

A randomized, double-blind clinical trial on the efficacy of cortical direct current stimulation for the treatment of major depression



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Abstract

Preliminary findings suggest that transcranial direct current stimulation (tDCS) can have antidepressant effects. We sought to test this further in a parallel-group, double-blind clinical trial with 40 patients with major depression, medication-free randomized into three groups of treatment: anodal tDCS of the left dorsolateral prefrontal cortex (active group – ‘DLPFC’); anodal tDCS of the occipital cortex (active control group – ‘occipital’) and sham tDCS (placebo control group – ‘sham’). tDCS was applied for 10 sessions during a 2-wk period. Mood was evaluated by a blinded rater using the Hamilton Depression Rating Scale (HDRS) and Beck Depression Inventory (BDI). The treatment was well tolerated with minimal side-effects that were distributed equally across all treatment groups. We found significantly larger reductions in depression scores after DLPFC tDCS [HDRS reduction of 40.4% ($\pm 25.8\%$)] compared to occipital [HDRS reduction of 21.3% ($\pm 12.9\%$)] and sham tDCS [HDRS reduction of 10.4% ($\pm 36.6\%$)]. The beneficial effects of tDCS in the DLPFC group persisted for 1 month after the end of treatment. Our findings support further investigation on the effects of this novel potential therapeutic approach – tDCS – for the treatment of major depression.

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Introduction

Different neurostimulation techniques are considered for treatment of depression: electroconvulsive therapy (UK ECT Review Group, 2003), vagus nerve stimulation (Sackeim et al., 2001), deep brain stimulation (Mayberg et al., 2005), repetitive transcranial magnetic stimulation (rTMS) (Gershon et al., 2003; Herrmann and Ebmeier, 2006; Martin et al., 2003); or magnetic seizure therapy (Kosel et al., 2003). Despite mixed findings in the past (Lolas, 1977), recent preliminary

data suggest that transcranial direct current stimulation (tDCS), another non-invasive method of brain stimulation, might be useful in depression if appropriate currents, electrode sizes, and montages are employed (Fregni et al., 2006b).

In tDCS, low-amplitude direct currents are injected into the brain via scalp electrodes (Nitsche and Paulus, 2000). As shown by a recent modelling study, a significant amount of electric current can reach the brain using appropriately large electrodes and suitable placements (Miranda et al., 2006). Recent studies with up-to-date parameters of stimulation have shown that tDCS is a powerful neuromodulation technique (Nitsche et al., 2003b). Compared with other brain stimulation techniques tDCS has the advantage of being non-invasive, simple and inexpensive, offers reliable sham conditions, and provides a true neuromodulatory intervention, whereby neuronal

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membrane resting potentials are shifted (Bindman et al., 1964). Thus responsivity of the targeted brain regions to afferent input or efferent demand is modified.

We report the findings of a phase II, parallel-group, sham controlled, double-blind clinical trial with 40 patients. We hypothesized that active stimulation of the anodal prefrontal cortex would result in a mood improvement superior to sham stimulation and active stimulation of the occipital cortex.

Methods

Study population

Forty patients with major depression participated in the study [28 females, mean age 49.4 ± 7.4 yr (mean $\pm$ S.D.)]. Diagnosis of unipolar major depressive disorder was confirmed by a licensed, senior clinical psychiatrist (S.P.R.) using the Structured Clinical Interview for DSM-IV Axis I Disorders. All patients were right-handed as assessed by the Edinburgh Handedness Inventory. In order to exclude the confounding effect of medications, patients were required to be off medications (antidepressants) for 2 months prior to the trial – indeed patients were untreated (we did not request antidepressant wash-out). Use of other psychotropic medications were allowed; however, only four patients were using benzodiazepines [two in the left dorsolateral prefrontal cortex (DLPFC), one in the occipital and one in the sham tDCS group]. Exclusion criteria were neurological disorders, any comorbid Axis I disorders, or substance abuse within 3 months of study participation. Furthermore, patients with major depression with psychotic features, bipolar disorder or Axis II disorders were excluded.

The study was performed in accordance with the Declaration of Helsinki (1964). Written, informed consent was obtained from all participants before inclusion in the study, which was approved by the local ethics committee and registered in the national ethics committee [SISNEP (National System of Ethics in Research) 0900.0.015.000-04]. The study was performed at the Psychiatric Institute of the University of Sao Paulo.

