Letter to the Editor

COGNITIVE EFFECTS OF REPEATED SESSIONS OF TRANSCRANIAL DIRECT CURRENT STIMULATION IN PATIENTS WITH DEPRESSION

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To the Editor:

The clinical utility of transcranial direct current stimulation (tDCS) has been discussed and explored for almost 40 years. In tDCS, a constant electric field is applied to the brain using two electrodes (anode and cathode) that results in a modulation of the cortical excitability and activity, and that depends on the stimulation polarity: Anodal stimulation increases cortical excitability and cathodal decreases it [Nitsche et al., 2003]. In psychiatry, tDCS studies of major depression and schizophrenia from the 1960s and 1970s showed mixed results [see review by Lolas, 1977]. The negative results of some of these trials can be attributed to the different methodology; in fact, recent investigations using different electrodes size and position, and different stimulation parameters have demonstrated that this technique is a robust method to modulate brain excitability probably on the basis of shifts in neuronal membrane excitability [Nitsche et al., 2003], and suggested that it might be helpful for stroke recovery [Hummel et al., 2005] and depression treatment [Fregni et al., 2006]. Much of this work is only preliminary and in need for further studies. However, the limited safety data available about tDCS restrict the design of larger clinical trials. In a recent study, Iyer et al. [2005] showed that a single session of tDCS (up to 2 mA) is safe in normal subjects. However, similar to repetitive transcranial magnetic stimulation treatment, long-lasting therapeutic effects of tDCS might be associated with repeated, rather than single, sessions of tDCS, and no cognitive safety data on this have been published to date. We report results from a preliminary double-blind, randomized, controlled study that evaluated the cognitive adverse effects of five sessions of tDCS of the left dorsolateral prefrontal cortex (DLPFC) in patients with major depression.

In this trial, we investigated the cognitive effects of 5 days of anodal stimulation of the left DLPFC in 18 patients with major depression (46.4 ± 9.4 years). Outpatients with unipolar major depression and without use of antidepressants for the last 3 months were recruited at the University of Sao Paulo (see demographic and clinical characteristics in Table 1). Patients with bipolar disorder or other psychiatric disorders were excluded. Recruited subjects were randomly assigned to one of two groups: active or sham tDCS. All patients were evaluated by the same rater, who remained blind to the results of the study group assignment. Because tDCS was applied over the DLPFC, we assessed cognitive performance through a battery of neuropsychological tests associated with prefrontal function. Furthermore, all adverse events were recorded. The neuropsychological battery, assessed immediately before the first day of treatment and immediately after the last treatment day (fifth session), consisted of the following tests: (1) Mini-Mental State Examination (MMSE) to measure global cognitive function; (2) Symbol Digits Modalities Test (SD) to measure processing speed; (3) Digit Span (subtest of the Wechsler Adult Intelligence Scale–III)—Forward (DSF) and Backward (DSB) to measure attention and working memory capacity; (4) Stroop (Victoria version): Colors (StC), Words (StW), and Interference Card (StIC) to measure complex focused and sustained attention; and (5) Five-Point Test (FP) to measure design fluency. We applied tDCS via a saline-soaked pair of surface sponge electrodes (35 cm^2).

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TABLE 1. Clinical and demographic characteristics

	Active tDCS		Sham tDCS		
	M	*SD*	*M*	*SD*	*P*-value
Number of patients	9		9		
Age (years)	47.56	10.38	45.33	9.27	NS
Gender (female/male)	5/4		6/3		NS
Handedness (right/left)	9/0		9/0		NS
Duration of disease (years)	9.78	5.87	9.22	4.21	NS
Number of previous episodes	2.33	1.41	2.78	1.79	NS
Baseline BDI	34.44	5.98	36.22	9.34	NS
Baseline HDRS	23.56	5.03	25.89	4.26	NS
Baseline MMSE	25.89	2.98	25.33	2.87	NS
Previous use of SSRI	5		4		NS
Previous use of TCA	7		7		
Previous ECT treatments	0		0		

ECT, electroconvulsive therapy; BDI, Beck Depression Inventory; HDRS, Hamilton Depression Rating Scale; NS, not significant; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressants; MMSE, mini-mental state examination.

The anode electrode was placed over F3 (10–20 International EEG System) of each subject. The cathode (reference electrode) was placed over the contralateral supraorbital area. A constant current of 1-mA strength was applied for 20 minutes per day (administered for 5 alternate days) during the morning (8:00 to 10:00 A.M.). For sham stimulation, the stimulator was turned off after 5 seconds (as previously reported by Siebner and colleagues 2004). Written informed consent was obtained from all participants prior to inclusion in the study, which was approved by the local ethics committee (University of Sao Paulo).

All patients tolerated tDCS without complications. The mean cognitive performance after the treatment compared to baseline in the active tDCS group improved for all the evaluated tests (see Supplementary Table 1S for details). One-way analysis of variance (ANOVA; factor treatment: active and sham tDCS) showed a significant difference in the working memory performance between the two groups of treatment as indexed by DSF [$F(1, 16) = 8.81$, $P = .009$] and DSB [$F(1, 16) = 4.56$, $P = .048$]. There was a trend toward a significant difference between the two treatments for the StC [$F(1, 16) = 3.69$, $P = .072$], StW ([$F(1, 16) = 3.31$, $P = .087$] and SD [$F(1, 16) = 3.9$, $P = .066$; for details see Supplementary Table 1S and Figure 1]. In all these comparisons, the active treatment induced a beneficial effect—cognitive improvement. There was a significant mood improvement in the active compared to sham tDCS group [58.5% ($\pm$20.4) vs. 13.1% ($\pm$23.4) Hamilton Depression Rating Scale (HDRS) reduction in the active and sham tDCS group, respectively; $F(1, 16) = 19.2$, $P < .001$] and this improvement was not correlated with the cognitive improvement for any of these cognitive tests, including the two working memory tests that showed a significant cognitive improvement following real, but not sham, tDCS ($r = .10$, $P = .79$ for DSF; $r = .27$, $P = .47$ for DSB; Pearson's correlation).

