

Accepted for *publication in Neuromodulation*

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Enhancement of affective processing induced by bi-frontal transcranial direct current stimulation in patients with major depression

Running title: Emotional Stroop and tDCS

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Source of financial support: This study was partially funded by FAPESP (São Paulo Research Foundation) grants (2009/0572807 and 2011/00212-2). The sponsor had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Authorship statement: All authors contributed to the manuscript according to the International Committee of Medical Journal Editors' (ICMJE) criteria.

Conflicts of interest: None.

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Abstract

Objective: Our aim was to evaluate whether one single session of transcranial direct current stimulation (tDCS), a neuromodulatory technique that non-invasively modifies cortical excitability, could induce acute changes in affective processing in patients with major depression.

Subjects and Methods: Randomized, double-blind, sham-controlled, parallel design enrolling 24 age-, gender-matched, drug-free, depressed subjects. Anode and cathode were placed over the left and right dorsolateral prefrontal cortex. We performed a word Emotional Stroop Task collecting the response times (RTs) for positive-, negative- and neutral-related words. Three analyses of covariance were used to evaluate changes in the RT difference between positive, negative and emotional vs. neutral words before and during tDCS.

Results: At baseline, RTs were similar for emotion- and neutral-related words. We found a large, significant group effect for the positive Emotional Stroop, i.e., subjects during active tDCS responded faster to positive vs. neutral words, whereas the opposite was observed for sham tDCS. The same effect was observed for emotional (positive and negative) vs. neutral words, but not for negative only vs. neutral words.

Conclusion: Active tDCS induced faster RTs for non-neutral vs. neutral and positive- vs. neutral-words, contrary to sham tDCS and inverting the pattern observed at baseline. These findings add evidence that a single tDCS session transiently induces potent

changes in affective processing, which might be a mechanism of tDCS functioning in ameliorating depression.

Keywords: transcranial direct current stimulation; affective processing; depressive disorder; emotional Stroop effect; cognition; prefrontal cortex.

1. Introduction

Major depressive disorder (MDD) is associated with dysfunctional processing in affective-related neural circuits^{1,2}. Cognitive theories acknowledge that a biased, preferential processing of valence-related information makes negative thinking patterns more easily available, which maintains the ruminative cognitive style of depression and might trigger and perpetuate depressive episodes³. Transcranial direct current stimulation (tDCS) is one novel non-invasive brain stimulation technique that induces significant polarity-dependent changes in cortical excitability⁶. In fact, although single-session tDCS studies in healthy samples observed acute improvement in affective and cognitive processing⁷ and recent randomized clinical trials and meta-analyses showed generally positive results for repeated, daily tDCS in treating MDD {Kalu 2012; Loo 2012; Berlim 2013; Brunoni 2013} it has been insufficiently investigated whether tDCS induces acute effects in affective processing in MDD, which is important to understand the putative mechanisms of action of tDCS in depression.

In fact, only two studies investigated the acute effects of tDCS on an affective task in MDD, both suggesting an enhancement of affective processing¹⁰ and control¹¹. Importantly, these studies did not evaluate the “bifrontal” montage (anode over the left and cathode over the right DLPFC), which could have greater effects in MDD through a simultaneous increase in left and decrease in right DLPFC activity that are theoretically hypo- and hyperactive in MDD {Koenigs 2008}. In fact, although this montage was found to be associated with significant depression improvement in a large, randomized trial {Brunoni 2013}, it has been less investigated than others {Brunoni priori} and thus, its effects in affective processing are less known.

Therefore, the aim of this study was to evaluate the acute effects of the bifrontal tDCS montage in affective processing in MDD patients using a Word Emotional Stroop Task (WEST). Based on previous studies using other tDCS montages, our hypothesis was that affective processing would be enhanced by active bifrontal tDCS.

2. Methods

2.1 Patients

The present study employed a double blind, sham-controlled, randomized, parallel design, in which 24 depressed participants were randomized to receive either active (n=12) or sham (n=12) tDCS. A research assistant not involved in other aspects of the trial performed the block randomization, and allocation was concealed using a central randomization method.

