

Research Project

Treatment of Bipolar Depression with tDCS: a randomized, double-blind, placebo-controlled clinical trial

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Abstract

Bipolar disorder is a condition that affects up to 5% of the world population, being a disorder characterized by episodes of mania - when the patients experience racing thoughts, euphoria, grandiosity and decreased need for sleep - and depression - characterized by sadness, feelings of guilt, loss of interest or pleasure in usually enjoyed activities. Contrary to what most people think, depressive episodes in Bipolar Disorder are more common and dangerous than manic episodes. Currently, the treatment of bipolar depression is limited to some drugs, all of them with important side effects. Therefore, developing new treatments for Bipolar Depression is necessary. Transcranial Direct Current Stimulation (tDCS) consists in application of a low intensity and continuous electric current in the cerebral cortex via electrodes placed on the scalp in order to modify the cerebral activity in the area where the current is applied. In a previous study of the group, it was observed that tDCS is as effective as the antidepressant sertraline in the treatment of unipolar depression. Moreover, it was observed that the tDCS has low side effects. Because of the encouraging results previously found, we decided to investigate whether tDCS is an effective treatment for Bipolar Depression. The study will be a double-blind clinical trial in which 60 patients with Bipolar Depression will be randomly assigned to two groups, one of them tDCS will be performed and the other to receive *sham* tDCS. At the end, it will be evaluated which group – active or *sham* tDCS - will display decrease of depressive symptoms. Whether it is noticed that active tDCS has a better outcome than *sham* tDCS, the present study will provide evidence of a possible new, non-pharmacological treatment for Bipolar Depression, which would have an important impact on quality of life of that patients.

Key words: Transcranial Direct Current Stimulation; Bipolar Depression; Non-invasive Brain Stimulation; Bipolar Disorder.

1. Problem Statement

Bipolar Disorder (BD) is a psychiatric disorder characterized by the presence of episodes with clinically significant symptoms of hypomania or mania frequently alternated by periods of normal mood and depression. The estimated lifetime prevalence in Brazil is approximately 0.9 to 2.1% (Merikangas et al., 2011). BD generally starts (up to 60% of cases) in late adolescence or early adulthood. It is recurrent, with mood swings frequently present throughout the life, with depressions being more prevalent than euphoria, occurring in up to 1/3 of the lifetimes of the patients. Morbidity and mortality rates are high, including suicide risk, that reach up to 15% (Geddes & Miklowitz, 2013; Yatham et al, 2013).

The affective, cognitive and neurovegetative symptoms of BD are associated with anatomical, neurochemical or metabolic changes in the striatum, thalamus, prefrontal cortex, limbic structures (amygdala and hippocampus) and cerebellum, among others. The hyperfunction of limbic and subcortical areas (striatum, thalamus, amygdala) and the decrease of modulation of the prefrontal areas would be responsible for the deregulation of emotions and cognition. Cellular changes are found, such as reduction in number and volume of neurons and glial cells in the dorsolateral prefrontal cortex, anterior cingulate gyrus, hippocampus and amygdala. Such cellular changes may sometimes represent cell loss and atrophy throughout the course of the disease (Gigante et al, 2011). Neurotransmitter changes (in mania, adrenergic and dopaminergic hyperactivity and depressed serotonergic activity have been observed) are consequences of complex dysfunctions of intracellular signal transduction and gene expression. In addition, changes in the neurotransmission systems of gabaergic, glutamatergic and neuropeptides were also found (Geddes & Miklowitz, 2013; Phillips & Kupfer, 2013).

Patients with BD present difficulties in several cognitive domains, even euthymic, being the executive functions (which regulate and monitor cognitive processes and involve planning, operational memory, attention, problem solving, inhibitory control and mental flexibility) one of the most impaired. Executive dysfunctions may, in part, explain difficulties in the psychosocial adaptation of patients with BD. During mood changes, even subtle, impairments of attention, memory, psychomotor speed and learning are commons (Depp et al, 2012). Therefore, BD etiopathogenesis seems to include, in addition to modifications in neurotransmitters, complex structural and functional changes in neuronal plasticity and in brain circuits influenced by genetic and environmental factors.

