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Acute working memory improvement after tDCS in antidepressant-free patients with major depressive disorder

Janaina F. Oliveira[a,b], Tamires A. Zanão[a,b], Leandro Valiengo[a,b], Paulo A. Lotufo[a], Isabela M. Benseñor[a], Felipe Fregni[c], André R. Brunoni[a,b,*]

[a] Clinical Research Center, University Hospital, University of São Paulo, São Paulo, Brazil
[b] School of Medicine, University of São Paulo, São Paulo, Brazil
[c] Laboratory of Neuromodulation, Spaulding Rehabilitation Hospital, Harvard Medical School, Boston, MA, USA

HIGHLIGHTS

- TDCS is a non-invasive technique that modifies cortical excitability.
- We evaluated whether tDCS enhances working memory (WM) in depression using the *n*-back task.
- One session of active but not sham tDCS acutely enhanced WM in depression.
- M enhancement was showed in increased hit rate, discriminability and response criterion.
- We found that tDCS has acute effects in WM in depression.

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ABSTRACT

Based on previous studies showing that transcranial direct current stimulation (tDCS), a non-invasive brain stimulation technique that employs weak, direct currents to induce cortical-excitability changes, might be useful for working memory (WM) enhancement in healthy subjects and also in treating depressive symptoms, our aim was to evaluate whether tDCS could acutely enhance WM in depressed patients. Twenty-eight age- and gender-matched, antidepressant-free depressed subjects received a single-session of active/sham tDCS in a randomized, double-blind, parallel design. The anode was positioned over the left and the cathode over the right dorsolateral prefrontal cortex. The *n*-back task was used for assessing WM and it was performed immediately before and 15 min after tDCS onset. We found that active vs. sham tDCS led to an increase in the rate of correct responses. We also used signal detection theory analyses to show that active tDCS increased both discriminability, i.e., the ability to discriminate signal (correct responses) from noise (false alarms), and response criterion, indicating a lower threshold to yield responses. All effect sizes were large. In other words, one session of tDCS acutely enhanced WM in depressed subjects, suggesting that tDCS can improve "cold" (non affective-loaded) working memory processes in MDD. Based on these findings, we discuss the effects of tDCS on WM enhancement in depression. We also suggest that the *n*-back task could be used as a biomarker in future tDCS studies investigating prefrontal activity in healthy and depressed samples.

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1. Introduction

MDD is a psychiatric condition characterized by depressive mood, inability to experience pleasure and other affective, psychomotor and neurovegetative symptoms. It is also associated with decreased cognitive functioning, as evidenced by clinical reports (e.g., slow thoughts, cognitive blurring) and neuropsychological assessments, which show decreased attention, processing speed and WM performance [29,30]. Such impairment in executive functions is probably associated with DLPFC dysfunction, which is both related to executive functioning (as observed in functional neuroimaging studies showing DLPFC activation during WM tasks) and MDD (particularly decreased left DLPFC activity in depressed subjects) [22,23,29,30,35,37]. Notably, WM dysfunction and MDD might not only be correlated but also *causally* associated – for instance, activation of the DLPFC during a WM task is relatively

Abbreviations: TDCS, transcranial direct current stimulation; DLPFC, dorsolateral prefrontal cortex; MDD, major depressive disorder; WM, working memory.

* Corresponding author at: Centro de Pesquisas Clínicas, Av. Prof. Lineu Prestes 2565, 3o andar, Hospital Universitário, São Paulo (SP), CEP 05508-000, Brazil. Tel.: +55 11 3091 9241.
E-mail address: brunoni@usp.br (A.R. Brunoni).

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decreased in the acute depressive episode but not after antidepressant treatment [17]. Possibly, WM dysfunction favors ruminative thinking [49] and increased stress response [16], findings that are involved in the pathophysiology of depression.

In this framework, brain DLPFC activation could enhance WM functioning and ameliorate depressive symptoms. Non-invasive brain stimulation therapies can, in fact, focally target cortical areas and are being used as tools for improving executive functioning and treating depression [8,18,20]. One relatively novel brain stimulation therapy is tDCS that increases/decreases cortical excitability according to the parameters of stimulation [10,33]. Several tDCS studies showed WM improvement in healthy subjects [2,4,21,25,43]. Recently, randomized clinical trials and meta-analyses have shown mixed albeit generally positive results suggesting that tDCS is effective for treating depression [3,5,12,26–28].

