Neuropsychopharmacology

ARTICLE

Efficacy and safety of transcranial direct current stimulation as an add-on treatment for obsessive-compulsive disorder: a randomized, sham-controlled trial

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Obsessive-compulsive disorder (OCD) is a frequent, disabling disorder with high rates of treatment resistance. Transcranial direct current stimulation (tDCS) is a safe, tolerable noninvasive neuromodulation therapy with scarce evidence for OCD. This double-blind, randomized, and sham-controlled study investigates the efficacy of tDCS as add-on treatment for treatment-resistant OCD (failure to respond to at least one previous pharmacological treatment). On 20 consecutive weekdays (4 weeks), 43 patients with treatment-resistant OCD underwent 30 min active or sham tDCS sessions, followed by a 8 week follow-up. The cathode was positioned over the supplementary motor area (SMA) and the anode over the left deltoid. The primary outcome was the change in baseline Y-BOCS score at week 12. Secondary outcomes were changes in mood and anxiety and the occurrence of adverse events. Response was evaluated considering percent decrease of baseline Y-BOCS scores and the Improvement subscale of the Clinical Global Impression (CGI-I) between baseline and week 12. Patients that received active tDCS achieved a significant reduction of OCD symptoms than sham, with mean (SD) Y-BOCS score changes of 6.68 (5.83) and 2.84 (6.3) points, respectively (Cohen's *d*: 0.62 (0.06–1.18), $p = 0.03$). We found no between-group differences in responders (four patients in the active tDCS and one in the sham group). Active tDCS of the SMA was not superior to sham in reducing symptoms of depression or anxiety. Patients in both groups reported mild adverse events. Our results suggest that cathodal tDCS over the SMA is an effective add-on strategy in treatment-resistant OCD.

Neuropsychopharmacology (2021) 46:1028–1034; https://doi.org/10.1038/s41386-020-00928-w

INTRODUCTION

Obsessive-compulsive disorder (OCD) is a disabling neuropsychiatric disorder characterized by recurrent, intrusive thoughts or images that are uncomfortable and distressful (obsessions), usually followed by repetitive mental acts or physical behaviors (compulsions) that are performed to relieve the discomfort caused by the obsessions [1]. First-line treatments include selective serotonin reuptake inhibitors (SSRIs) and cognitive behavioral therapy (CBT) [2]. However, up to 40% of patients do not respond adequately to SSRIs [3, 4] and approximately one third remain impaired after optimal administration of CBT and SSRIs [5].

Noninvasive neuromodulation techniques such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) have been recently tested in OCD. Repetitive TMS has been approved by the U.S. Food and Drug Administration for OCD [6], but this clearance was limited to specific coils that are not standardly used yet. In contrast, tDCS is a low-cost technique that delivers low-intensity currents to the brain via two large electrodes. It is often placed over a target cortical region in order to induce a neurophysiological change locally and in connected brain areas [7].

Neuroimaging studies have proposed that OCD is associated with hyperactivation of cortical-striatum-thalamus-cortical (CSTC) circuitry [8, 9]. Some activities of this circuitry are crucial to ensure the execution of habitual actions and physiological functions. Therefore, several components of the circuitry have been tested as targets in studies of tDCS and OCD [10]. Our group conducted a systematic review of these studies [11], in which uncontrolled studies produced a favorable response in patients with OCD [12–14].

The few extant controlled trials of tDCS for OCD pointed to a favorable response as well. However, these studies employed different montages and are limited by small sample sizes. Most adopted the pre-SMA as the tDCS target, based on findings of pre-SMA hyperactivity in OCD patients during the performance of

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Received: 4 August 2020 Revised: 27 October 2020 Accepted: 20 November 2020
Published online: 15 January 2021

cognitive tasks related to attentional aspects of action control [15, 16] and on the association of this region with mechanisms of response inhibition. Also, this region is easily accessed by therapeutic neuromodulation and when stimulated could influence CSTC circuitry activities. A small ($n = 25$) sham-controlled, OCD trial showed superiority of anodal pre-SMA tDCS [17]. A crossover trial evaluating cathodal versus anodal stimulation over pre-SMA found that cathodal tDCS was associated with improvement of OCD [18]. Based on these trials, pre-SMA stimulation seems a promising target for the neuromodulation treatments of OCD.