Study design

Following initial evaluation, patients were randomly assigned to receive active tDCS of the DLPFC, active tDCS of occipital cortex, or sham tDCS treatment in a 2:1:1 ratio. This randomization strategy (2:1:1) was chosen in order to have the same number of

patients receiving active and control stimulation. Randomization was performed using the order of entrance in the study and a previous randomization list generated by computer. To determine the sample size, we used the results of our previous pilot study (Fregni et al., 2006b). In this study, after treatment, a mean reduction of Beck Depression Inventory (BDI) scores of 69.4% (± 25.7) in the active group and 29.9% (± 28.4) in the sham group was reported (we used the BDI as this scale is more effective in capturing the placebo effect, therefore it is a more conservative choice for sample size calculation). Considering a power of 90% and a critical alpha of 5%, 20 patients (10 in each group) were needed to detect group differences. As we decided to have another control condition, we added 20 additional patients (10 for active stimulation and 10 for active control). Therefore 40 patients were entered into the study. Finally the blind was broken at the end of the follow-up period and patients were then offered a standard treatment with antidepressants.

Outcome measures

Subjects were assessed at baseline and immediately, 15 d, and 30 d after the end of treatment. Rating scales included the 21-item Hamilton Depression Rating Scale (HDRS), which was the primary outcome measure, and the BDI that was the secondary outcome measure. Rating was performed by a trained experienced psychologist (M.L.M.) blinded to the patients' treatment group assignment. Clinical response was defined as a $\geq 50\%$ decrease in HDRS score from baseline, and remission was defined as an HDRS score of ≤ 7 (Frank et al., 1991).

Transcranial direct current stimulation

Direct current was transferred by a saline-soaked pair of surface sponge electrodes and delivered by a specially developed, battery-driven, constant current stimulator with a maximum output of 2 mA (for more technical details, please contact S. A. Boggio at: sboggio@colband.com.br). This device has a special feature that makes it particularly reliable for double-blind trials and was developed by our group as we had noted in our previous trials that patients attempted to look at the tDCS display during the stimulation and encountered situations in which we had to hide the device from patients receiving sham treatment. We therefore incorporated a switch in the back of the tDCS device that could be activated by the researcher to interrupt the electrical current while maintaining the display 'ON' and displaying the parameters of

stimulation throughout the procedure. Electrode montage varied across treatment groups:

- (1) Active group – anodal tDCS over the left DLPFC (cathode electrode over the right supraorbital area – 21 patients).
- (2) Control groups (9 and 10 patients, respectively) – we decided to have two different types of control: active control – in which anodal tDCS was applied over the occipital cortex; and placebo control – in which sham tDCS was applied over the left DLPFC. We included an active control condition (occipital tDCS) in order to control for non-specific effects of tDCS (as occipital activity is not changed in patients with depression compared to healthy subjects) and also to test whether the reference electrode (right supraorbital area) was responsible for the effects of anodal stimulation of the left DLPFC.

For these three conditions, the reference electrode (in this case, the cathode electrode) was placed over the contralateral supraorbital area.

Electrode position was determined by the International 10/20 System for EEG Electrodes, such as that F3 corresponded to the DLPFC. For occipital stimulation, the anode electrode was placed in the midline and 2 cm above the inion. Patients were comfortably seated and awake during the stimulation period. Electrodes were placed on the scalp and fixed with two rubber bands. At the beginning of the session, the impedance was tested and if detected as excessively large, adjustment of the electrodes in respect to the contact and the degree of wetness was performed.

For the active conditions, patients received 2 mA tDCS for 20 min for 10 d (Monday–Friday on two consecutive weeks). These parameters of stimulation were chosen based on recent studies showing that 2 mA of stimulation induces a larger behavioural effect compared to 1 mA tDCS (Boggio et al., 2006; Iyer et al., 2005) and a study suggesting that effects of tDCS are cumulative (Fregni et al., 2006a). For sham stimulation, the stimulator was turned on for 30 s only (Gandiga et al., 2006) and current intensity was gradually increased (at the beginning of the session – ‘ramp up’) and decreased (at the end of the session – ‘ramp down’) to diminish its perception.

Data analysis

Analyses were performed with SAS statistical software (version 9.1, Cary, NC, USA). We used a mixed linear model to analyse mood changes throughout the trial. We modelled mood change (as

indexed by HDRS) using the covariates of time, group and interaction term between group and time. In this model, we accounted for the repeated measures of time, modelling the covariance using the compound symmetry covariance structure that appeared to be the best fit to our data according to the log-likelihood test. In addition we used a model with two-part linear spline functions – thus allowing us to have different slopes over different time-points – as we predicted a-priori that patients would improve after 10 d of treatment and then maintain these effects; thus changing the slope significantly after 10 d of treatment. For post-hoc comparisons, a Bonferroni correction for multiple comparisons was performed. We also calculated the effect size of Cohen’s *d* between the active and sham tDCS treatment groups.

We repeated this analysis for our secondary outcome measure – the BDI. We also compared the number of responders (immediately after treatment) across the groups of treatment using the χ^2 test. There were no dropouts, and the few missing data (<3% of the data) were considered at random.

