

COMPARATIVE BENEFITS OF TRANSCRANIAL DIRECT CURRENT STIMULATION (TDCS) TREATMENT IN PATIENTS WITH MILD/MODERATE VS. SEVERE DEPRESSION

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Abstract

Objective: Major depressive disorder (MDD) is a psychiatric condition with high prevalence and poor treatment outcomes. Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation method with pilot trials showing promising results; however, it is still unclear the profile of patients in which tDCS is better indicated. Therefore, the aim of this study is to compare tDCS efficacy according to depression severity.

Method: Thirty-two hospitalized patients (24 women) aged 30-70; with MDD according to DSM-IV-TR criteria were included. Drug treatment was not changed during the study. Mood was evaluated using the Hamilton Depression Rating Scale (HDRS) and Beck Depression Inventory (BDI). Patients were divided into two groups according to MDD severity, as measured by BDI (mild/moderate vs. severe). Anodal tDCS was bilaterally delivered to the Dorsolateral Prefrontal Cortex (DLPFC), using a stimulating current of 2 mA intensity for 20 minutes, twice a day, for 5 days consecutively. Depression was measured at baseline and after 5 (T1), 12 (T2) and 35 (T3) days from the start of tDCS treatment.

Results: Treatment was well tolerated without side effects. tDCS was effective in ameliorating depressive symptoms, with a significant mean BDI reduction of 11.1 ($p < 0.01$) and HDRS of 7.1 ($p < 0.01$) after one month of treatment (T3). Our mixed ANOVA model also showed significant time, depression severity, and time vs. depression severity effects for BDI ($F_{120,3} = 11.0$, $p < 0.01$) and HDRS ($F_{119,3} = 8.1$, $p < 0.01$) scales, indicating a greater tDCS effect for severe MDD. Similar results were found when depression severity was managed as a continuous variable. We observed no gender differences in tDCS effects.

Conclusions: tDCS is especially effective in patients with severe MDD, providing sustained antidepressant effects after one month of intervention. These initial findings suggest tDCS could target this subgroup of patients to maximize clinical efficacy.

Key Words: major depressive disorder, transcranial direct current stimulation, non-invasive brain stimulation, mood

Declaration of interest: none

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Introduction

Major depressive disorder (MDD) is a psychiatric condition with a significant burden worldwide that persists besides the continuous research in the field (Andrews 2008). One of the reasons for this is that treatments are not completely effective: a recently large effectiveness trial showing one third of patients remaining symptomatic after four anti-

depressant drug trials (Trivedi and Daly 2008). Therefore, new therapeutic approaches are needed; one of them is a neurostimulation technique known as transcranial direct current stimulation (tDCS) (Priori 2003) - a non-pharmacological intervention in which a weak direct current generated by a small, portable device equipped with chargeable batteries is applied on the scalp with the anodal electrode placed over the brain region to be stimulated, while the cathodal

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electrode is over the region to be inhibited. This weak current (usually 0.5 - 2 mA) is able to reach the brain and then to promote discrete shifts in membrane resting potentials – thereby depolarizing or hyperpolarizing neurons (Priori et al. 1998, Nitsche et al. 2003). In fact, although Galvani used a device to generate weak currents as early as in 1780, it was not until the late 20th century that the effects of direct current started to be more profoundly investigated (Priori 2003, Zaghi et al. 2009). More recently, the interest in non-pharmacological treatments motivated reappraisal of tDCS.

Despite some conflicting results (Loo et al. 2009) recent studies suggest that tDCS might be a useful intervention in MDD. In a comprehensive review of these studies, Nitsche and colleagues acknowledge, however, that all the studies so far enrolled patients with mild to moderate symptoms (Nitsche et al. 2009a). Though one study showed the effectiveness of drug-resistant patients (Ferrucci et al 2009) it is still unclear the type of patient that could optimally respond to tDCS.

Therefore, the aim of this study is to assess the effectiveness of tDCS in patients with severe MDD, by comparing its effects in a subgroup of patients with mild-to-moderate depressive symptoms.

Materials and methods

Patients

Our sample size was composed by 32 hospitalized patients aged 32-68, with major depressive disorder according to DSM-IV-TR (APA, American Psychiatric Association 2004) criteria. The patients who participated in the study were selected from a larger sample of hospitalized patients diagnosed of major depression. Patients with schizophrenia, substance use disorders, eating disorders, personality disorders, mental retardation and other significant medical diseases were excluded.

During the entire cycle of tDCS patients were maintained on the same pharmacological treatment. This therapy included the range of drugs commonly used in the treatment of major depression: tricyclic antidepressants, monoamine oxidase inhibitor (MAOI), selective serotonin reuptake inhibitors (SSRI), benzodiazepines, etc.