Therefore, we conducted a randomized, sham-controlled trial to determine the efficacy and safety of tDCS in 43 patients with OCD who had failed at least one previous first-line pharmacological treatment. The electrode montage adopted in this trial (cathode over the SMA and the anode over the left deltoid) was chosen in line with a systematic review of TMS and deep brain stimulation trials in OCD, involving computational modeling of tDCS-induced electrical fields. This review suggested that such a montage is promising for modulating regions relevant to OCD pathophysiology [19].

The primary outcome was the reduction of the baseline Yale-Brown Obsessive Compulsive Scale (Y-BOCS) [20] score at 12 weeks after treatment initiation. Secondary outcomes were improvements in symptoms of depression and anxiety, as well as the frequency and severity of adverse events. Our primary hypothesis was that patients in the active tDCS group would achieve greater improvement than those in the sham group at the end of the follow-up period (12 weeks after treatment onset).

METHODS

Overview

This trial was conducted at the Institute of Psychiatry of Hospital das Clínicas, University of São Paulo, Brazil, from April 2016 to August 2018. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008 [21]. All procedures involving human subjects were approved by our Institutional Ethic Committee (1.015.347) registered at ClinicalTrials.gov (NCT02743715). The study is reported according to the CONSORT guidelines for nonpharmacological interventions [22]. Differences between this trial and the original protocol are described in Appendix 1 (Supplementary Material).

Study design

A randomized, sham-controlled design was employed. Forty-four patients were randomly assigned to two parallel groups (22 patients in each group) and received 20 daily sessions of either active or sham tDCS over a 4-week period (Monday to Friday). The protocol had an overall duration of 12 weeks, the patients being assessed at baseline, on week 6 and on week 12. The choice to conduct the second assessment at week 6 and not 4 was to accommodate any replacements of sessions lost due to potential holidays or absences. The endpoint was set at 12 weeks in line with OCD treatment guidelines, which indicate 8–12 weeks as the optimal duration of an SSRI trial to determine efficacy [23].

Patients were allocated to active or sham tDCS using a computer-based intentional allocation method (adaptive allocation), designed to maintain balance between groups according to variables previously described as predictors of OCD treatment response (including sex, age, baseline Y-BOCS score, and number of previous treatments). This method has been described in detail elsewhere [24] and has been adopted in previous controlled trials [25, 26]. One member of our group (not involved in the assessments or statistical analyses) entered the participant's allocation data in the computer-based randomization model and obtained the participant's group allocation code; and informed the tDCS operators, who delivered the treatment according to the allocation code. All staff except the researcher who obtained the allocation codes and the tDCS operators remained blind to the participant's treatment condition. Patients and care providers were blinded.

Participants

Participants were recruited from among those under treatment at the Outpatient Clinic of the OCD Spectrum Disorders Program of the Institute of Psychiatry, through media announcements and direct referrals. They were prescreened using electronic questionnaires and brief telephone interviews. Eligible individuals were invited to on-site interviews. The first author (RMFS) was in charge of the enrollment of participants. The following inclusion criteria were applied: being 18–65 years of age; having been given a primary diagnosis of OCD based on *DSM-IV* criteria; having a baseline Y-BOCS total score ≥ 16 or a score ≥ 10 for the presence of only compulsions or only obsessions; and failure to respond to at least one previous first-line pharmacological treatment for OCD (an SSRI or clomipramine, at the maximum recommended or tolerated dose, for at least 12 weeks). There is no consensus in the literature regarding the definition of resistance to treatment [27]. In this trial we considered treatment-resistant OCD, patients who had failed to respond to at least one previous first-line pharmacological treatment for OCD.

We excluded patients presenting a structured suicide plan or who attempted suicide within the last 4 weeks, and those diagnosed with bipolar substance use, psychotic, and neurocognitive disorders. These patients were excluded to ensure a more clinically homogeneous sample. In addition, effects of stimulation could be more uncertain on these comorbidities, since there are few trials testing the efficacy of tDCS in patients with bipolar or psychotic disorders [28]. Also, we excluded pregnant women and those with specific contraindications to tDCS (e.g., metallic plates over the head). Comorbid depression and anxiety disorders were not considered criteria for exclusion.

