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Research article

Effects of acute transcranial direct current stimulation in hot and cold working memory tasks in healthy and depressed subjects

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HIGHLIGHTS

- MDD patients present non-emotional and emotional working memory impairment.
- The DLPFC is associated with MDD and cognitive deficits.
- We used tDCS to acutely increase DLPFC activity in MDD and controls.
- MDD patients presented improvement in emotional and non-emotional cognition.
- We discuss pathophysiological mechanisms and clinical implications of our findings.

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ABSTRACT

Dorsolateral prefrontal cortex (DLPFC) hypoactivity and subcortical hyperactivity have been associated to cognitive impairment for non-emotional ("cold") and emotional ("hot") working memory tasks in major depressive disorder (MDD). We investigated whether an increase of DLPFC activity using transcranial direct current stimulation (tDCS) would differently influence the performance in working memory tasks in depressed and healthy subjects. Forty young adult participants (20 with MDD and 20 healthy controls) were randomized to a single, sham-controlled, bifrontal (left anodal/right cathodal), 2 mA, 30 min tDCS session in a parallel design. The *n*-back and the internal shift task (IST) were used as proxies of cold and hot working memory performance, respectively. Active tDCS compared to sham promoted more accurate and faster responses to the *n*-back task for both patients and controls. Conversely, only patients presented an improvement in response times for the IST task. Our findings suggest that the mechanisms of tDCS in MDD involve modulation of both cold and hot working memory. We discuss these findings considering the modulatory top–down effects of tDCS on subcortical structures via prefrontal activation, and how spreading of activation might be different for healthy volunteers versus depressed patients. We also discuss the role of tDCS in cognitive amelioration for depressed patients. Finally, the distinct effects of tDCS in the "hot" cognition task for healthy and depressed participants are indicative that tDCS outcomes are also regulated by differences in baseline activity of the stimulated network.

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1. Introduction

Patients with depression present cognitive deficits in several domains (i.e., psychomotor speed, executive functions, memory and attention) [24], factors like older age and depression severity are related to greater cognitive deficits and lower remission rates, even after antidepressant treatment [24]. These issues highlight the importance of investigating cognitive deficits in MDD.

Abbreviations: MDD, major depressive disorder; DLPFC, dorsolateral prefrontal cortex; itDCS, transcranial direct current stimulation; IST, internal shift task; MINI, mini international neuropsychiatric interview; HDRS, hamilton depression rating scale; ANOVAs, analyses of variance; RTs, response times; SD, standard deviation.

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Table 1
Sample characteristics at baseline.

	Healthy subjects ($n = 20$)			MDD subjects ($n = 20$)			Healthy vs. MDD[a]
	Active	Sham	p	Active	Sham	p	p
Gender (M/F)	5/5	5/5	–	5/5	5/5	–	–
Age (mean, SD)	26.3 (7.8)	26.6 (8.8)	0.91	34.5 (4.1)	32 (4.7)	0.17	<0.01
HDRS-17	–	–	–	24 (5.4)	21.5 (2.5)	0.14	–
n-back							
Accuracy	0.91 (0.07)	0.93 (0.06)	0.69	0.81 (0.18)	0.87 (0.08)	0.36	0.02
RT	644 (151)	752 (207)	0.07	840 (243)	887 (115)	0.4	0.06
IST - Switch costs							
Gender	445 (281)	400 (201)	0.42	428 (338)	372 (237)	0.39	0.38
Face	307 (186)	436 (268)	0.09	409 (246)	388 (232)	0.7	0.41

[a] Comparison corrected by age. RT, response time; M/F, male/female; HDRS-17, Hamilton Depression Rating Scale, 17-items version; IST, internal shift task. Data in the table are mean\\ (standard deviation).

At the neural level, the frontolimbic system, which encompasses the DLPFC, the amygdala, the anterior cingulate cortex and other brain areas, regulates cognitive and emotional processing [19] – interestingly, a double dissociation between behavioral management and disinhibition with these brain areas is observed [12]. Hypoactivity of the DLPFC and hyperactivity of subcortical structures are associated to MDD and its cognitive deficits [13,17]. Moreover, two modalities of impaired cognitive processing are observed in MDD, namely 'cold' and 'hot' cognition, which refer to information processing in the absence or presence of emotional influence, respectively [18]. Non-emotion and emotion-laden tasks recruit and activate distinct yet overlapping neural networks. For example, in an fMRI study evaluating non-emotional and emotional inhibitory control, emotional inhibition engaged not only the neural circuitry involved in the non-emotional task, but also the paralimbic region and part or the anterior cingulate cortex [21].

However, research efforts on this topic have been to a large extent correlational, while the causal relationship between cortical activity and non-emotional and emotional processing in MDD deserves further investigation. In this context, tDCS is a useful tool to induce prefrontal cortex activation. TDCS is a non-invasive neuromodulatory technique that employs weak direct currents (0.5–2 mA) to modulate brain activity by regulating the frequency of action potentials triggered in the neuronal network [2].

We therefore employed tDCS to induce prefrontal activation in depressed and healthy subjects, exploring its effects on emotion-laden and non-emotional working memory tasks. The bifrontal tDCS montage that was already demonstrated to be an effective montage for the treatment of the acute depressive episode [14] was used, considering the positive effects in emotional and non-emotional cognition in depressed patients after tDCS [1,15,22]. For the non-emotional working memory task, we used the *n*-back task that assesses the short-term storage, selective and sustained attention, online manipulation of information in a mental workspace and is robustly associated with prefrontal cortex activation. *N*-back has been strongly associated with certain cognitive deficits (such as slower processing speed and impaired executive functioning) observed in MDD [3,10,16]. The IST was used to evaluate the ability to update and shift between emotional representations in working memory [8].