Patients were adults (18-65 years) who fulfilled criteria for major depressive disorder per DSM-IV criteria (codes 296.32, 296.33, 296.22 and 296.23, which correspond to single (296.2x) or recurrent (296.3x), moderate (296.x2) or severe non-psychotic (296.x3) depressive episodes)¹³. As several psychopharmacological drugs interact with tDCS (for a complete review see {Stagg Nitsche 2011}), all included participants were completely drug-free.

As to decrease between-group variability, the patients were matched by age, baseline depression and gender. All patients provided informed consent and were

screened and evaluated by trained psychiatrists who confirmed the diagnosis using the Mini International Neuropsychiatric Interview ¹⁴. The local internal review board and ethics committee of the University Hospital, University of São Paulo approved the study.

2.2 Procedures

The WEST task consists in asking participants to name the colors in which valence-related words are displayed. For the procedure, we first selected 300 words of positive, negative and neutral valence from the Affective Norms of English Words (ANEW) ¹⁵, a database in which several words are rated according to their emotional content. These pre-rated words were translated into Portuguese and further re-validated in 40 healthy subjects, who were asked to score each word according to its valence, from 1 (strongly negative words) to 9 (strongly positive words), being 5 a “completely neutral word”.. Thereafter, the mean score of each word was calculated and we selected the 150 (50 for each valence) words that consecutively scored <2.5 (negative words), from 4.5-5.5 (neutral words) and >7.5 (positive words). Importantly, this procedure was adopted since the first Portuguese-translated ANEW list had not been published {Kristensen Gomes Justo 2011} when we conceived our study – nonetheless, we found that the words we used in our experiment present similar valence than in that list.

The words were presented on a 15’’-computer screen using the SuperLab 4.0 software (Cedrus Corp, CA). Each word was presented for 1000ms and then the subject was asked to press the button corresponding to its color, from 4 possible choices (green, yellow, red, blue). For each patient, two WEST tests were performed: (1) immediately

before tDCS and (2) 15 minutes after tDCS onset. As to avoid learning effects, the word dataset was randomized in 10 blocks of 15 words, each having five words of positive, neutral and negative valence.

We collected mean response time (RT) and number of correct responses (accuracy) for each valence group (positive, negative and neutral) – in fact, we only present data regarding RT as no effects were observed for accuracy (possibly due to a ceiling effect, since participants responded correctly in >90% of trials). For our analysis purposes (see below), we also considered the RT for emotional words (i.e., non-neutral words). Subjects were instructed to respond as quickly and accurately as possible.

Regarding tDCS (Chattanooga Ionto Device, Chattanooga Group), the anode was positioned over the left and the cathode over the right DLPFC, which is located 5cm laterally and 5cm ventrally from the center of the scalp (where the sagittal and coronal planes cross). We used a current of 2mA in a surface area of 25 cm². For the sham condition, the device was turned off after 60 seconds of stimulation as to mimic tDCS effects, a blinding method previously described ⁶. Two certified nurses administered the tDCS intervention. Since they were not blinded to the treatment (they were responsible for turning off the device), they did not participate in the assessment of any outcome or in any other aspect of the trial.

2.3 Analysis

All analyses were performed in Stata 12 (Statacorp, TX). Statistical tests were considered significant at a $p \leq 0.05$. We compared baseline data using Chi-square or *t* tests,

when appropriate. The efficacy of blinding was assessed using a Fisher's exact test, asking participants to guess whether they had received active vs. sham tDCS.

The first step was data reduction. We calculated mean RTs for each valence. We excluded RTs < 200 or > 1500 ms, since the former is too fast to represent a conscious response and the latter was considered an outlier probably related to momentary distraction. The data excluded represented $< 2\%$ of the total collected data and was evenly distributed between groups and emotion vs. non-emotion words.

Our primary outcomes were the difference in RT of valence-related vs. neutral words (i.e., $RT_{\text{positive}} - RT_{\text{neutral}}$; $RT_{\text{negative}} - RT_{\text{neutral}}$ and $RT_{\text{emotional}} - RT_{\text{neutral}}$), which reflect the “emotional Stroop effect”, i.e., the attentional bias for valence-related as compared to neutral words. Thus, difference values > 0 represent greater latency (slower response) for valence-related words, whereas difference values < 0 indicate a faster response for valence-related vs. neutral words (for a complete review on the literature of the Emotional Stroop Task, see Williams et al. ¹).