Concurrent use of certain medications (SSRIs, clomipramine, antipsychotics, and benzodiazepines) was allowed if doses had been stable for at least 6 weeks prior to treatment onset. To minimize pharmacological-tDCS interactions, the maximum allowed dosage of benzodiazepines was 20 mg/day of diazepam equivalent [29] and the use of other psychotropic drugs (e.g., anticonvulsants, mood stabilizers, and anticholinesterases) was not allowed. All medications were maintained at a stable dose during the study. Medications were prescribed and provided at the outpatient clinic where the study took place, which ensured that the dose remained stable during the study. Patients were instructed not to attend CBT sessions during the study period. All subjects provided written, informed consent after receiving a complete description of the study.

Intervention

Participants received tDCS at a stimulation intensity of 2 mA for 30 min on 20 consecutive weekdays. Current intensity was based on previous tDCS trials in psychiatry, particularly depression, and the few case reports using tDCS in OCD available at study design [28, 30]. The device (1 × 1 CT; SoterixMedical, New York, NY, USA) was connected to two rubber electrodes (25 cm^2), each placed inside a sponge soaked in a saline solution. The cathode was positioned over the supplementary motor area (SMA), and the anode was placed in an extracephalic position (over the left deltoid). We employed the EEG 10–20 system for electrode positioning. Cathodal tDCS was placed 1.5 cm anteriorly to the measured location of Cz. For sham tDCS, the device was automatically turned off after 30 s of active stimulation to mimic the somatosensory artifacts of active tDCS. This method has been found to be as effective as is the "gold-standard" placebo

condition [31]. Patients randomized to the sham group were offered the active treatment after the end of the follow-up period.

Assessment

Trained clinicians who were blinded to the treatment allocations assessed the participants at baseline, at week 6, and at week 12 (primary endpoint), using the following instruments: the Y-BOCS [20] and the Clinical Global Impression-Improvement scale [32], to measure OCD symptoms; and the Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI) [33, 34] to assess the severity of depressive and anxiety symptoms, respectively. Adverse events were evaluated weekly with the Systematic Assessment for Treatment Emergent Effects (SAFTEE) scale [35].

Outcomes. The primary outcome was the reduction of the Y-BOCS score from baseline to week 12. Secondary outcomes were reductions in BDI and BAI scores at week 12, as well as the frequency of adverse events, assessed weekly during the study period with the SAFTEE scale.

Statistical analysis

No sham-controlled trials of tDCS in OCD were available when this study was designed. Therefore, we estimated our sample size based on a TMS meta-analysis for OCD [36], in which active TMS was shown to be superior to the sham procedure, with a Hedges' g of 0.59 ($z = 2.73$; $P = 0.006$) for a two-tailed P value of 0.05 and a power of 95%. Using those parameters, the total sample size required was estimated to be 33. To allow for a maximum attrition rate of 30%, we aimed to obtain a sample of 44 participants.

Statistical analyses were performed with the software R, version 4.0.2 (lme4 package; R foundation for Statistical Computing, Vienna, Austria) [37]. Values of $P \leq 0.05$ were considered statistically significant. For continuous variables (Y-BOCS, BDI, and BAI scores), we employed linear mixed-effects models, assuming a continuous linear relationship over time with three repeated measurements per patient (at baseline, week 6, and week 12). Measures were considered as nested within patients, assuming an unstructured covariance structure. The independent variables were time, group, and their cross-level interaction. Intercepts and slopes were consecutively included as random effects to account for patient-specific variation in baseline values and trajectories. Nested models were compared using χ^2 likelihood-ratio tests. No imputation was required for the linear hierarchical model. An intention-to-treat analysis was performed. In addition, we employed a similar Growth-Curve analysis but using endpoint at week 6 to assess whether patients presented earlier improvement, as a secondary outcome. Cohen's d was computed from the regression estimates, with the formula $d = \frac{\beta(Time)}{SD_{raw}}$ [38] to provide effect sizes for linear growth models in the same metric as for classical analyses for repeated measures.