We then performed correlation tests – using Pearson’s correlation – to evaluate whether there was a correlation between mood changes after stimulation of the left DLPFC vs. demographic and baseline clinical characteristics. Data are reported as mean and standard deviation (s.d.). Statistical significance refers to a two-tailed *p* value <0.05.

Results

The tDCS treatment was well tolerated by the patients. There were few, mild adverse events that were equally distributed across the three treatment groups (*p* = 0.95): mild transient headache (lasting <1 h) (in 14.2%, 11% and 10% of subjects in the DLPFC, occipital and sham tDCS groups, respectively), itching sensation on the site of stimulation (19.1%, 33.3% and 20%, respectively) and mild transient redness of skin at the site of stimulation (5%, 11.1% and 10%, respectively) – that lasted <40 min after the end of stimulation. There were no adverse effects related to application of tDCS during the follow-up period. Demographic characteristics were not significantly different across the treatment groups as detailed in Table 1. As previously mentioned, patients were not taking antidepressants.

For our primary outcome (HDRS), the mixed model revealed a significant main effect of group ($F_{2,111}=5.2$, *p* = 0.01), time ($F_{3,111}=12.0$, *p* < 0.0001) and significant interaction term group vs. time ($F_{6,111}=2.6$, *p* = 0.02). When comparing the effects of tDCS on mood

Table 1. Demographic and clinical characteristics

	Active DLPFC tDCS	Active occipital tDCS	Sham tDCS	<i>p</i> value ^b
<i>n</i>	21	9	10	
Age [yr (s.d.)]	51.6 (7.7)	46.3 (5.8)	46.5 (7.1)	0.25
Gender (F/M)	14/7	6/3	7/3	0.98
Duration of disease [yr (s.d.)]	7.1 (6.2)	8.3 (7.6)	6.4 (7.4)	0.88
Refractoriness ^a (s.d.)	1.6 (1.2)	1.7 (1.2)	1.5 (1.5)	0.89
Baseline HDRS (s.d.)	21.1 (4.4)	21.6 (4.9)	21.9 (4.8)	0.89

tDCS, Transcranial direct current stimulation; DLPFC, dorsolateral prefrontal cortex; HDRS, Hamilton Depression Rating Scale; s.d., standard deviation.

^a As indexed by the number of failed antidepressants.

^b *p* value: one-way ANOVA for continuous variables and Fisher's exact test for categorical variables.

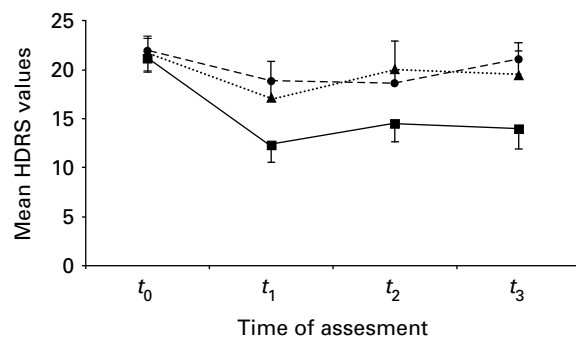


Figure 1. Plots showing mood scores changes [as indexed by the Hamilton Depression Rating Scale (HDRS)] over time (*t*₀, baseline; *t*₁, immediately after treatment; *t*₂, 15 d after end of treatment; *t*₃, 30 d after the end of treatment). Each data-point represents HDRS mean score; error bars indicate s.e.m. —■—, DLPFC tDCS;▲....., occipital tDCS; - -●- -, sham tDCS.

immediately after the end of treatment, there was a significant difference between DLPFC and sham groups ($p=0.0018$), and between DLPFC and occipital groups ($p=0.009$), but not between occipital and sham groups ($p=0.6$). In addition the effects of this treatment lasted for 30 d after the end of treatment as shown by a significant difference between sham and DLPFC at the follow-up assessment ($p=0.04$) (Figure 1; see also Supplementary Table 1 – available in the online version of the paper).

Our model using spline transformation showed a significant interaction term ($F_{2,114}=4.87$, $p=0.009$) up to the first evaluation (immediately after treatment) but not for the follow-up – 15 d and 30 d after treatment ($F_{2,114}=0.04$, $p=0.95$); suggesting that after the 10 d treatment, the three groups had a similar performance (i.e. no further improvement or worsening

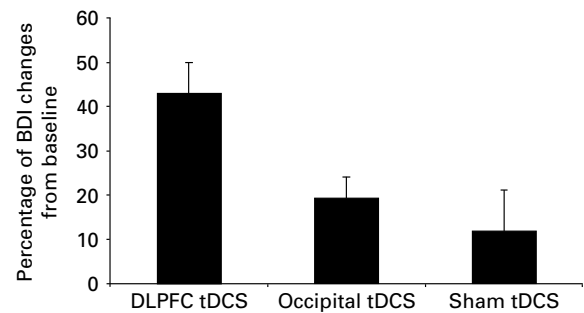


Figure 2. Depression scores changes immediately after 10 d of stimulation compared with baseline in the three groups of treatment. Each column represents mean Hamilton Depression Rating Scale (HDRS) score reduction; error bars indicate s.e.m.

over time. Indeed this model explained the data better than the linear model that used time as a continuous variable [Akaike Information Criterion (AIC) for the model with spline function=951.0 and for the linear model=998.3].