DSM-V continues to divide bipolar disorders into: type I, characterized by the presence of a manic episode, emphasizing the need of the presence of increased activity or energy; type II, characterized by the alternation of hypomanic and depressive episodes (this is not, however, understood as a more attenuated form of the disease, since individuals spend a lot of time in depression and have relevant consequences due to the constant mood instability); cyclothymic disorder in which symptoms of mood elevation alternate with depressive symptoms for at least

2 years (and for children a minimum of 1 year) without, however, meeting criteria for manic, hypomanic or depression episodes. Differently to DSM-IV-TR, previous version, mixed episodes (explained in more detail below) are no longer an independent category but may be present during episodes of mania / hypomania or major depression. Other specifiers added were "with anxiety" (at least 2 of the following symptoms: tension, restlessness, trouble concentrating from worry, fear that something horrible might happen, feeling of loss of control of self) and "suicidal risk."

Suicide is the leading cause of early mortality in that patients, who have a 28-fold increased risk of suicidal behavior compared to the general population. The ratio of suicide attempt to full-blown suicide in BD is 5: 1 versus 15: 1 in the general population, indicating that these patients tend to use more violent and lethal methods. The relationships between suicidal behavior and BD seem to be more striking than in other psychiatric disorders, being the most important among men and secondarily among women. From 20% to 55% of BD patients have already had at least one lifetime suicide attempt and complete suicide rates are between 10% and 15% (Goodath and Jamison, 2007; Yatham et al, 2013).

The goal of TB treatment is to achieve euthymia, promote the prevention of new episodes, and the recovery of social and occupational functioning. Once the treatment is carried out throughout the life, attention must be paid to its long-term effects and its possible health damage. BD is still a difficult-to-treat psychiatric condition, especially bipolar depression, mixed states, and rapid-cycling. Therapeutic options for depression can worsen the phases with manic symptoms and medications for mania can bring a later depression. The limited knowledge of the etiology of BD hampers the development of specific treatments (Geddes & Miklowitz, 2013).

The ideal mood stabilizer would have antidepressant and antimanic efficacy, without inducing symptoms of opposite polarity to that in treatment and having efficacy in prevention of new episodes, both depressive and manic. The simpler and with fewer side effects the better the adherence to treatment. Despite this, it is common to combine the use of two or more mood stabilizers in the treatment of an acute episode or even in prophylactic treatment. BD is a disease that affects the individual throughout life, with periods of euphoria and more frequently depression and is associated with an important family risk. Clinical and psychiatric comorbidities are frequent. The treatment is complex and varies according to the patients' symptoms. In spite of the numerous efforts made so far, new therapeutic perspectives are still needed to improve the quality of life of this population and of all linked to them.

In this context, Transcranial Direct Current Stimulation (tDCS) is a new therapeutic intervention that has been presenting a fast development in recent years, seeming to be a promising technique in the therapy of many neuropsychiatric disorders (Fregni & Pascual-Leone, 2007). The technique consists of applying a low intensity of continuous electric current

to the brain via electrodes placed on the scalp. It has been demonstrated that, using adequate doses, electrodes and equipment, a significant amount of electrical current reaches the neural networks (Miranda, Lomarev & Hallett, 2006), leading to neuromodulation (Nitsche et al 2003). Most standard protocol of the technique uses two surface electrodes - one as a cathode and the other anode (Nitsche et al, 2008). The anode is usually applied over the area of the brain to be stimulated and the cathode is applied either in the opposite hemisphere or in a saline solution. An electric current of one or two milliampares lasting 20 minutes is applied (Nitsche et al, 2008). It is believed that the anode exerts an excitatory effect on the applied region, by depolarizing the neurons, whereas the cathode exerts an inhibitory effect by hyperpolarizing the neurons of this region (Been et al, 2007). Some translational studies have already demonstrated the clinical utility of this method, for example, in decreasing smoking craving (Fregni et al, 2008), improving the cognitive performance of elderly people with Alzheimer's disease (Ferrucci et al, 2008) and reducing pain in patients with fibromyalgia (Roizenblatt et al, 2007).