Pearson's χ^2-test with Yates' continuity correction were used to compare the frequency of adverse events between groups. In addition, the same tests were used to conduct a post hoc analysis with treatment response as a categorical variable, following the response criteria established by an expert consensus [39]. According to that consensus, a positive response corresponds to a ≥ 35% decrease in baseline Y-BOCS scores plus a CGI-I rating of 1 (much improved) or 2 (improved). Although our study was not powered to assess the superiority of the active over sham tDCS using such response criteria, this analysis allows for comparisons between our results and those from other trials.

Finally, we evaluated whether clinical response in OCD symptoms could be explained or correlated with the effects of tDCS on depression symptoms and also with doses of medications. We conducted a simple linear regression to evaluate interactions between depression and OCD symptoms. Moreover, we conducted a logistic regression to evaluate interaction between clinical response and fluoxetine equivalent doses.

RESULTS

Participants

Nine hundred and sixty-seven patients were initially contacted by telephone or email, thus completing an electronic questionnaire. Of them, 91 were selected for in-person screening interviews. For a variety of reasons (Fig. 1), 47 subjects were excluded. Therefore, 44 patients were randomized to either active tDCS ($n = 22$) or sham tDCS ($n = 22$). Forty-two patients (95%) completed all sessions and assessments, and two patients dropped out of the study. Another patient was found to have never received treatment for OCD and was excluded prior to the statistical analyses, due to a deviation from the study protocol, in accordance with Cochrane Collaboration [40]. Therefore, 43 were included in intention-to treat analyses (60% were women, and 91% had failed two or more previous treatments). The two treatment groups did not differ in terms of any of the demographic or clinical characteristics evaluated (Table 1).

Primary outcome

We found a significant time × group interaction ($F_{1,84.06} = 84.06$; $P = 0.030$), demonstrating that the baseline-corrected reduction in Y-BOCS scores per measurement was greater in the active tDCS group than in sham (Cohen's d: 0.62 (0.06–1.18), $P = 0.03$) at the end of follow-up, as it can be seen in Fig. 2 and Table 2. We could observe a significant decline in the mean baseline Y-BOCS scores in the active tDCS group (improvement of 21.8% versus 10.2% in the sham group). We found the optimal model fit using a random-intercept fixed-slope solution, given that including symptomatic change as a random factor resulted in no significant improvement in the model fit according to the χ^2 likelihood-ratio test ($\chi^2 = 1.98$; $P = 0.371$).

Secondary outcomes

Adverse events. There were no statistically significant between-group differences regarding the proportion of patients experiencing adverse events—23% in the active tDCS group and 38% in the sham tDCS group ($\chi^2 = 0.585$; $P = 0.445$) (Supplementary Material). Regarding severity, most of the events were classified as mild; although three events were classified as moderate (somnolence, change in appetite, and muscle tic), none of the events required any specific intervention.

Depression and anxiety. A nonsignificant trend was observed for greater reduction in symptoms of depression and anxiety in active tDCS, for the BDI scores ($F_{1,75.79} = 3.01$; Cohen's d: 0.43 (−0.06–0.92); $P = 0.086$) and for the BAI scores ($F_{1,76.21} = 3.66$; Cohen's d: 0.48 (−0.02–0.97); $P = 0.059$) (Table 2 and Supplementary Material).

Post hoc analyses and regression analyses. Considering the expert consensus criteria for treatment response in OCD [40], we found no significant between-group differences in responders. Four (19%) patients in the active tDCS group met response criteria, whereas only one (5%) in the sham group ($\chi^2 = 1.01$; $P = 0.314$) responded. Also, post hoc analyses of Y-BOCS scores using endpoint at week 6 showed no difference between active and sham groups ($F = 0.73$, $P = 0.4$). Regression analyses conducted to evaluate influence of depression symptoms and doses of medications found no correlation between these variables and OCD symptoms (Supplementary Material).