However, it has been insufficiently appraised whether tDCS improves WM in patients with MDD. In fact, only two MDD studies explored acute tDCS effects on executive functioning, using an affective go/no-go task [6] and an affective inhibitory control task [50]. In the present study, we investigated whether a single tDCS session over the DLPFC would improve WM (assessed by the *n*-back task) in MDD patients. Given previous results in healthy samples, our hypothesis was that an improvement in WM would be observed after acute but not sham tDCS.

2. Materials and methods

2.1. Subjects

We enrolled 28 adult (18–65 years) patients with MDD from a larger trial described elsewhere [11]. They presented moderate-to-severe, acute, unipolar depression according to the evaluation of trained psychiatrists (LV and ARB) who confirmed the diagnosis using the Mini International Neuropsychiatric Interview [39]. Participants were completely drug-free except for 4 patients (2 in each group) using low-dose benzodiazepines (mean dose 13.4 mg/day of diazepam-equivalent).

Patients were matched by age, baseline depression (assessed using the Montgomery–Asberg Depression Rating Scale) and gender (although for technical reasons we could not match gender in one case). The local internal review board and ethics committee of the University Hospital, University of São Paulo approved the study.

2.2. Design

We employed a sham-controlled, double blind, randomized, parallel design, in which participants were randomized to receive either active ($n = 14$) or sham ($n = 14$) tDCS. The participants originally belong to a larger, factorial trial (clinicaltrials.gov identifier: NCT01033084) in which placebo-controlled pharmacotherapy was used [12] – here we report the acute effects of the *first* tDCS session, therefore *before* sertraline/placebo onset and, for this reason, the present study can be considered a parallel, two-arm trial.

2.3. The n-back task

The task consists in continuously presenting a pseudo-random set of stimuli (usually letters), the subject being required to load and keep in memory the previously presented information. The "*n*" determines test difficulty – e.g., for $n = 0$ the subject has only to compare the present stimulus to the one just presented.

We used a 2-back task, presenting a pseudo-random set of six letters (A–F), each one being displayed on the screen for 300 ms, with an interstimulus interval of 2000 ms. Two *n*-back sessions (each of which having a distinct pseudo-random set of 120 letters with a maximum of 18 correct responses) were performed: (1) immediately before tDCS onset ("offline") and (2) 15 min after tDCS onset ("online"). The *n*-back was presented in a 15″ computer screen using the SuperLab™ (Cedrus Corp., San Pedro, CA) software. The response was given by pressing the spacebar. Before the test, subjects underwent a brief practice session ensuring they had understood the task (if not, the practice session would be re-run). The sequence employed in the practice session was not included in the task. Finally, subjects were asked to respond as accurately as possible.

2.4. Transcranial direct current stimulation

Transcranial DC stimulation was delivered through two 5 cm × 5 cm electrodes: the anode was placed over the left and the cathode over the right DLPFC areas (F3 and F4 positions, respectively, according to EEG 10–20 system). For active tDCS, we used a 2 mA direct current (current density: 0.08 mA/cm^2) for 30 min. For sham tDCS, the electric current was turned off 60 s after stimulation onset as to mimic initial tDCS peripheral, skin sensations, but without inducing any neuromodulatory effect since the stimulation period is short [34].

2.5. Statistical analysis

Statistical analyses were done with Stata 12 for Mac OSX (Statacorp, College Station, TX). Variables were normally distributed per the Shapiro–Wilk test and therefore parametric tests were applied. Results were considered significant at $p \leq 0.05$.

We used paired *t*-tests to compare baseline characteristics between groups. The efficacy of blinding was assessed using a Fisher's exact test, asking participants to guess whether they had received active/sham tDCS.

