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Bifrontal tDCS prevents implicit learning acquisition in antidepressant-free patients with major depressive disorder

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ABSTRACT

The findings for implicit (procedural) learning impairment in major depression are mixed. We investigated this issue using transcranial direct current stimulation (tDCS), a method that non-invasively increases/decreases cortical activity. Twenty-eight age- and gender-matched, antidepressant-free depressed subjects received a single-session of active/sham tDCS. We used a bifrontal setup — anode and cathode over the left and the right dorsolateral prefrontal cortex (DLPFC), respectively. The probabilistic classification-learning (PCL) task was administered before and during tDCS. The percentage of correct responses improved during sham; although not during active tDCS. Procedural or implicit learning acquisition between tasks also occurred only for sham. We discuss whether DLPFC activation decreased activity in subcortical structures due to the depressive state. The deactivation of the right DLPFC by cathodal tDCS can also account for our results. To conclude, active bifrontal tDCS prevented implicit learning in depressive patients. Further studies with different tDCS montages and in other samples are necessary.

1. Introduction

Major depression presents cognitive impairment in functions such as memory and learning. In fact, although explicit memory deficits are more evident, implicit memory also seems to be compromised in depression (Mulligan, 2011). This type of memory involves skill retention and acquisition without fully conscious awareness of the learning strategies and typically involves subcortical circuitries such as the basal ganglia (Halsband and Lange, 2006). Thus, one hypothesis is that implicit memory is impaired in depression since this disorder is associated with frontal–striatal (i.e. cortical–subcortical) dysfunction (Naismith et al., 2006). However, results have been mixed (Aizenstein et al., 2005; Joel et al., 2005), possibly due to the heterogeneity of depression and use of antidepressant drugs (Exner et al., 2009). In fact, one issue for a longitudinal investigation of this matter is that after a course of antidepressants it is difficult to disentangle whether implicit memory improvement was due to a restoration of frontal-subcortical activity or, rather, to a global improvement of mood and cognition that occurs when depression remits. Another possible reason for the mixed results is that implicit learning tests might also activate other regions of the brain (e.g., the occipital cortex) besides the frontal–striatal circuitry that is more associated with major depression pathophysiology.

To overcome this issue, transcranial direct current stimulation (tDCS) might be an interesting tool. tDCS consists in applying weak, electric direct currents over the scalp to non-invasively and focally modify cortical activity, with anodal stimulation and cathodal stimulation respectively increasing and decreasing brain excitability (Nitsche and Paulus, 2000). tDCS is being used in cognitive research due to its potent and transitory changes in specific brain areas (Utz et al., 2010) as well as its ability to induce "top-down" effects, i.e., increasing cortical activity, and subsequently provoking a decrease in subcortical activity. Recently, Kincses et al. (2004) used the probabilistic classification learning (PCL) task to evaluate implicit learning with tDCS in healthy samples. They found that anodal tDCS improved implicit learning,

Abbreviations: tDCS, transcranial direct current stimulation; DLPFC, dorsolateral prefrontal cortex; PCL, probabilistic classification-learning; MDD, major depressive disorder; RT, reaction time; MADRS, Montgomery–Asberg Depression Rating Scale; DSM-IV, Diagnostic and Statistic Manual of Mental Disorders, 4th edition.

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suggesting that tDCS effects occurred due to the activation of frontal–striatal circuits.

Therefore, considering that (1) implicit learning involves subcortical circuitries; (2) major depression presents frontal–striatal dysfunction and; (3) tDCS directly modulates cortical activity, with indirect, "top-down" effects in subcortical structures; we aimed to investigate whether tDCS over the prefrontal cortex could interfere in aberrant procedural learning acquisition. Specifically, based on previous studies that suggest that the prefrontal cortex is underactive, our hypothesis was that implicit learning would be improved in depressive subjects following anodal tDCS over the prefrontal cortex. The importance of this study is to increase our understanding in implicit memory processes, particularly in depressed subjects, and also to evaluate whether tDCS, a potential clinical tool for depression (Brunoni et al., 2012), modulates implicit learning in this disorder.