DISCUSSION

In line with our primary hypothesis, active tDCS was found to be superior to sham in reducing OCD symptoms in treatment-resistant patients with multiple comorbidities. Although the improvement in depression and anxiety symptoms was greater in the active tDCS group compared to the sham, the differences

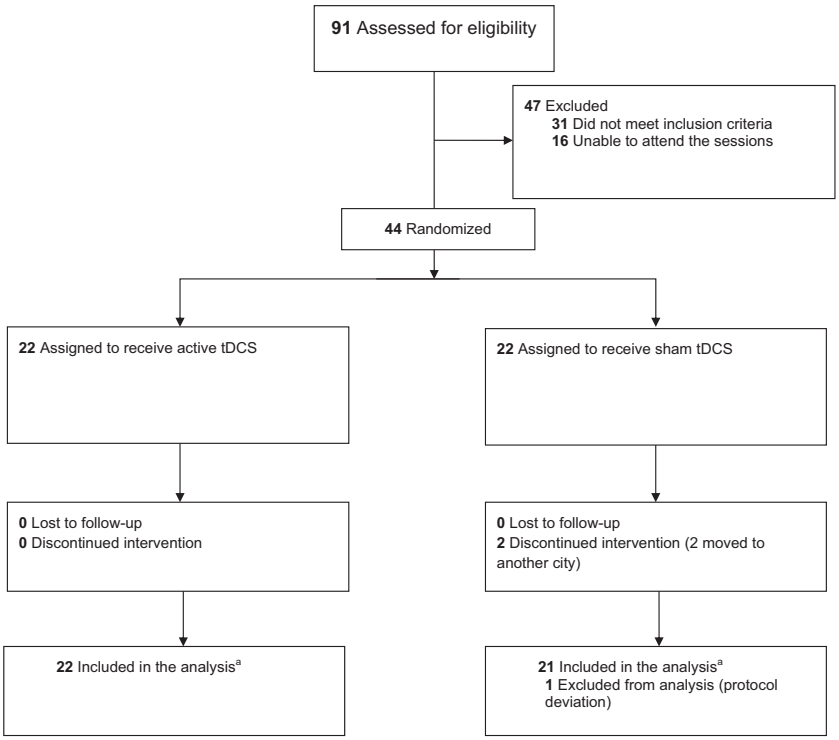

Fig. 1 CONSORT flow diagram for a study of transcranial direct current stimulation for the treatment of obsessive-compulsive disorder. tDCS transcranial direct current stimulation, OCD obsessive-compulsive disorder. [a]The analysis was performed in the intention-to-treat sample.

were nonsignificant. In addition, tDCS was determined to be safe and well tolerated, as epitomized by the low attrition rate and the benign profile of adverse events. Importantly, tDCS was applied as add-on treatment in patients with OCD and multiple comorbidities, under treatment with high doses of SSRIs, which confers external validity to our findings in regard to patients with treatment-resistant OCD.

Our findings corroborate previous uncontrolled trials of tDCS [12, 13, 41] that have stimulated the pre-SMA. One recent open label trial ($n = 21$) evaluated the efficacy of cathodal tDCS over the SMA and anodal tDCS over the right supraorbital area in patients with treatment-resistant OCD. The authors found a reduction of 26% in the Y-BOCS score from baseline to 3 months follow-up and 15% of subjects were considered responders to treatment at that time point. These results are similar to ours (mean reduction of the Y-BOCS score of 21.8% from baseline and 19% of responders in the active tDCS group). Furthermore, our results corroborate those of one randomized controlled trial [17] that adopted an electrode montage different from ours (the anode over the pre-SMA with the cathode over the right supraorbital area).

Despite the lack of a significant difference in the treatment response rates in our study, a symptom reduction of 21.8% could be considered clinically relevant, given the paucity of available treatment options. We speculate that the efficacy of tDCS would be even greater in patients with less severe forms of OCD, or in patients who had failed fewer previous treatments. Moreover, a larger effect could have been observed in case more tDCS sessions had been performed. However, applying more sessions would translate into a higher burden to patients (i.e., more visits to the clinic).