Our group conducted a double-blind, factorial, randomized, placebo-controlled, double-blind clinical trial with 120 patients allocated to 4 groups: *sham* tDCS/placebo; *sham* tDCS/sertraline; active tDCS/ placebo; active tDCS/sertraline. Patients had moderate to severe depression and did not use antidepressants. The results, published in 2013 in the JAMA Psychiatry (Brunoni et al., 2013), showed that the efficacy of the tDCS and sertraline were similar over the course of 6 weeks, that the active tDCS was superior to the *sham* tDCS, and that the tDCS combined with sertraline was superior to the other treatments. These findings open new doors for further research using tDCS as an alternative therapeutic for the treatment of depression. Current research seeks to define the therapeutic role of tDCS.

1.2 Rationale and Hypotheses

Clinically, bipolar depression is an important condition in which therapeutic alternatives have been poorly studied. In this line, we will be able to evaluate if the tDCS is a therapeutically effective alternative, and also with few side effects, for this population. This may bring short-term clinical gains to the patients who do not tolerate antidepressants or have been refractory to them.

2. Expected Results

The main objective of the study is to compare the antidepressant effects of tDCS with *sham* tDCS in 60 refractory patients with bipolar depression who use mood stabilizers. The hypothesis is that active tDCS will have a greater antidepressant effect than *sham* tDCS in patients with bipolar depression. To test this, we will use the Montgomery-Åsberg Depression Scale (MADRS), the Hamilton Depression Scale 17 Items (HAMD-17), and the Beck Depression Inventory (BDI) to measure depressive symptoms early in the study (week 0),

immediately after 10 tDCS sessions week 2), after the session of week 4 and immediately after the last session (week 6).

The secondary objectives to be explored are: (a) to assess the adverse effects associated with tDCS in bipolar depression, with emphasis to the hypomanic and manic switches. In a systematic review (Brunoni et al., 2011a), no side effects linked to tDCS were found, however there are reports of hypomanic and manic switches episodes both individually and in combination with antidepressants. Thus, Young's mania rating scale will be applied at treatment weeks 0, 2, and 6; (b) to evaluate clinical predictors of antidepressant response, such as age, refractoriness, gender, type of bipolar disorder, drug class, chronicity, severity, and comorbidity with anxiety disorders.

3. Scientific challenges and methods

3.1. Design

We will conduct a controlled, randomized, double-blind clinical trial in which eligible patients will be recruited through specialized outpatient clinics, internal and external disclosure of the research project. They will be allocated to one of the groups: simulated stimulation group (*sham* tDCS) or active tDCS group (active tDCS). Patients who are randomized to the active tDCS group will place the anode and cathode on the right and left dorsolateral prefrontal cortex areas respectively (corresponding to F3 and F4 according to the EEG 10-20 system). Treatment will be applied consecutively for 10 days, excluding weekends and then once every two weeks until the end of the study at week 6. All subjects will be evaluated by the MADRS, YMRS, CGI HAMD-17 and BDI scales at weeks 0, 2, 4 and 6.

Volunteers who have undergone improvement and have been allocated to the active tDCS group may choose to voluntarily continue to receive active tDCS for 3 months with weekly sessions in order to maintain the benefits gained and provide maintenance data for the survey.

3.2. Randomization and allocation

Participants will be randomly distributed according to a computer-generated list. The assignment will be performed using sealed opaque envelopes containing the code corresponding to the group designated for each participant. This code will be imputed in the tDCS device that automatically provides active or *sham* stimulation, without the staff knowledge. For *sham* tDCS, the device stops the application of the current 30 seconds after its initiation, therefore, mimetizing the initial side effects on the skin (scratching, paresthesia), but without inducing neuromodulatory effects.

3.3 Inclusion and exclusion criteria

The study will include 60 adults (18-75 years), men or women, diagnosed with acute bipolar depression, despite an appropriate course of treatment with mood stabilizers. For inclusion, they should also have a score on the HDRS ≥ 17 scale, corresponding to a depressive episode of moderate to severe intensity. Finally, patients should be able to read and understand the portuguese language.