2. Material and methods

2.1. Subjects

The present study employed a sham-controlled, randomized, parallel design, in which participants were randomized to receive either active or sham tDCS. This was also a "double-blind" trial, since both the participants and the staff did not know the intervention status. Of note, these participants originally belong to a larger, factorial trial in which sertraline/placebo-pill were also used. However, this study was done *before* sertraline/placebo onset and, for this reason, the present study can be considered a parallel, two-arm trial. After providing written, informed consent the participants were randomly allocated to either active or sham tDCS and thereafter they performed the experiments described in the present study. The first PCL was performed at baseline, prior to receiving active or sham tDCS, and the second PCL was performed during the tDCS session.

We enrolled 28 patients with major depressive disorder (MDD) from a larger trial (clinicaltrials.gov identifier: NCT01033084) described elsewhere (Brunoni et al., 2011). They were adults (18–65 years) who presented moderate-to-severe, acute, unipolar depression per DSM-IV criteria (APA, 2000). Depression severity was matched using the MADRS.

Participants were either antidepressant-naïve ($n=18$) or antidepressant-free ($n=10$). The antidepressant drugs that were washed-out were: fluoxetine 20 mg/day ($n=4$), citalopram 20 mg/day ($n=2$), paroxetine 20 mg/day ($n=2$) and venlafaxine 75 mg/day ($n=2$). The washout period was at least 5 half-lives of the antidepressant drug. In fact, since patients were only examined on Mondays, the minimum period of washout was 2 weeks (5 weeks for fluoxetine), and the mean drug washout period was 18 days. In fact, all participants were not only antidepressant but also completely drug-free except for 4 patients (2 in each group) who were using low-dose benzodiazepines (mean dose 13.4 mg/day of diazepam-equivalent). As to decrease between-group variability, the patients were matched by age, baseline depression and gender (although for technical reasons we could not match gender in one case). All patients provided informed consent and were screened and evaluated by trained psychiatrists who confirmed the diagnosis using the Mini International Neuropsychiatric Interview (Sheehan et al., 1998). The local internal review board and ethics committee of the University Hospital, University of São Paulo approved the study. Depressive symptoms were evaluated using the Portuguese-validated version of the Montgomery–Asberg Depression Rating Scale (Gorenstein et al., 2000).

2.2. Probabilistic classification learning task

The probabilistic classification learning (PCL, also known as "the weather prediction task") task consists in continuously presenting different image sets (composed by one to three geometric figures) each of them holding a probability to a weather forecast (sunny or rainy weather). In this task, the subjects implicitly learn the association between the cue card combinations and the outcome (rain/sunny). Therefore, PCL is an implicit memory test (Knowlton et al., 1994).

Our experiment consisted of two PCL sessions (each one lasting for 15 min) that were performed: 1) 15 min before tDCS onset and 2) 15 min after tDCS onset — therefore, the second PCL ended concurrently with the 30-min tDCS session. The PCL was presented on a 15″ computer screen using the SuperLab™ (Cedrus Corp, San Pedro, CA) software. Each image set was composed of four possible geometrical shapes (square, circle, diamond, and triangle) (Fig. 1). For each given trial one, two, or three geometrical shapes with a time exposure of 1000 ms was presented. After that, subjects were asked whether the given combination of geometrical shapes predicted rainy or sunny weather. The response was given by pressing either the letter "s" (*sol*, sunny in Portuguese) or "c" (*chuva*, rainy in Portuguese). Thereafter, feedback was given acknowledging the subject whether the answer was right or wrong. Each combination was associated with four different, randomized probabilities of sunny/rainy weather (25/75, 43/57, 57/43, and 75/25). At each session, 99 trials were presented (although the initial number of trials was one-hundred, a technical mistake programmed only 99 trials). Before the test, volunteers underwent a brief practice session with 12 trials thus ensuring that they had understood and were able to perform the task (if not, the practice session would be re-run). Stimuli employed in the practice session were not included in the PCL task. Finally, the number of trials was evenly distributed among the different probability schedules.

2.3. Transcranial direct current stimulation

The tDCS was delivered by a constant current stimulator using a pair of electrodes in 5×5 cm pieces of water-soaked synthetic sponge: the anode was placed over the left and the cathode over the right DLPFC (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 for 60 s after stimulation onset: this way, the subject can experience the initial tDCS peripheral, skin sensations, but since the stimulation period is short, there is no neuromodulatory effect (Nitsche and Paulus, 2000).