In the present study, the between-group comparison of the Y-BOCS scores at week 6 did not show a significant difference in symptom reduction, which became evident only at week 12, suggesting that tDCS produces a delayed response, as observed in previous trials [42, 43]. The delayed effects of tDCS might be explained by several factors. Firstly, there are vanishing sham effects over time. There was a marked response in the sham group at the beginning of the study, however, it progressively faded away over time. This is possibly due to factors such as regression to the mean, daily visits to the clinic and interaction with the staff, and finally higher expectancy in the trial results. Secondly, effects of tDCS are expected to increase over time. This has been observed in several tDCS trials in psychiatry. For instance, in a large trial enrolling 245 patients with depression, tDCS effects were only evident at week 8, whereas pharmacotherapy presented earlier effects. It is possible that tDCS effects involve long-term neuroplasticity that takes several weeks to translate into clinical effects. Finally, there are specific characteristics associated with OCD treatment, since patients with OCD are expected to show a measurable response after 8–12 weeks of treatment onset [23]. Therefore, neuromodulation trials in patients with OCD must consider a large follow-up time in order to best evaluate the effects of the intervention.

There were no between-group differences regarding the changes in symptoms of depression and anxiety after tDCS, suggesting some specificity of this treatment for OCD symptoms. Even though some improvement in OCD could be related to non-specific antidepressant effects of tDCS, there were no correlations between the Y-BOCS and BDI scores in neither the active tDCS group nor the whole sample.

Both active and sham tDCS were well tolerated, as evidenced by the absence of severe adverse events and the low attrition rate, as well as by the fact that none of the adverse events required specific interventions. Tolerability may represent an advantage of tDCS over pharmacological combined treatment, since it was associated with fewer adverse events than pharmacological augmentation strategies for OCD treatment [44].

In tDCS, the electrode montages are often derived from TMS stimulation sites. One recent systematic review found that low-frequency TMS over the SMA may be more effective for OCD

Table 1. Demographic and clinical characteristics of the sample.

Characteristics	Active tDCS ($n = 22$)				Sham tDCS ($n = 21$)			
	n	Mean	%	SD	*n*	Mean	%	SD
Demographic characteristics								
Age in years	22	38.41		10.95	21	36.9		12.23
Female	13		59		13		62	
Unemployed	12		55		6		29	
Not married	13		59		14		67	
Self-declared White ethnicity	19		86		19		90	
Clinical characteristics								
Y-BOCS score	22	30.64		5.47	21	29.24		6.65
More than one previous treatment[a]	20		91		19		90	
Current pharmacological treatment								
Monotherapy with SSRI or clomipramine, or combination of SSRI and clomipramine	16		73		17		81	
SSRI or clomipramine augmented with an antipsychotic	4		18		2		10	
None	2		9		2		10	
Psychiatric comorbidity								
Generalized anxiety disorder	20		91		16		76	
Current major depressive disorder	20		91		14		67	
Previous major depressive disorder	17		77		11		52	
Post-traumatic stress disorder	4		18		2		10	
Social phobia	3		14		2		10	
Panic disorder	2		9		2		10	
Separation anxiety disorder	2		9		2		10	
Excoriation disorder	1		5		1		5	
Trichotillomania	2		9		0		0	
Specific phobia	1		5		0		0	

tDCS transcranial direct current stimulation, *Y-BOCS* Yale-Brown Obsessive Compulsive Scale, *SSRI* selective serotonin reuptake inhibitors.
[a]SSRI or cognitive behavior therapy.

symptoms [45]. A crossover trial demonstrated that cathodal tDCS, in contrast to anodal tDCS, over the pre-SMA significantly improved OCD symptoms [18]. Therefore, it is possible that inhibition of the SMA by low frequency of TMS or cathodal tDCS improves OCD symptoms. In contrast, the authors of a clinical trial involving patients with OCD chose to use the anodal tDCS over the pre-SMA [17]. It is possible that the target area is more important for the clinical response than the polarity; since polarity can be modified or inverted according to individual factors such as baseline cortical activity or medications [46].