Exclusion criteria are: (1) other neuropsychiatric conditions, such as schizophrenia, drug dependence, dementia, cranial traumas, epilepsy, and so on (although participants with anxiety disorders may be included if the primary diagnosis is DB), (2) mixed states, defined as having simultaneously manic symptoms, measured by the Young Mania Scale (YRMS > 8); (3) pregnancy, (4) specific contraindications for tDCS, (5) serious clinical conditions. In relation to the use of psychoactive drugs, these should be in stable therapeutic doses for at least 6 weeks or without the use of psychotropic drugs. Benzodiazepine drugs will be allowed, although only at low doses ($\leq 20\text{mg}$ / day of diazepam or equivalent).

3.4 Blinding

The study will be double-blind, that is, researchers, assessors and patients will not be aware of the treatment until the end of the study. The tDCS technique is particularly advantageous for ensuring blinding when compared to other non-invasive brain stimulation techniques. This is because the tDCS generates a slight tingling in the region of the application of the electrodes, in the first minutes of the intervention, generating no further effects. We will use an tDCS device that allows you to program a code in which the device automatically turns off the power without the need for an operator. This guarantees a double blindness.

3.5 Interventions

For true stimulation the anodes and cathodes will be placed respectively in the left and right dorsolateral prefrontal cortical areas (corresponding to F3 and F4 according to the EEG system 10-20). We will use 5 x 5cm electrodes, electric current of 2mA for 30 minutes daily. This arrangement is known as bifrontal and has already been used in major depression studies (Kalu et al., 2012). The tDCS will be applied for 10 consecutive days, excepting on the weekends and thereafter once every 2 weeks until the end of the study (week 6).

3.6 Clinical variables

Patients who will participate of the research will be evaluated by psychiatrists or clinical psychologists with appropriately trained for the purpose. The diagnosis will be confirmed using the Mini International Neuropsychiatric Interview (MINI). The MADRS, YMRS, CGI HAMD-17 and BDI will be applied at weeks 0, 2, 4 and 6.

3.7 Calculation of the sample size

Based on the meta-analysis of Kalu et al (2012), which verified an efficacy favoring active tDCS vs. *sham* with a Hedges *g* of 0.743 (95% Confidence Interval = 0.21 to 1.27), for a two-tailed *p* of 0.05 and a power of 80%, the total sample size will be between 58 to 60 patients.

3.8 Statistical analysis

The primary analysis will be performed with analysis of variance of repeated measures (in 2 levels: active procedure and placebo) with the tDCS being the intra-groups independent variable and time (in 4 6 levels: week 0, 2, 4 and 6) the independent variable between-groups. HDRS will be the dependent variable. Our hypothesis is that the interaction of tDCS over time will be significant, with active tDCS being superior to placebo at week 6. We will also use Global Clinical Impression and Depressive Symptomatology Inventory as dependent variables and we will make multivariate logistic regressions having response (reduction of HDRS \geq 50%) and remission (HDRS \leq 7) as dependent variables. Hypomanic and manic switches frequency (Young's Mania Scale $>$ 8) will be compared between the groups using the Chi-square test or the Fisher's exact test when necessary.

3.9 Study Flowchart

The flow chart for each patient is shown below. It is worth remembering that the tDCS will be applied 12 times: 10 consecutive sessions (week 0 through week 2), and a single session in the following weeks (4th and 6th week) until the 6th week. Still, patients who receive simulated stimulation and who still present symptoms may receive active stimulation - or other available treatments as described in the design - at the end of the study.

Study	Screening	Week 0 (Baseline)	Week 2	Week 4	Week 6 (EndPoint)
Inclusion and exclusion criteria	X				
MINI	X				
Consent term	X				
tDCS session		X	X		
MADRS		X	X		X
HAMD17		X	X		X
BDI		X	X		X
CGI		X	X		X

YMRS		X	X		X
Adverse effects questionnaire			X		X

3.10 Strategies to preserve adherence

The research and stimulation service will work throughout the afternoon, allowing the patient to choose the most appropriate time. In addition, the research assistant will make regular telephone and/or email contact with all participants to prevent absents. We will also allow three non-consecutive absences of patients during the fifteen days of stimulation, taking into account the problems of urban mobility in the city of São Paulo. Finally, we will run a one-week *run-in* between sorting and starting the search. *Run-in* lets you exclude participants who do not return to the beginning of the search, avoiding early dropouts. All the strategies described increase adherence to clinical trials (Fregni, Boggio & Brunoni, 2012).