2.4. Statistical analysis

All statistical analyses were done with Stata 12 for Mac OS X (Statacorp, College Station, TX). Variables were normally distributed and therefore parametric tests were applied. Results were considered significant at $p\leq0.05$.

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 vs. sham tDCS.

To test for within-group differences, we performed two paired *t*-tests comparing the percentage of correct answers (correct answers divided by the total answers) and the mean RTs before and during tDCS, per group. No participant was excluded due to missing responses; in fact, the rate of missing responses was low (<5%) for the entire sample. For RT, we considered only correct responses. Also, RTs that were <200 ms or >1500 ms were excluded from the analysis, since the former was considered too fast to represent a conscious response and the latter was considered an outlier probably related to momentary distraction.

Lastly, we compared the changes in accuracy in the PCL task using repeated-measures, 2 (tDCS: active and sham)×3 (blocks: early blocks, intermediate blocks, late blocks, each of them encompassing 33 trials) ANOVA. The dependent variable was the difference in accuracy between the active or sham conditions and the baseline PCL

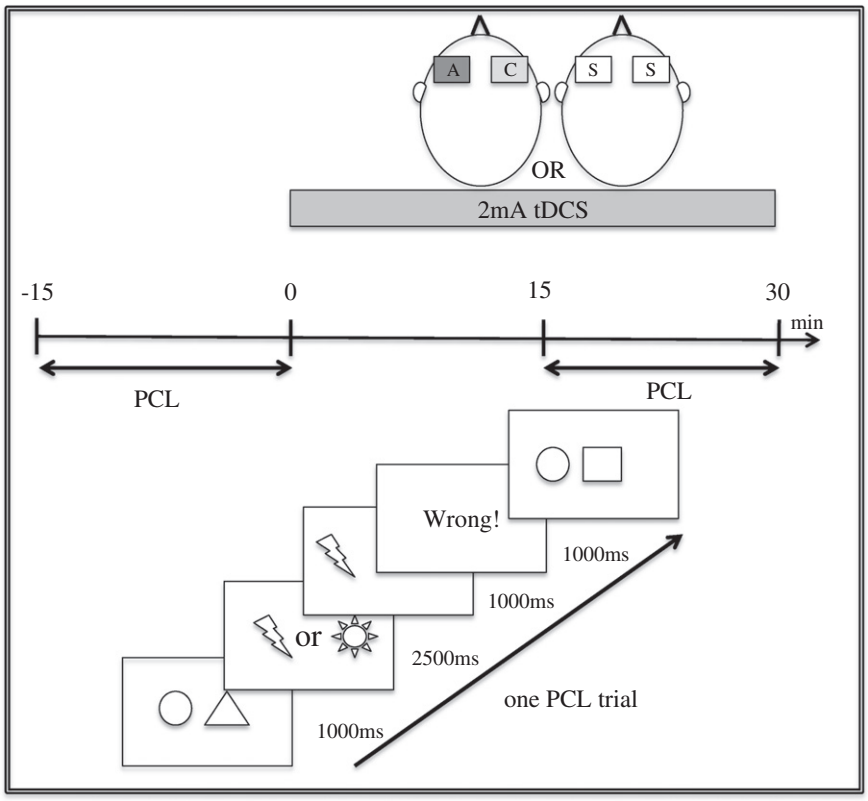

Fig. 1. Experimental design of the present study. Subjects were randomized to receive either active or sham transcranial direct current stimulation (tDCS) in a parallel design. Probabilistic classification learning (PCL) task was performed twice: before and during tDCS.

assessment. Therefore, values > 0 indicate an increase and <0 a decrease in accuracy. There is no consensus regarding the size (number of trials) of the blocks for this analysis; thus, we divided the trials into three blocks as to show changes in performance occurring over time, similarly as employed by Cho et al. (2012).

Since benzodiazepines could have an influence in the task (since they impact in memory and learning) we performed an additional analysis excluding the patients on benzodiazepines.

3. Results

Patients receiving active vs. sham tDCS were not different regarding gender, age and other variables. Importantly, they presented similar performance in the PCL at baseline. Also, blinding was adequate, since participants did not correctly guess their stimulation group beyond chance ($p = 0.23$) (Table 1).