To assess the effects of tDCS in WM improvement, we employed three analyses of covariance (ANCOVA), all having tDCS (active/sham) as the independent variable and the dependent variable at baseline as the co-variate. The ANCOVA model was used to compare *n*-back performance during tDCS ("online") adjusted by individual performance before tDCS ("offline"). This model was chosen because, due to some characteristics of our study (randomized, relatively small sample) it was considered to be more advantageous than other approaches such as gain scores [47] and repeated-measures ANOVA [24]. We also did not employ a multivariate analysis of variance/covariance (MANOVA/MANCOVA) since the outcome variables discriminability and response criterion are calculated from the same raw variables (hits and false alarms). The effect size measure was the partial eta-squared ($_p\eta^2$). Values of 0.01, 0.06 and 0.14 are considered, respectively, small, medium and large effect sizes [15].

Three outcomes were evaluated. The first was the correct response ("*hit*") rate -the probability to correctly answer to the signal, according to the formula:

$$hit = \mathrm{P}(\text{correct answer}|\text{total number of correct answers})$$

The second and third outcomes evaluated *discriminability* and *response criterion* (for a review see [42]). According to the signal detection theory, *n*-back can yield two pairs of response: correct/missed responses (reflecting the success or failure in responding to the signal) and false alarm/correct omission (reflecting the failure or success in not responding to the noise). The d' was the discriminability index, measuring the distance between the signal and the noise (higher values of d' reflects a larger distance between

Table 1
Clinical and demographic data at baseline.

	Active tDCS	Sham tDCS	*p* value
Demographics			
Male/female	7/7	8/6	0.7
Age, years	36.9 (9.3)	38.7 (11.7)	0.63
Years of schooling	13.5 (3)	12.8 (3.4)	0.52
Clinical characteristics			
MADRS	25.9 (4.8)	27.7 (4.9)	0.3
Duration of index episode (weeks)	21.7 (24)	17.7 (24)	0.6
n-Back task (*Offline*)			
Hit rate (%)	46.8% (26)	45.23% (27)	0.87
Discriminability (d')	1.05 (0.99)	0.92 (0.95)	0.72
Response criterion (c)	0.03 (0.66)	−0.03 (0.53)	0.79

signal and noise, thus greater discriminability) according to the formula:

$$d' = z\text{-score}(\text{P(hit)}) - z\text{-score}(\text{P(false alarm)})$$

Finally, the response criterion reflects the threshold of responding. The c index was the response criterion rate, which estimates the mean point where neither response nor no-response is favored. Negative values ($c < 0$) reflects a lower threshold for responding (more liberal), whereas positive values ($c > 0$) reflects a tendency towards non-responding (more conservative). The formula is:

$$c = -(z\text{-score}(\text{P(hit)}) + z\text{-score}(\text{P(false alarm)}))/2$$

3. Results

3.1. Overview

Patients receiving active vs. sham tDCS were not different regarding gender, age and other variables, including *n*-back performance at baseline (Table 1). They also did not correctly guess their stimulation group beyond chance ($p = 0.23$) and described no side effects.

3.2. Hit rate

Before tDCS (offline), the hit rate was similar in both groups. Conversely, during tDCS (online), patients in the active group presented a hit rate of 57.5% (SD = 20) vs. 42.4% (20) in sham tDCS (Fig. 1A). Accordingly, ANCOVA displayed a significant, large tDCS effect ($F_{27,1} = 4.68$, $p = 0.04$, ${}_p\eta^2 = 0.15$), showing that patients who underwent active but not sham tDCS increased the number of correct responses.

3.3. Discriminability

The ANCOVA showed a significant, large effect of tDCS ($F_{25,1} = 4.2$, $p = 0.04$, ${}_p\eta^2 = 0.14$), revealing that the d' index increased only during active but not sham tDCS (Fig. 1B). Thus, patients receiving active tDCS presented increased discriminability.

3.4. Response criterion

For the c score, we also found a significant, large effect for tDCS ($F_{25,1} = 4.28$, $p = 0.049$, ${}_p\eta^2 = 0.14$), revealing that c scores decreased during active tDCS (Fig. 1C)–thus, patients receiving active tDCS presented a lower threshold for response. This means that active tDCS yielded more responses than sham tDCS, although the increased discriminability and hit rate indicate that this occurred only for correct responses and not false alarms.