3.11 Ethical aspects and safety

tDCS is a technique used for approximately 12 years and no serious adverse events have been reported. Studies in animals show that the electrical dose required to cause brain injury is about two orders of magnitude (that is, 100 times) greater than that used in clinical practice (Liebetanz et al, 2009; Brunoni et al. 2011b).; investigated the use of electric currents in high doses with the purpose of provoking tissue damage, observing that these occurred only from catodal stimulation above 100 A / m², two orders of magnitude higher than those used in humans (always below 1 A / m², with average densities between 0.4 and 0.8 A / m²). In a systematic review, we observed that the most serious side effects of the tDCS were tingling and mild discomfort at the application site (Brunoni et all 2011c). Therefore, from the ethical point of view, tDCS seems to be a very safe technique with few adverse effects. In this clinical trial, patients taking antidepressants (since a stable dose 6 weeks ago) will be included. In addition, we will evaluate patients 12 times over 6 weeks - in this way, we can quickly identify any worsening of the clinical picture and perform early intervention.

Data collection will only begin after approval of the project by the Research Ethics Committee and, for each volunteer, after signing the free and informed consent form. The study will also be prospectively registered on clinicaltrials.gov. All the procedures described present minimal risk. If a volunteer presents a risk of major suicide, he/she will be excluded from the study, adopting the standard procedure for the management of this type of patient (ie, if the outpatient management is possible, we will refer the patient to the family for treatment - if this we will be in contact with PS-Lapa, which is the reference for cases of this type). We will be in contact with Lapa Emergency Service of Psychiatry, which is the reference for cases of this

type. Participants may have access to their data and may leave the study at any time, without impair to any treatment they may perform within the institution. The data will be collected, analyzed and published in order to preserve the anonymity of the individual. In addition, the study will be conducted in accordance with all requirements of the Research Ethics Committee and also based on the recommendations established in the Helsinki Declaration (1964), as amended in Tokyo (1975), Venice (1983) and Hong Kong (1989).

As a benefit, participants will be able to participate in a clinical trial to treat their clinical condition. This will be possible even if they receive placebo stimulation, as they may receive active stimulation at the end of the study if they still persist with depressive symptoms.

4. Timeline

	Month 01 to 03	Month 04 to 06	Month 07 to 09	Month 10 to 12	Month 13 to 15	Month 16 to 18	Month 19 to 24
Purchase of materials							
Team training / qualification							
Data collect							
Entering data							
Statistical analysis of data							
Elaboration of reports and scientific publications derived from research data							

5. Dissemination and evaluation

The methods for evaluating the results obtained were previously described in the statistical analysis section of the data.

Among the products of the project, we highlight: (1) to evaluate a new therapeutic modality for the treatment of bipolar depression, with few adverse effects; (2) to increase the understanding of the mechanisms of action of this new technique of non-invasive neuromodulation - transcranial direct current stimulation - in the treatment of depression; (3) to generate scientific articles, scientific initiation projects and graduate theses; (4) generate hypotheses for future studies, phase III in the areas of non-invasive brain stimulation and bipolar depression; (5) to support the development of tDCS devices, thus promoting the generation of biomedical technology; (6) to consolidate research projects in the area of neuropsychiatry and neuromodulation.

The results will be disseminated through presentation at congresses and scientific articles. Taking into account the originality of the study, the quality of previous publications of

similar articles and the importance of the subject in medical practice, we believe that the clinical outcomes of this project will be published in a major impact journal, such as *Biological Psychiatry*. Other outcomes should be published in specialized journals such as *Brain Stimulation*, *Journal of Affective Disorders*, *Archives of Clinical Neuropsychology*, or *Journal of the International Neuropsychological Society*.

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