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
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
Probabilistic classification learning			
Correct responses (%)	51.3% (7.9)	50.1% (6.8)	0.67
RT for correct responses	979 (163)	1006 (264)	0.74

3.1. Percentage of correct responses

Within-group comparison between the percentage of correct answers before and during tDCS revealed that, for sham tDCS, there was a significant performance improvement when comparing before ($M = 50.1\%$ $SD = 6.8$) and after ($M = 54.3\%$ $SD = 7.8$, 95% confidence interval = 49.8% to 58.8%), with an improvement of 7.7% ($t = -1.96$, $p = 0.03$). In other words, during sham stimulation, subjects presented better accuracy in the second PCL task, as compared to the first one, reflecting the expected implicit learning process. Conversely, for active tDCS, we observed no significant improvement when comparing before ($M = 51.2\%$ $SD = 7.6$) and after ($M = 51\%$ $SD = 6$, 95% confidence interval = 47.5% to 54.4%) PCL accuracy ($t = 0.12$, $p = 0.87$); suggesting that, in fact, anodal DLPFC stimulation prevented implicit learning.

Results were similar when excluding patients on benzodiazepines, since we found significant ($p = 0.01$) improvement for drug-naïve patients before ($M = 49\%$ $SD = 6.5$) and after ($M = 55\%$ $SD = 7.6$) sham tDCS, but not ($p = 0.88$) before ($M = 52.2\%$, $SD = 8$) and after ($M = 50.8\%$, $SD = 6$) active tDCS.

3.2. RT for correct responses

Within-group comparison between mean RTs before and during tDCS revealed that, for sham tDCS, there was a trend for improvement over time (baseline: $M = 1006$ ms, $SD = 264$; during tDCS: $M = 908$ ms, $SD = 288$, $t = 1.83$, $p = 0.08$). This was also observed for active tDCS comparison when comparing baseline ($M = 979$ ms, $SD = 163$) to tDCS treatment.

3.3. Improvement over time

Our model analyzing changes in accuracy between the 2nd and 1st PCL tasks over time found a trend towards a main effect of time ($F =$

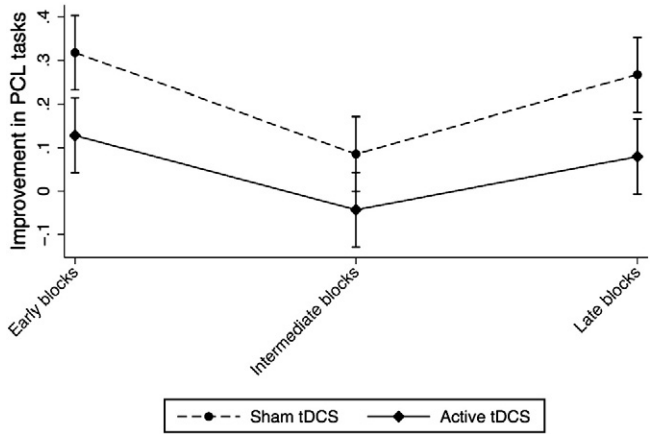

Fig. 2. Improvement in PCL performance (post minus pre percentage of correct answers, y-axis) over trials (divided in 3 blocks of 33 trials) in the active vs. sham transcranial direct current stimulation (tDCS) group. As depicted, the sham tDCS group presented consistently higher improvement than the active tDCS along the trials. Bars represent ±1 standard deviation.

2.92, p = 0.06); although there were main effects of tDCS (F = 5.66, p = 0.01), with sham tDCS presenting higher values than active tDCS (Fig. 2). There were no interaction effects between tDCS and time (F = 0.08, p = 0.92). Therefore, acquisition occurred during sham tDCS although not during active tDCS.

4. Discussion

We found that bifrontal tDCS induced no accuracy improvement in PCL whereas PCL accuracy increased in the sham tDCS group — in other words, bifrontal tDCS prevented acquisition of implicit memory. Conversely, Kincses et al. (2004) found that, in fact, accuracy *increased* in the PCL after anodal tDCS over the left DLPFC, possibly due to indirect basal ganglia modulation. We further discuss two main differences between their study and ours that can account for these disparate findings.