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.

Mood Measurement

Mood was evaluated using the 21-item Hamilton Depression Rating Scale (HDRS) and the Beck Depression Inventory (BDI). The HDRS and the BDI scales rated the severity of depressive symptoms such as depressed mood, insomnia, agitation, anxiety, weight loss, cognitive and physical symptoms (Beck et al. 1961, Hamilton 1960).

Study Design

Patients were divided into two groups according to MDD severity - those considered with severe depression had a BDI score >28 and those with mild/moderate MDD had a BDI score of 28 or less.

All patients were evaluated before the treatment (baseline), and after 5 (T1), 12 (T2) and 35 (T3) days from the start of tDCS treatment.

We choose to perform an open-label study rather than a randomized, placebo-controlled trial because our sample was composed by patients with a distress that was severe enough (e.g. suicidal attempt or suicidal risk) to require hospitalization - thus, due to ethical issues we did not adopt a placebo arm in our study.

Transcranial direct current stimulation (tDCS)

Direct current generated by a DC stimulator was bilaterally delivered through a saline soaked pair of surface sponge electrodes. The parameters of stimulation were: 2 mA of intensity (current density: 0.06 mA/cm²) for 20 minutes, twice a day, with at least a 4-hours interval between each session, for 5 days consecutively. Anodal electrode was placed on the left dorsolateral prefrontal cortex and cathode electrode on the contra-lateral area, as described elsewhere (Ferrucci et al. 2009).

Statistical analysis

Analyses were performed with SPSS statistical software and Excel software. A mixed ANOVA model was used to assess mood changes during the trial. The dependent variable was mood symptoms (indexed by HDRS and BDI scores) and the covariates were time (T0, T1, T2, T3) and group (severe vs. mild/moderate). For exploratory analyses, the same model was used, covarying for gender, previous use of ECT, previous suicidal attempts, age, and other clinical significant characteristics. There were no dropouts; however it was observed a small number of missing data (5-10% of the data) for the dependent variable measurement in T1 and T2. The missing data was considered at random and we used a regression imputation method to handle with this issue - such technique allowed us to substitute missing values for values derived from a regression model using baseline variables as well as mood scores measured at endpoint.

Results

The tDCS treatment was well tolerated without side effects. The baseline clinical characteristics of the patients are described in **Table 1**. The most used medications were the antidepressants venlafaxine (13 patients, mean dose = 225mg/day), mirtazapine (9 patients, mean dose = 30 mg/day), sertraline (7 patients, mean dose = 100mg/day). Also, 19 patients were using two different classes of antidepressants (e.g. venlafaxine and mirtazapine), thus characterizing a sample with a high degree of refractoriness.

Table 1. Baseline characteristics of patients. HDRS= Hamilton Depression Rating Scale; BDI= Beck Depression Inventory; SD=standard deviation; ECT= electroconvulsive therapy

Baseline characteristics of subjects	
Mild/Moderate depression	13 (40%)
Severe depression	19 (60%)
Females	24 (75%)
Previous use of ECTs	13 (40%)
Previous suicidal attempts	11(34%)
Age - Mean (SD)	49.8 (12.87)
Education (years) - Mean (SD)	9.8 (3.88)
Baseline BDI scores - Mean (SD)	30.0 (10.61)
Baseline HDRS scores- Mean (SD)	25.6 (8.87)
Duration of Disease - Mean (SD)	18.0 (11.16)

Table 2. Response and remission rates after one month of tDCS onset. BDI= Beck Depression Inventory; HDRS= Hamilton Depression Rating Scale. Response is an improvement of symptoms above 50%, partial response is an improvement of symptoms between 25 and 50%, remission was defined as a severity score of BDI (≤ 7).

BDI	Severe (19)	Mild-Moderate (13)
<i>Partial Response</i>	1 (5%)	1(5%)
<i>Response</i>	11 (58%)	2(10%)
<i>Remission</i>	6 (31.6%)	2 (10%)
HDRS		
<i>Partial Response</i>	7 (38.9%)	3 (16.7%)
<i>Response</i>	6 (33.3%)	1 (5%)
<i>Remission</i>	3(16.7%)	1(5%)

For our main results, the repeated-measures ANOVA model showed significant time ($F_{90,3} = 6.2$, $p < 0.01$) and time x group interaction effects ($F_{90,3} = 9.6$, $p < 0.01$) for BDI scores (Figure 1). Similar results were observed for HDRS scores in this model ($F_{87,3} = 4.62$, $p = 0.01$ for time x group effects), showing that the treatment was effective and patients with severe depression improved significantly more along time than those with mild/moderate depression. This subgroup of patients showed no significant improvement after one month of tDCS intervention onset (mean BDI improvement = 8.5%, $SD = 57\%$) when compared to those patients with severe depression (mean BDI improvement = -50.33%, $SD = 33.7\%$; $p < 0.01$). Post-hoc analysis showed a significant improvement in severe patients when comparing baseline scores vs. T3 ($p < 0.01$) but not when comparing T1 vs. T3 ($p = 0.24$ for BDI, $p = 0.27$ for HDRS) and T2 vs. T3 ($p = 0.9$ for BDI, $p = 0.22$ for HDRS) (Figure 1, Figure 2).