For the statistical analysis we used three analyses of covariance (ANCOVAs), each of which having the difference in valence as the dependent variable (second measurement) and as a covariate (baseline measurement) and “group” (active/sham tDCS) as the independent variable. The effect size measure was the partial eta-squared (η^2). Values of 0.01, 0.06 and 0.14 are considered, respectively, small, medium and large effect sizes {Cohen 1988}.

3. Results

Between-group clinical and demographic characteristics were not different at baseline, including gender, age and depression scores. Participants also did not differ regarding RTs and the difference in emotional vs. neutral words (Table 1). Finally, participants did not correctly guess their stimulation group beyond chance ($p=0.23$).

(Table 1)

3.1 Emotional Stroop effect for emotional vs. neutral words

In the comparison between emotional (positive and negative) vs. neutral words, we found a significant, large effect of group ($F_{2,1,1}=4.36$, $p=0.049$, $p \eta^2=0.17$) (Figure 1A). In fact, participants receiving active tDCS were faster to respond to emotional words in comparison with neutral words, whereas those receiving sham tDCS displayed slower RTs for emotional vs. neutral words (Table 1).

(Figure 1)

3.2 Emotional Stroop effect for positive vs. neutral words

The ANCOVA model showed a significant, large effect of group ($F_{2,1,1}=7.33$, $p=0.01$, $p \eta^2=0.26$). Accordingly, during active stimulation, participants responded faster to positive vs. neutral words, whereas subjects receiving sham tDCS presented slower RTs for positive words as compared to neutral words (Table 1) (Figure 1B).

3.3 Emotional Stroop effect for negative vs. neutral words

For negative vs. neutral words, the ANCOVA model did not present a significant effect of group ($F_{2,1,1}=1.7$, $p=0.2$, $\eta^2=0.07$). Therefore, in despite of patients in the active group showing faster RTs to negative vs. neutral words (and vice-versa for sham tDCS), this effect did not reach statistical significance (Figure 1C).

4. Discussion

An intervention enhancing excitability at left DLPFC and diminishing at right DLPFC resulted in a modification of emotional affect processing in MDD patients – in fact, there was actually an inversion of affective processing, since participants receiving active tDCS were faster to respond to emotional vs. neutral and positive vs. neutral words and those receiving sham tDCS presented opposite results. Boggio et al.¹⁰, using a different montage (anode over the left DLPFC, cathode over the right supraorbital area), also observed that, after a single, sham-controlled, tDCS session, there was an increase in accuracy for positive but not negative imagery. Of note, Boggio et al. {Boggio 2007} did not compare the latency between positive vs. neutral stimuli, since only affective-loaded imagery were used in their study. We extend these results, observing that such enhancement also occurs for the bifrontal tDCS montage, supporting the antidepressant effects of this montage.

Another recent study by Wolkenstein and Plewnia {Wolkenstein Plewnia} demonstrated that anodal tDCS over the left DLPFC improves emotional cognitive control in MDD. The authors used a working memory task (stimuli identification) that was preceded by either an emotional or neutral picture, finding that during active tDCS the working memory performance was similar regardless of the valence (emotion vs. neutral) of the preceding picture whereas for sham tDCS the performance was worse for valence-loaded preceding pictures. Therefore, Wolkenstein and Plewnia tested whether tDCS could modulate the *interference* of affective and neutral pictures in working memory, showing an abolishment of this interference during active tDCS. In this regard, this study can be compared to one previous study that showed that anodal left tDCS abolished hypothalamic-pituitary-adrenal response to negative vs. neutral imagery {Brunoni Vanderhasselt}. Rather, in our present study and in the previous study of Boggio et al. {Boggio go no go} the identification of affective stimuli were directly tested, and not the neuropsychological {Wolkenstein} and neurophysiological {Brunoni Vanderhasselt} consequences of the stimuli presentation.