4.1. The role of the right prefrontal cortex

While we used cathodal tDCS stimulation over the right prefrontal cortex, Kincses et al. positioned it over the right supraorbital area. Even considering the poor spatial resolution of tDCS, our montage likely had more prominent excitability-decreasing effects on the right prefrontal cortex. In this context, neuroanatomical and neuroimaging studies showed that the left DLPFC is specialized in decision-making for logic, complete contents whereas the right DLPFC performs decision-making for indeterminate content (such as the PCL task) (Goel and Dolan, 2007; Goel et al., 2009). Thus, cathodal over the right DLPFC could have decreased this lateralized cognitive ability and, as a result, prevented implicit learning. This effect might be even more important in depression, characterized by prefrontal asymmetry with relatively left DLPFC under activity and right DLPFC overactivity, in which the right DLPFC might have a major role in regulating subcortical structures (Johnstone et al., 2007).

4.2. Healthy vs. psychiatric samples

We enrolled depressed subjects whereas Kincses et al. (2004) recruited healthy subjects. Previous observations have showed that the rate of implicit learning in depressed patients is much lower than in control subjects (Naismith et al., 2006) and that different brain structures are activated during an implicit learning task, with similar basal ganglia activation but greater DLPFC activation in healthy than in depressed subjects (Naismith et al., 2010). This suggests that implicit learning strategies are different in depressed patients, characterized by lower DLPFC activation when compared with healthy controls. In fact, decreased DLPFC activation was also observed during cognitive tasks in adolescents with MDD (Halari et al., 2009). Our findings expand these previous observations by suggesting that DLPFC activation via tDCS in fact impaired implicit learning in depression. One possible explanation is that depressed patients have low cognitive flexibility in tasks involving frontal–striatal circuits. DLPFC probably contributes to implicit learning due to its broader role in directing attention and awareness (Robertson and Pascual-Leone, 2003). Therefore, DLPFC activation might not have been adequately integrated with striatum functioning, which, as a result, prevented implicit learning. Along these lines, the bifrontal montage (vs. studies positioning the cathode over the right supraorbital area) could have lead to greater prefrontal activation (and less subcortical activation), thus inducing bolder effects in preventing implicit learning. Of note, some tDCS studies in depression showed improvement in other cognitive functions such as attention and working memory (Loo et al., 2012; Utz et al., 2010).

Vercammen et al. (2011) investigated tDCS effects on PCL performance in schizophrenia. Although they did not observe differences in active vs. sham tDCS when considering the whole sample, they found, in a subgroup of patients, superior performance after active vs. sham tDCS. However, there are a number of methodological differences in their study and ours such as the cathode position (right supraorbital area vs. right prefrontal cortex), study design (within- vs. between-subjects design) and psychiatric disorder (depression vs. schizophrenia). Interestingly, Vercammen et al. (2011) found positive tDCS effects only for participants with higher baseline cognitive functioning. Nonetheless, we were not able to identify such a group in our study — in fact, as shown by the confidence intervals of improvement, the improvement/lack of improvement was quite homogenous on each group.

4.3. Methodological considerations

Limitations include the lack of a healthy control group that would allow comparing changes in implicit learning with our depressed sample. In addition, we also did not test other tDCS montages, such as anodal/cathodal tDCS over the left/right DLPFC using an extracephalic reference that would allow disentangling the specific effects of tDCS over each brain area. Another limitation is the relatively small sample — in fact, a larger sample could have shown different results. Therefore, our findings should be seen as hypothesis-driven for further studies to explore the role of the DLPFC in implicit memory.

The strengths of our study include the enrollment of an antidepressant-free sample, avoiding confounding effects of antidepressant use. Our randomized, between-subjects design also minimized learning effects due to PCL (compared with within-subjects designs). Lastly, we matched patients in the sham and active groups according to gender, age and baseline depression, avoiding confounding effects from these variables.

5. Conclusion

To conclude, we found that bifrontal tDCS (anodal over the left and cathodal over the right DLFPC) prevented learning acquisition as compared to sham tDCS in depressed subjects. This finding expands the knowledge of mechanisms of implicit learning acquisition in depression, specifically that it was prevented by focal cathodal stimulation of the right DLPFC, which decreased the activity of this area. Considering our results, further studies should evaluate the use of different montages to assess the effects of the DLPFC in implicit memory.

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