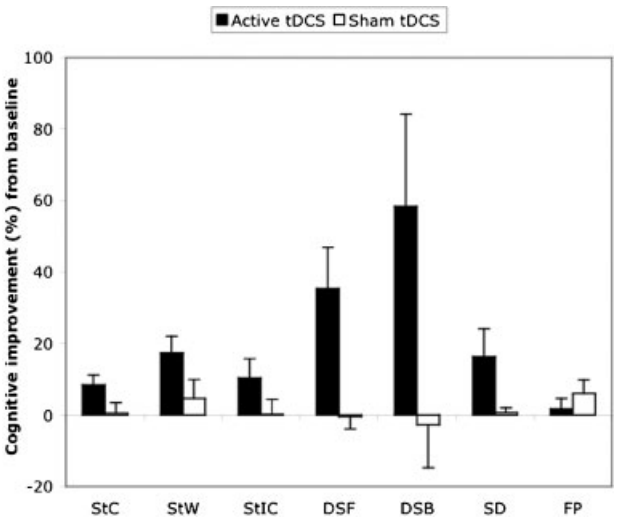

Figure 1. Mean cognitive performance change after active (black column) and sham tDCS (white column) compared to baseline values in patients with major depression. Note that a positive change indicates a treatment-related performance improvement in these tests compared to baseline. Each column represents the percentage of mean test performance change from baseline $\pm$ standard error of the mean.

Repeated sessions of active tDCS do not result in cognitive impairment compared to placebo tDCS in patients with major depression; on the contrary, they appear able to improve one aspect of cognitive function—working memory. This cognitive enhancement was not observed after sham tDCS and was not correlated with mood effects. This is in line with a previous study that showed an enhancement of working memory after a single session of tDCS of the left DLPFC in healthy subjects [Fregni et al., 2005]. In addition, we showed no correlation between mood improvement and cognitive improvement, suggesting

that independent mechanisms were responsible for cognitive and mood changes. In accordance, it has been demonstrated that cortical stimulation with transcranial magnetic stimulation results in a cognitive improvement of some neuropsychological functions that is independent of the mood improvement [Hausmann et al., 2004; Moser et al., 2002; O'Connor et al., 2003].

An important consideration is that other electrode montages that may also result in an antidepressant effect, such as cathodal stimulation of the right DLPFC, were not tested in our study. Our results, therefore, have to be further investigated in studies with larger sample sizes, using other strategies of stimulation, such as different electrode montages and sizes, and with other tools of brain investigation, such as neuroimaging techniques, to explore the optimum stimulation strategy systematically. However, the preliminary findings of our small study are important to support further trials investigating the antidepressant effects of repeated sessions of tDCS.

REFERENCES

Fregni F, Boggio PS, Nitsche M, Bermpohl F, Antal A, Feredoes E, Marcolin MA, Rigonatti S, Silva MTA, Paulus W, Pascual-Leone A. 2005. Anodal transcranial direct current stimulation of prefrontal cortex enhances working memory. Exp Brain Res 166: 23.

Fregni F, Boggio PS, Nitsche M, Marcolin MA, Rigonatti S, Pascual-Leone A. 2006. Treatment of major depression with transcranial direct current stimulation. Bipolar Disord 8:203–204.

Hausmann A, Pascual-Leone A, Kemmler G, Rupp CI, Lechner-Schoner T, Kramer-Reinstadler K, Walpoth M, Mechtcheriakov S, Conca A, Weiss EM. 2004. No deterioration of cognitive performance in an aggressive unilateral and bilateral antidepressant rTMS add-on trial. J Clin Psychiatry 65:772–782.

Hummel F, Celnik P, Giraux P, Floel A, Wu WH, Gerloff C, Cohen LG. 2005. Effects of non-invasive cortical stimulation on skilled motor function in chronic stroke. Brain 128:490–499.

Iyer MB, Mattu U, Grafman J, Lomarev M, Sato S, Wassermann EM. 2005. Safety and cognitive effect of frontal DC brain polarization in healthy individuals. Neurology 64:872–875.

Lolas F. 1977. Brain polarization: Behavioral and therapeutic effects. Biol Psychiatry 12:37–47.

Moser DJ, Jorge RE, Manes F, Paradiso S, Benjamin ML, Robinson RG. 2002. Improved executive functioning following repetitive transcranial magnetic stimulation. Neurology 58:1288–1290.

Nitsche MA, Liebetanz D, Antal A, Lang N, Tergau F, Paulus W. 2003. Modulation of cortical excitability by weak direct current stimulation—technical, safety and functional aspects. Suppl Clin Neurophysiol 56:255–276.

O'Connor M, Brenninkmeyer C, Morgan A, Bloomingdale K, Thall M, Vasile R, Leone AP. 2003. Relative effects of repetitive transcranial magnetic stimulation and electroconvulsive therapy on mood and memory: A neurocognitive risk-benefit analysis. Cogn Behav Neurol 16:118–127.

Siebner HR, Lang N, Rizzo V, Nitsche MA, Paulus W, Lemon RN, Rothwell JC. 2004. Preconditioning of low-frequency repetitive transcranial magnetic stimulation with transcranial direct current stimulation: Evidence for homeostatic plasticity in the human motor cortex. J Neurosci 24:3379–3385.