The BDI scores revealed similar results: a significant interaction term ($F_{6,111}=4.2$, $p=0.0007$) and significant difference between DLPFC and sham groups immediately and 30 d after treatment ($p=0.0045$ and $p=0.03$, respectively) (Figure 2) [see Supplementary Table 2 (available online) for further details]. The effect size of Cohen's *d* when comparing the DLPFC and sham groups immediately after treatment, as indexed by HDRS, was 1.11.

There was a significantly greater number of responders after DLPFC tDCS (8 responders) compared with sham and occipital tDCS (2 and 0 responders, respectively) ($\chi^2_1=5.43$, $p=0.019$). In addition, there were five remissions in the DLPFC group and no remissions in the other two controls group ($\chi^2_1=5.17$, $p=0.02$).

There were no significant correlations between mood improvement as indexed by HDRS and clinical variables (baseline HDRS and duration of disease) or demographic characteristics (age and, gender).

Discussion

The results of this study show that cortical stimulation with tDCS is associated with a significant reduction in depression scores that is specific to the site of stimulation and lasts for at least 30 d after the end of treatment. Furthermore, 10 d of treatment induced only minor adverse effects during the treatment period and follow-up similarly distributed in the three groups of stimulation.

tDCS might offer some advantages compared with rTMS as a relatively safe, non-expensive and easy-to-administer technique of non-invasive brain stimulation (for review see Nitsche et al., 2003b). Besides the fact that we observed only mild adverse effects; in other studies, we showed that tDCS of the prefrontal cortex is not associated with cognitive impairment (Fregni et al., 2006c) but, on the contrary, leads to an improvement of performance in a go/no-go task (Boggio et al., *In Press*). In addition, stimulation of the occipital cortex does not result in performance worsening of the go/no-go task (Boggio et al., *In Press*). The intrinsic limitations in focality of tDCS (given the stimulation area roughly corresponds to the size of the electrode that has 35 cm²) make the precise placement of the electrodes less critical than the demands on targeting with a focal TMS coil. The portability of the device and the absence of associated sensations such as pain and scalp sensations, make it particularly well suited for ambulatory treatment in combination with behavioural or other therapies that might amplify the effects of the stimulation.

The mechanisms of tDCS in alleviating depression might be related to a modulation of the activity in the DLPFC. It has been shown that tDCS changes cortical excitability by modulating the membrane resting potential especially during the period of stimulation – and also by modifying synaptic transmission (long-term potentiation and depression-like mechanisms) according to pharmacological studies (Liebetanz et al., 2002; Nitsche et al., 2003a). Therefore, it is reasonable to assume that DLPFC tDCS might have induced a change in the DLPFC activity, a critical area in the cortico-subcortical, mood-related neural network.

Because tDCS is a technique that modulates brain activity in two areas (under the anode and cathode electrode), one may argue that cathodal stimulation of the right supraorbital area might be responsible for the

effects of anodal tDCS of the left DLPFC. However, this alternative explanation is unlikely as anodal stimulation of the occipital cortex, which used the same electrode reference (cathodal over the supra-orbital area), did not result in a significant change in depression scores compared with sham tDCS. Although a decreased placebo effect and increased response in the active treatment group due to a blind break is possible, this alternative explanation is unlikely for several reasons. First, tDCS with a stimulation protocol comparable with the one used in the current study is a reliable tool for sham-controlled experiments as shown by a recent study (Gandiga et al., 2006). Second, we included an active control; therefore any potential blind break would have been captured by this group. Third, because subjects were naive to tDCS and patients received only active or sham tDCS, any potential differences in the sensation associated with stimulation would not be detected by patients. Finally, although we consider that a blind break is improbable, we did not assess it directly and therefore this should be viewed as a limitation of the present study.

The positive results of this initial study have some implications for the prospect of this technique as a potential treatment for major depression. First, future studies need to explore different parameters of stimulation in order to optimize the clinical effects of this treatment; including also the combination of this treatment with cognitive behavioural therapy and, perhaps, antidepressants. Second, larger studies and studies in different populations are needed to confirm the results of our initial findings. Third, further studies investigating higher dosages of tDCS are warranted; however, safety, in this case, still needs to be assessed.

Note

Supplementary information accompanies this paper on the Journal's website (<http://journals.cambridge.org>).

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Statement of Interest

None.

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