Ustohal et al., 2012). Such a considerable negative effect on emotions is noteworthy but not fully unexpected. It is known that 2 mA anodal left/cathodal right prefrontal tDCS (Brunoni et al., 2013) and low-frequency rTMS of the right DLPFC is used in the treatment of depressive disorder (Fitzgerald et al., 2003) and, on the contrary, high-frequency rTMS of this area has been used in patients with mania (Grisaru et al., 1998).

3.5. Integrity of blinding

At the end of the study, time 4, only 50% and 62.5% of patients in the active and sham stimulation groups, respectively, guessed correctly in which group they were (p=1). Besides, physicians guessed correctly 25% of their patients in the active group, and 62.5% of their patients in the sham group (p=0.31).

4. Discussion

In this study on the effects of tDCS in ADHD patients, those submitted to active stimulation presented significantly lower ASRS and SDS scores compared to the sham stimulation. In addition, the effects tend to decrease over time, indicating that continuity of treatment may be necessary to maintain the benefits. To the best of our knowledge,

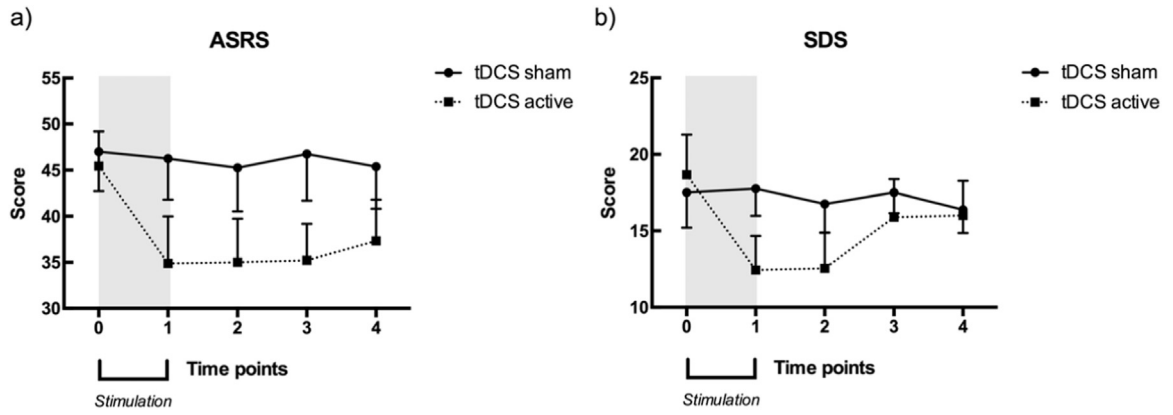

Fig. 1. : Effects of transcranial direct current stimulation (tDCS) on Adult ADHD Self-Report Scale Symptom Checklist-v1.1 (ASRS, a), and Sheehan Disability Scale (SDS, b) scores. Data is presented as mean+standard error of the mean. Time points: 0 - baseline; 1- end of tDCS protocol (TP); 2 - one week after TP; 3 - two weeks after TP; 4 - four weeks after TP.

Table 3
Side effects.

	Side effects during stimulation		Side effects after stimulation	
	tDCS sham (%) n=8	tDCS active (%) n=9	tDCS sham (%) n=8	tDCS active (%) n=9
Tingling	8 (100)	4 (44.4)	0 (0)	1 (11.1)
Itching	5 (62.5)	4 (44.4)	1 (12.5)	2 (22.2)
Burning sensation	5 (62.5)	4 (44.4)	1 (12.5)	0 (0)
Headache	2 (25)	1 (11.1)	4 (50)	2 (22.2)
Fatigue	2 (25)	5 (55.6)	2 (25)	4 (44.4)
Anxiety	1 (12.5)	2 (22.2)	1 (12.5)	2 (22.2)
Visual symptoms	1 (12.5)	3 (33.3)	0 (0)	1 (11.1)
Nausea	0 (0)	0 (0)	0 (0)	3 (33.3)
Insomnia	0 (0)	0 (0)	2 (25)	1 (11.1)
Acute mood change	0 (0)	0 (0)	0 (0)	1 (11.1)

tDCS, transcranial direct current stimulation

this is the first study examining tDCS effects in reducing ADHD symptoms using clinical measures of symptomatic and functional improvement.