Finally, when categorizing depression improvement in complete remission (absence of clinical significant depression symptoms) or response (improvement of $>50\%$ in depression symptoms) we observed that 31.6% and 58% of severe patients achieved remission or response, respectively, when indexed by BDI scale (Table 2).

Exploratory analyses also suggested that tDCS intervention was particularly more effective in patients with previous suicidal attempts ($F_{84,3} = 6.6$, $p < 0.01$ for HDRS and $F_{87,3} = 3.6$, $p = 0.02$ for BDI) but there was no relation with gender ($p = 0.2$ for HDRS; $p = 0.09$ for BDI), previous use of ECT ($p = 0.68$ for HDRS; $p = 0.47$ for BDI), duration of disease ($p = 0.32$ for HDRS; $p = 0.27$ for BDI), years of study ($p = 0.47$ for HDRS; $p = 0.77$ for BDI), or age ($p = 0.22$ for HDRS, $p = 0.25$ for BDI).

Discussion

The main finding of our study is that tDCS was particularly effective in patients with severe depression who showed symptoms improvement of about 50% in both BDI and HDRS scales. It should be underscored that, in this subgroup of patients, all were drug-resistant (i.e., they failed to achieve remission of symptoms after two or more antidepressant trials), 35% had had previous suicidal attempts and 40% had already used ECT. In STAR*D trial (Sequenced Treatment Alternatives to Relieve Depression), a large, multicentric, pragmatic trial that evaluated several strategies to treat MDD at different levels of refractoriness; it was found that, after two failed antidepressant trials, the observed remission and response rates were around 15-25% using either lithium or T3 augmentation strategies (Gaynes et al. 2008a). In our study, for a similar profile of patients (i.e. severe, drug-resistant MDD) the remission rates were 16.7% (HDRS) and 31.6% (BDI) and the response rates, 33.3% (HDRS) and 58% (BDI). Therefore, these initial findings suggest a possible role of tDCS therapy in patients with severe depression, especially taking into account that tDCS is an affordable therapy with minimal side effects (Oquendo et al. 2002, Palm et al. 2008, Poreisz et al. 2007, Priori et al. 2009).

Our post-hoc analysis between baseline and T1 also showed a fast improvement of depression symptoms after five days of treatment onset, which sustained for, at least, one month. This tDCS feature was also observed in other studies – Boggio and colleagues, for instance, also observed a fast tDCS effect right after treatment (Boggio et al. 2008); while the same group observed, in a later study, that tDCS was as effective as fluoxetine; but tDCS improvement was already significant after two weeks of treatment onset (Rigonatti et al. 2008). Since early response to treatment is strongly associated with long-term MDD outcomes (Mulder et al. 2006), tDCS might also have a role in potentiating antidepressant drug therapies to achieve sustained symptoms remission. Along these lines, the association of citalopram (a SSRI antidepressant) with tDCS greatly enhanced tDCS neurophysiological effects in healthy volunteers (Nitsche et al. 2009c), thus suggesting future lines of clinical research in tDCS-antidepressant drugs combination strategies.

Finally, we observed that previous suicidal attempts were positively correlated with tDCS efficacy. Since suicidal behavior worsens MDD outcomes and vice-versa, and previous suicidal attempts are a major risk factor for future attempts (Mann et al. 2005, Oquendo et al. 2002); tDCS could be also of clinical relevance in this subgroup of patients. However, it should be underscored that this is an exploratory result and further studies are needed to clarify this topic.

Although the tDCS response in severe MDD patients was quite homogeneous and substantial, in those with mild-to-moderate MDD it was more heterogeneous and less important, with remission and response rates of 5-10% - contrastingly from other tDCS-depression studies that observed a satisfactory response in these patients. However, all patients in our study were drug-resistant and using psychopharmacological drug therapies, and therefore it is possible that some of them were using drugs that interfere tDCS effects (e.g., benzodiazepine or anticonvulsant drugs) (Nitsche et al. 2004) – also, because the drugs used were not controlled, we could not analyze the influence of each class of drugs in tDCS effects. Moreover, it is still unknown how to measure the amount of discharge delivered for each patient (Nitsche et al. 2009b) and therefore each subject might need specific parameters for brain stimulation.