Regarding impacts of SSRI in tDCS activity, one study found that chronic application of SSRI could increase and extend the duration of the facilitation induced by anodal tDCS, whereas it turned cathodal tDCS-induced inhibition into facilitation [47]. In a factorial study, Brunoni et al. showed that tDCS combined with sertraline was more effective than each treatment alone in improving depressive symptoms [42]. However, it is not clear how this influence could reflect in clinical response for OCD. In order to address this question, we converted SSRI in fluoxetine equivalent doses, but we did not find an interaction between response and fluoxetine equivalent doses.

Some perspective for future trials includes overcoming the relatively low focality of tDCS. For that, one possible alternative is high-definition (HD-TDCS) tDCS that can induce high electric fields in the regions of interest with low or absent electric fields in the surrounding areas. However, it is still unclear whether such approach translates into larger clinical effects [48]. Our results can be also employed in the design of future tDCS trials and network meta-analysis in OCD aiming to compare the efficacy of the electrode positioning with other active tDCS montages.

There are several implementation barriers to tDCS in clinical practice in case its efficacy in OCD is confirmed. For instance, we showed that tDCS effects were delayed and only evident after several weeks of treatment. This might be an issue to guarantee adherence in real-world settings. Moreover, tDCS requires daily applications for 30 min; by contrast, pill-taking is "instantaneous" and therefore more straightforward. Conversely, tDCS also has interesting advantages for clinical practice, such as portability and fewer adverse events. Importantly, the tDCS montage used is relatively easy to use compared to other approaches, such as neuronavegated methods. It could also be in fact further simplified for lay use to avoid EEG measurements, as it was done with the Beam method [49] to simplify dorsolateral prefrontal cortex localization at F3.

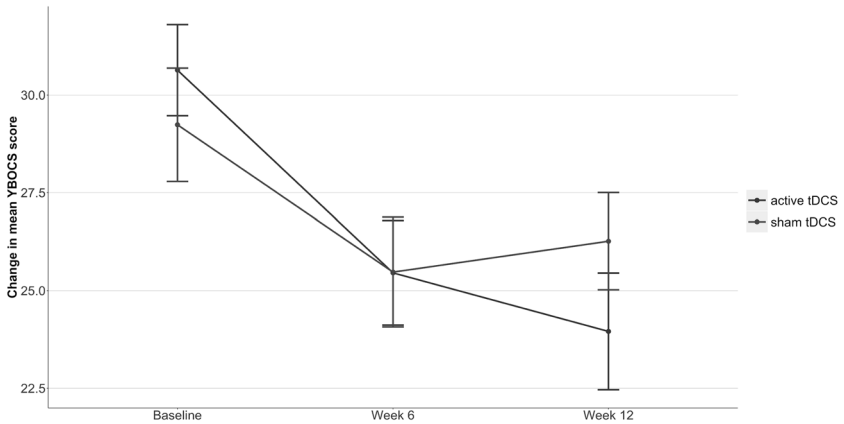

Fig. 2 Changes in the Mean Yale-Brown Obsessive Compulsive Scale (Y-BOCS) Score Over Time (tDCS group $n = 22$, sham tDCS $n = 21$). tDCS transcranial direct current stimulation. Mean reduction in Y-BOCS scores in both treatment groups from baseline to week 12 (intention-to-treat analyses). Error bars indicate 1 SD.

Table 2. Primary outcome (Yale-Brown Obsessive Compulsive Scale Score) and secondary outcomes (Beck Depression Inventory and Beck Anxiety Inventory Scores).

Score	tDCS group	Baseline		Week 6		Week 12			
		Mean	SD	Mean	SD	Mean	SD	*P* value[a]	Cohen's *d* (95% CI)[b]
Y-BOCS	Active	30.64	5.47	25.45	6.27	23.95	7.01	0.030	0.62 (0.06–1.18)
	Sham	29.24	6.65	25.47	6.43	26.26	5.69		
BDI, mean (SD)	Active	21.81	8.30	18.00	7.04	17.67	7.51	0.086	0.43 (−0.06–0.92)
	Sham	19.10	10.47	18.47	13.05	19.42	10.64		
BAI, mean (SD)	Active	19.14	9.59	14.95	7.91	13.67	8.84	0.059	0.48 (−0.02–0.97)
	Sham	17.19	10.42	15.00	12.32	16.37	13.33		

tDCS transcranial direct current stimulation, *Y-BOCS* Yale-Brown Obsessive Compulsive Scale, *BDI* Beck Depression Inventory, *BAI* Beck Anxiety Inventory.
[a]Based on the mean, baseline-corrected changes, as observed in the linear mixed-effects model, including all three assessments.
[b]Between groups effect size.