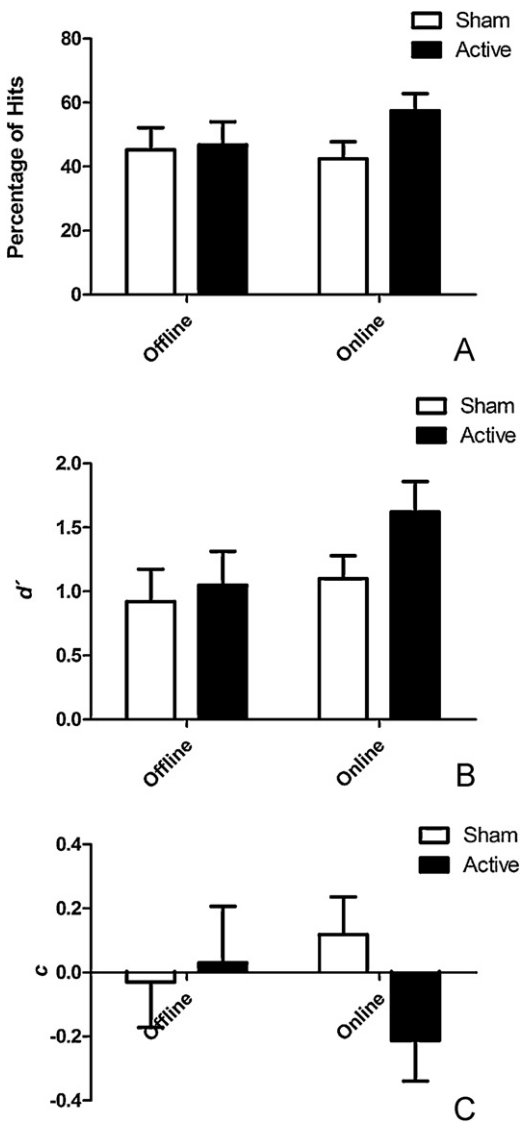


Fig. 1. Effects of active vs. sham tDCS on working memory, before ("offline") and during ("online") stimulation. (A) Effects on hit rate (correct responses). Higher numbers indicate more correct responses. (B) Effects on discriminability. Higher scores indicate increased discernment between the signal and the noise. (C) Response criterion. Values >0 indicate an increased threshold for response (more conservative), values <0 indicate a decreased threshold for response (more liberal). Bars represent ±1 SE.

4. Discussion

In this randomized, parallel study we evaluated WM performance (indexed by the *n*-back task) in 28 MDD patients before and during one sham-controlled tDCS session. Active, although not sham tDCS, increased the hit rate, the signal detection discriminability (the ability to discriminate between correct responses and false alarms) and the response criterion (i.e., subjects presented a less conservative attitude towards producing responses). As we further discuss, these findings indicate that bifrontal tDCS (anode on the left and cathode on the right DLPFC) acutely enhanced WM performance in MDD patients.

We employed two concepts from the signal detection theory – discriminability and response criterion that can analyze both the correct responses actively performed and the incorrect responses avoided. Increased discriminability suggests that tDCS improved the ability to detect signal from noise, confirming findings observed in healthy individuals [4,31,45]. One mechanism of action might

be that anodal tDCS led to excitability-enhancing effects on the DLPFC, perhaps increasing glutamate levels [14], an amino-acid associated with WM, recognition memory and stimulus-response learning [36]. Further, tDCS increased response criterion, suggesting a more liberal attitude towards responding. This could be related to physiologically decreased surround suppression induced by tDCS [40], possibly due to decreased GABA activity [41,44], the main neurotransmitter of inhibitory interneurons that generally act in increasing the threshold for behavioral responses [19,48]. Previous studies also showed that tDCS induces behavioral facilitation [32,46]. Interestingly, one study showed [32] that tDCS increased both discriminability and response criterion during a vigilance task. This study used the same bifrontal setup as we used, and acknowledged the laterality effects suggesting that tDCS distributed cognitive demands between hemispheres, favoring a "parallel" processing, instead of concentrating the cognitive load on a single hemisphere [32].