One limitation of our study is that it is an uncontrolled, open study; therefore we could not measure the placebo effects of tDCS intervention. However, our results are comparable with those of STAR*D trial that also did not use a placebo group (Gaynes et al. 2008b). Besides, placebo effects of non-invasive brain stimulation techniques in drug-resistant patients are low and comparable to the placebo effects of drug therapies (Brunoni et al. 2009).

In conclusion, severe, drug-resistant MDD patients tDCS significantly ameliorated depressive symptoms after 5 days of treatment onset, with sustained response after one month of therapy. This finding encourages further tDCS controlled studies in patients with severe MDD as well as it suggests a role for tDCS intervention in patients failing to respond to drug treatment.

Figure 1. Hamilton Depression Rating Scale (HDRS) (A) or Beck Depression Inventory (BDI) (B) scores and tDCS treatment in mild/moderate and severe patients: at baseline levels, 5 days after treatment onset (T1), 12 days after treatment onset (T2) and 35 days after treatment onset (T3). Error bars are SEM.

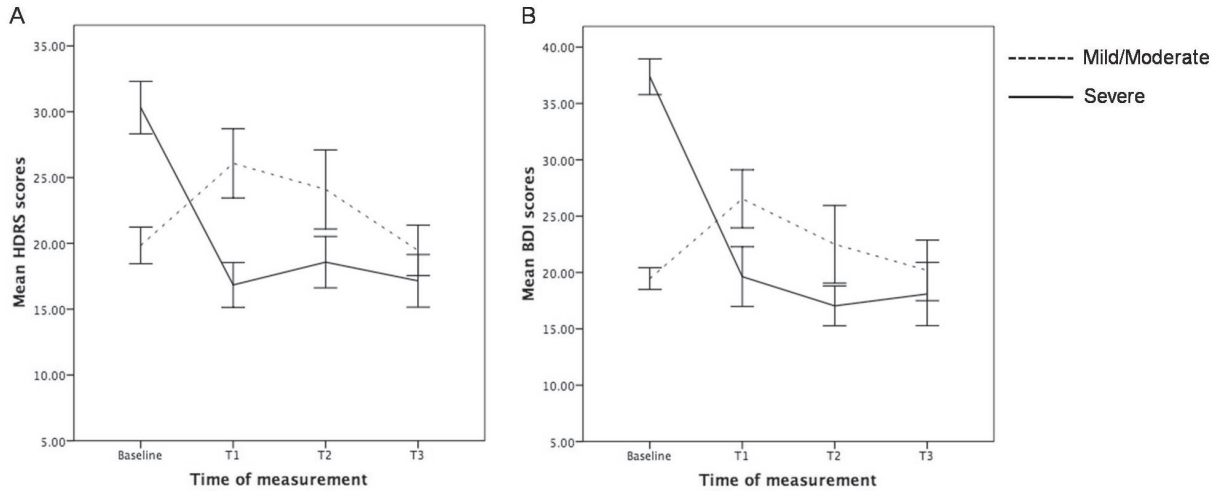
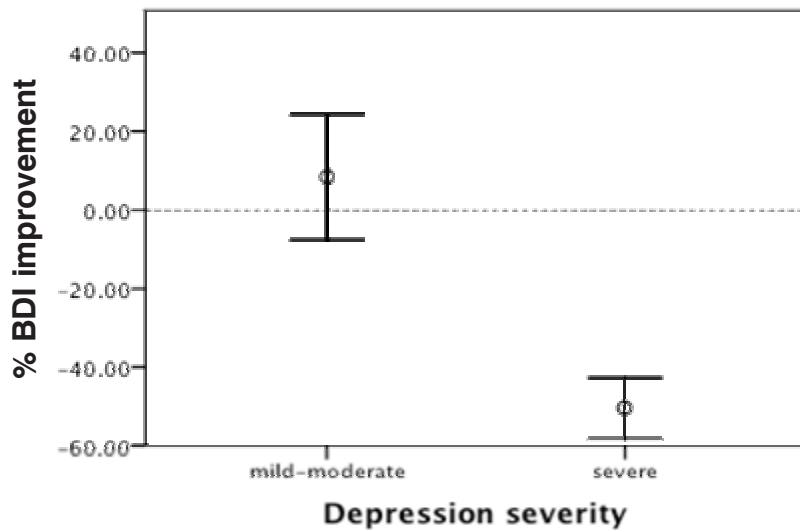


Figure 2. % Beck Depression Inventory (BDI) improvement after 35 days from treatment onset (T3) (severe vs. mild/moderate). Error bars are SEM.



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