Some limitations of our study merit consideration. First, it was conducted at a tertiary care hospital, which has favored the recruitment of patients with greater OCD severity. Second, the participants were not evaluated in relation to blinding. However, the updated CONSORT guidelines do not recommend evaluating the efficacy of blinding, because it is difficult to determine whether patients who correctly guess their treatment condition have done so because of insufficient blinding or because of their clinical response [22]. Third, despite the adequate sample size calculation, our sample could still be considered small, which generated large confidence intervals, making it necessary to replicate our findings in larger samples. Finally, individual-level e-field modeling, which is useful to optimize targeting, was not employed in the present study. However, this approach was not fully developed at the time this trial was designed. Nonetheless, electrode positioning was chosen based on a standardized head model e-field modeling [19]. The strengths of this study include the computer-based allocation (which ensured a balance between groups in terms of the factors that were likely to influence the response to treatment), the relatively long follow-up period, and the very low attrition rate.

The current clinical trial provides evidence that active tDCS is superior to sham stimulation in reducing OCD symptoms in a group of treatment-resistant patients. Because our sample was composed of patients with severe OCD, the finding that active tDCS was superior to sham tDCS is clinically meaningful. In addition, the low cost of tDCS and its tolerability profile point to the need for further studies evaluating its effectiveness in patients with less severe OCD, in patients for whom SSRIs are contra-indicated or those who refuse to take medication and/or to engage in CBT.

FUNDING AND DISCLOSURE

Funding and disclosureThis research was supported by grant 2011/21357-9 from São Paulo Research Foundation (FAPESP). The funding source had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the paper; and decision to submit the paper for publication. FP has received grants from the German Federal Ministry of Education and Research, personal fees from Brainswayand MAG & More, and nonfinancial support from MAG & More and neuroCare Group. JBD has received speaking fees from Jansen and consulting fees from Pfyzer in the last 24 months. ARB reports grants from São Paulo Research Foundation (2017/50223-6, 2018/10861-7), Brazilian National Council of Scientific Development productivity support (PQ-1B), and University of São Paulo Medical School productivity support (PIPA-A). Dr. Brunoni is Chief Medical Advisor of Flow Neuroscience (Malmö, Sweden) and has a small equity in this company. This role started in June 2019, after this study was finished. The Laboratory of Neuroscience receives financial support from the Beneficent Association Alzira Denise Hertzog da Silva and the CAPES/INCT program "National Institute of Biomarkers in Psychiatry" (INBioN) (FAPESP 14/50873-3). ECM reports grant from São Paulo Research Foundation (2011/21357-9). RMFS, SG, MCB, DLCC, GDU, and RGS have no competing interests of financial ties to disclose.

ACKNOWLEDGEMENTS

We thank Rosa Rios, BS, Marinês Joaquim, BS, and Ivanil Moraes, BS for administrative support.

AUTHOR CONTRIBUTIONS

RMFS, RGS, and ARB had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: ARB, MCB, DLCC, JBD, ECM, and RGS. Acquisition, analysis, or interpretation of data: RMFS, ARB, SG, MCB, DLCC, JBD, FP, GDU, ECM, and RGS. Drafting of the paper: RMFS, ARB, SG, MCB, DLCC, JBD, FP, GDU, ECM, and RGS. Critical revision of the paper for important intellectual content: RMFS, ARB, SG, MCB, DLCC, JBD, FP, GDU, ECM, and RGS. Statistical analysis: RMFS, ARB, and SG. Obtained funding: ARB, ECM, RGS. Administrative, technical, or material support: RMFS, ARB, MCB, DLCC, JBD, ECM, and RGS. Supervision: ARB, ECM, and RGS.

ADDITIONAL INFORMATION

Supplementary Information accompanies this paper at (https://doi.org/10.1038/s41386-020-00928-w).

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