Our results are in agreement with recent studies about tDCS in children and adolescents with ADHD. Bandeira et al. (2016) demonstrated that tDCS improved aspects of selective attention, reduced the time needed to select new information and reduced the total number of errors when alternating attention was used. Breitling et al. (2016) results suggest that anodal tDCS on the right inferior frontal gyrus improved interference control. Using oscillatory tDCS during slow wave sleep, Prehn-Kristensen et al. (2014) demonstrated an improvement of declarative memory performance on the next day as well as improved reaction times in a go/no go task in children with ADHD (Munz et al., 2015). Soltaninejad et al. (2015) showed positive results during Go/No-Go task using cathodal stimulation on the left DLPFC.

Our finding differs from Cosmo (2015), who reported no significant effect of tDCS on behavioral performance in the go/no-go task in ADHD patients. Several factors might have contributed to this difference between the studies. First, in this study (Cosmo, 2015), participants received a single anodal stimulation over the left DLPFC with a current intensity of 1 mA, whereas in the present study participants received five anodal stimulations over the right DLPFC with a current intensity of 2 mA. In our study, the stimulation of right DLPFC was chosen due to its reduced activation in ADHD patients during attention tasks (Hart et al., 2013). Besides, anodal tDCS in the right DLPFC has been already used in order to improve working memory in healthy populations (Berryhill and Jones, 2012; Jeon and Han, 2012; Giglia et al., 2014; Wu et al., 2014).

Repetitive Transcranial magnetic stimulation (rTMS), which is a different type of non-invasive brain stimulation technique that depolarizes neurons instead of excite their membrane, such as tDCS, has already been suggested to be effective in improving ADHD symptoms (Bloch et al., 2010; Niederhofer, 2012, 2008; Weaver et al., 2012). Differently from tDCS, rTMS modulates brain activity by using electromagnetic field in order to induce electric currents in the brain (Fregni and Pascual-Leone, 2007). TDCS offers advantages relative to rTMS, including easy applicability and low financial costs (Nitsche et al., 2008). Moreover, application requires less cooperation from the patient, which may be relevant for hyperactive children.

Evidence indicates that both tDCS and rTMS are able to modulate dopaminergic transmission in cortical and subcortical structures, which might be related to symptom improvement observed with both stimulations in patients with ADHD. Keck et al. (2002) reported that an acute TMS application in the frontal lobe of rats was able to increase dopamine (DA) concentration in the dorsal hippocampus, nucleus accumbens, and dorsal striatum. Similar studies demonstrated increased DA and glutamate levels in the nucleus accumbens and increased DA levels in the dorsolateral striatum (Zangen and Hyodo, 2002). Using tDCS in animal models of ADHD, increased DA levels were observed in the striatum (Tanaka et al., 2013) and hippocampus (Leffa et al. (2015).

Limitations of our study include small sample size and self report measurements. In addition, since tDCS is not focal in the brain, we cannot rule out that activity in neighboring regions to the targeted DLPFC might also play a role in ASRS improvement. The low spatial resolution of tDCS is an inherent limitation of this noninvasive brain stimulation technique. Thus, tDCS of the DLPFC might have influenced other frontal regions such as the orbitofrontal/ventromedial cortex, especially considering that they are densely interconnected (Ghashghaei and Barbas, 2002).

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Conflicts on interest

Luis A. Rohde has received Honoraria, has been on the speakers' bureau/advisory board and/or has acted as a consultant for Eli-Lilly, Janssen-Cilag, Novartis and Shire in the last three years. He receives

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