Importantly, we did not observe a direct effect on raw RTs, but rather on the emotional Stroop Effect when measuring the latency between emotional and positive vs. neutral words. This suggests that the effects observed were not solely related to a non-specific enhancement of prefrontal activity but rather to the modulation of affective-related circuits. Our results can be understood according to the valence-theory of DLPFC processing that conjectures that the right and left DLPFC are preferentially responsible for processing negative and positive stimuli, respectively ¹⁹; and also considering the theory of MDD prefrontal asymmetry ²⁰. Therefore, anodal tDCS could have transiently

increased activity of the left DLPFC, therefore resulting in an enhanced positive-affect processing. In addition, since effects for an overall improvement of emotional processing was observed, cathodal tDCS could also have transiently decreased right DLPFC activity. The absence of effects for the negative emotional Stroop effect could be partly explained due to an underpowered analysis due to a small sample size. Another explanation is that dysfunctional negative thoughts are a hallmark feature of MDD, being considered stable, difficult to change and a cognitive vulnerability for novel depressive episodes {Bradley 1983} – this could mean that the effects of tDCS on negative-related words could have been attenuated in our depressed sample. Nonetheless, future studies could evaluate whether tDCS coupled with cognitive-based psychological interventions induce increased effects in the attentional affective bias observed in depression.

Of note, we could not evaluate whether such effects were related to depression improvement since subjects further received placebo-controlled pharmacotherapy. Nonetheless, future studies could address whether these acute changes are associated with clinical outcomes. We also did not evaluate acute mood changes before and after the stimulation session, although such effect has not been observed in previous studies {Koenigs 2009; Wolkenstein Plewnia}. In addition, we did not observe an Emotional Stroop effect at baseline, which might be explained by the relatively small sample size and the small number of trials that each subject performed, when compared to other studies {Williams 1996}.

In summary, bifrontal tDCS (using opposite hemispheric polarities) had a significant effect in enhancing emotional and positive-related word processing. This result adds evidence that tDCS may have an early affective effect in MDD (which might

be a mechanism for its antidepressant effects) and also that it could be used as a neuromodulatory tool to explore and assess changes in affective processing.

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Table 1. Baseline clinical and demographic characteristics of active and sham tDCS.

| | Sham tDCS | Active tDCS | <i>p</i> |
|-----------------------|------------|-------------|----------|
| Gender (M/F) | 6/6 | 6/6 | — |
| Age (SD), years | 39 (11) | 38 (9.5) | 0.8 |
| Baseline MADRS (SD) | 27.7 (5.4) | 26.3 (4.8) | 0.51 |
| Before tDCS | | | |
| RT—positive words | 931 (122) | 881 (81) | 0.25 |
| RT—negative words | 947 (125) | 916 (88) | 0.49 |
| RT—neutral words | 927 (97) | 876 (76) | 0.21 |
| $RT_{neg} - RT_{neu}$ | -2 (40) | 30 (55) | 0.11 |
| $RT_{neg} - RT_{pos}$ | 16 (55) | 35 (40) | 0.34 |
| During tDCS | | | |
| RT—positive words | 927 (97) | 876 (76) | 0.16 |
| RT—negative words | 903 (103) | 873 (77) | 0.43 |
| RT—neutral words | 880 (108) | 890 (91) | 0.81 |
| $RT_{neg} - RT_{neu}$ | 22.5 (45) | -17 (55) | 0.07 |
| $RT_{neg} - RT_{pos}$ | -24 (59) | -4 (39) | 0.33 |

M/F, male/female; MADRS, Montgomery-Asberg Depression Rating Scale; RT, response time; SD, standard deviation; tDCS, transcranial direct current stimulation.

M/F, male/female; SD, standard deviation; MADRS, Montgomery-Asberg Depression Rating Scale; tDCS, transcranial direct current stimulation; RT, response time.

Figure 1. Difference in RT of negative vs. neutral words (a—upper picture) and negative vs. positive words (b—bottom picture). Differences >0 and <0 indicate slower and faster response for negative words, respectively. The figure shows that during sham stimulation, these values were not significantly different before (offline) and during (online) tDCS, whereas active tDCS significantly modulated the difference in RT. RT, response time; tDCS, transcranial direct current stimulation.