Although previous studies showed that tDCS enhances cognition in healthy individuals, this has been insufficiently appraised for MDD patients [18,45], a condition characterized by decreased neuroplasticity [9] and abnormal resting state activity due to glutamate/GABA activity [1]. Boggio et al. [6], in an affective go/no-go task, found that depressed patients improved the hit rate of positive-affect imagery whereas Wolkenstein and Plewnia [50] found that tDCS enhanced cognitive control, in fact completely abolishing the attentional bias observed in MDD. In contrast, our study assessed a purely cognitive WM task (i.e., "cold" and not "hot" WM). This is important to disentangle whether tDCS would have direct effects in WM in MDD or indirect effects due to a top-down modulation in subcortical structures such as the amygdala, as previously suggested [13,38]. Considering that it is unlikely that the *n*-back task induced important activation of affective/limbic structures per se, we suggest that tDCS also operates directly in MDD by modulating DLPFC activity, suggesting a specific dysfunction of this brain area in MDD that can be modulated by tDCS.

4.1. Implications for further studies

Our finding brings some perspectives for further studies:

(1) First, we suggest that the *n*-back task could be further investigated as a putative biomarker of antidepressant response in tDCS studies, due to its easiness of use and also in line with behavioral studies [23,29,37] showing that depressed patients present worse *n*-back performance compared to controls and with neuroimaging studies [22,30] demonstrating that depressed patients performing the *n*-back task have greater left prefrontal cortical activation as compared to controls. In fact, a meta-analysis of neuroimaging studies showed that the *n*-back task is robustly associated with activation of the prefrontal cortex [35]. In addition, the *n*-back task is an interesting tool for experimental settings, since it can be easily used and adapted to different scenarios. Finally, possible learning effects associated with the *n*-back task can be minimized by using different, random sequences of targets and distractors,
(2) Second, our finding that tDCS acutely increases WM performance in MDD stimulates further studies exploring whether such enhancement is pathophysiologically associated with improvement of depressive symptoms – of note, we were not able to investigate this hypothesis since subjects in our trial received placebo-controlled pharmacotherapy after tDCS onset.
(3) Third, we showed that bifrontal tDCS – a technique that has antidepressant effects [12]–also presents acute, positive effects on cognition.
(4) Lastly, further studies should investigate whether such WM enhancement is useful in clinical contexts – for instance, in combining tDCS with cognitive-behavioral therapies or as a tool for neuro-rehabilitation in MDD. This is mandatory to identify whether the observed improvement is either a byproduct of acute tDCS effects in depression – and therefore *n*-back would mainly serve as an index of tDCS effects or, conversely, that it *de facto* can induce maintained cognitive improvement – if so, tDCS could be a useful tool for depression treatment not only due to antidepressant but also, theoretically, to pro-cognitive effects.

4.2. Strengths and limitations

Although increased discriminability and response criterion might indicate that subjects found the task easier, we could only confirm such hypothesis whether we had manipulated task difficulty by using different WM loads (e.g., using 1-back, 2-back and 3-back). Also, we could have explored different tDCS dosages (e.g., 1 mA vs. 2 mA) to assess a biological dose-response effect, although this would not be feasible since this was a complementary study of a larger trial. For the same reason, we did not evaluate alternative montages. Nevertheless, Nelson et al. [32] tested two bifrontal montages (anodal/left and cathodal/right over the DLPFC and vice versa) and sham tDCS, finding positive effects in the two types of active tDCS – in fact, the most significant being for the same montage we used. Finally, the lack of a control group is a study limitation, although, as discussed, several studies found WM improvement after tDCS in healthy subjects.

Strengths of our study include an antidepressant-free sample and the use of matched controls, avoiding confounding effects of these variables [7].

5. Conclusion

The finding that WM performance, indexed by the *n*-back task, increased after tDCS in MDD patients confirms and expands previous studies enrolling healthy samples. One novel finding is that tDCS acutely improves "cold" cognition tasks in MDD – previous studies only evaluated acute tDCS effects in "hot" (cognitive/affective) tasks. Moreover, the increase in both discriminability and response criterion suggests that tDCS over the DLPFC is not only a tool that non-specifically increases performance by facilitating behavior, but in fact fine-tunes responses by increasing the signal-to-noise ratio. Finally, we suggest that the *n*-back could be a useful biomarker to assess tDCS effects over the prefrontal cortex in further MDD trials.

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