1.1. Study hypothesis

a) For the emotional task, tDCS would exert modulatory effects only in depressed compared to healthy subjects, considering that the former presents DLPFC hypoactivity that could be enhanced via direct current stimulation.
b) For the non-emotional task, the effects of tDCS would be exhibited in both depressed and healthy subjects.
c) At baseline, controls would have greater performance compared to patients in both non-emotional and emotional working memory tasks.

2. Material and methods

2.1. Subjects

This study was approved by the local and national Ethics Committee and all participants provided informed consent. Forty participants were recruited, 20 with depression and 20 controls. As controls were slightly younger than patients (Table 1), all analyses were controlled for age. Certified psychiatrists screened the participants and assessed depression severity using the Portuguese-translated versions of the MINI and the 17-items HDRS [11] (Table 1).

The depressed subjects were recruited from an ongoing non-inferiority, triple-arm, randomized trial (The Escitalopram vs. Electric Current Therapy for Treating Depression Clinical Study, ELECT-TDCS, clinicaltrials.gov: NCT01894815). Depressed subjects fulfilled the main eligibility criteria: (1) were antidepressant-free for at least 3 weeks (5 weeks for fluoxetine); (2) presented score of at least 17 on the HDRS-17; (3) aged between 18 and 40 years-old; (4) at least 12 years of schooling; (5) absence of other medical and psychiatric diagnoses (except for anxiety disorders whether in comorbidity with MDD). Healthy controls were matched according to gender and years of schooling, and were recruited among students and civil servants from the study site, in the University of São Paulo (São Paulo, Brazil).

2.2. Design

We used a double-blinded, sham-controlled, randomized, repeated-measures, parallel (between-subjects), single-session design. Each participant executed two computerized evaluations: the first was performed before the tDCS session and the second after the tDCS session was finished, which lasted 30 min.

2.3. Procedures

The *n*-back and the IST were programmed in E-prime 2.0 software (Psychology Software, Tools Inc Pittsburgh, Pennsylvania, USA) (Fig. 1). Images were presented on a 15-in. LCD computer screen and participants were seated at a distance of 60 cm from the screen. Before the test, a practise session, in which participants were instructed to respond as fast and accurately as possible, was done.

We used a 2-back task, presenting 3 blocks of 30 letters (from A to Z), each one being displayed on the screen for 500 ms, with an

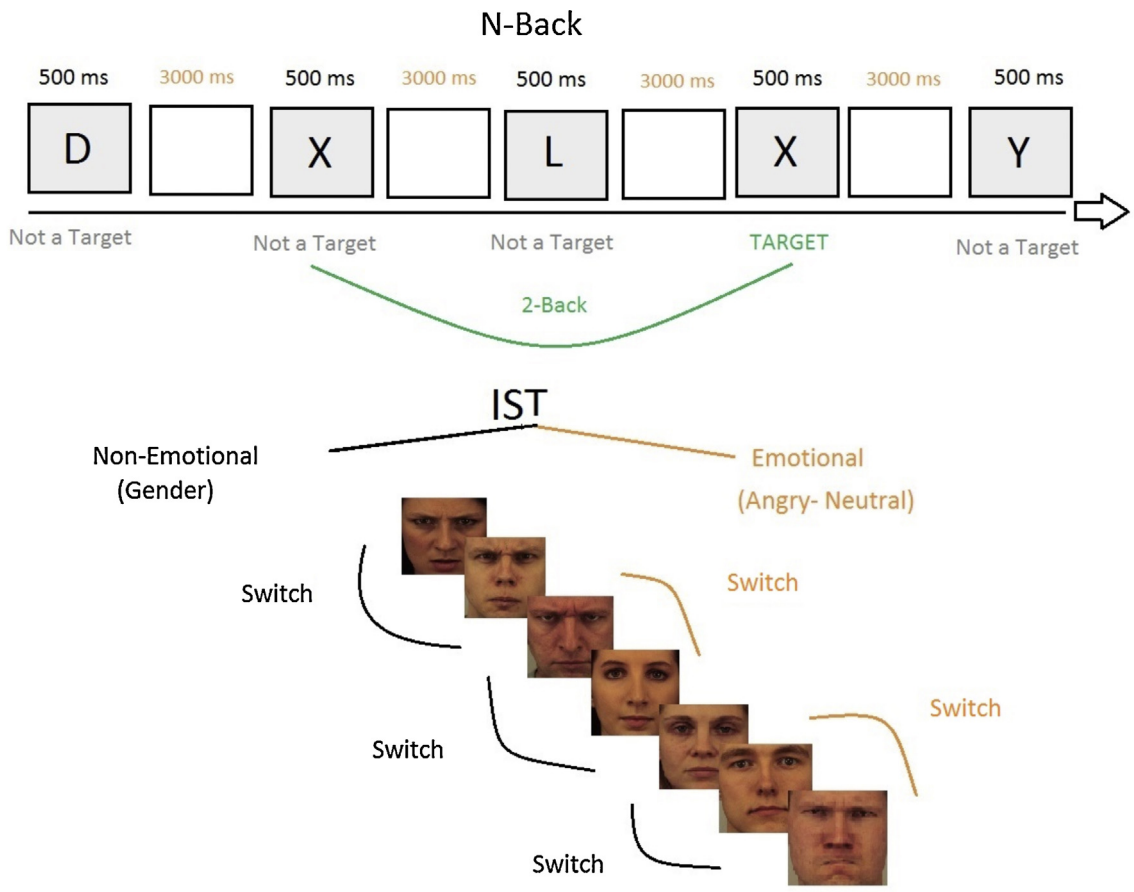

Fig. 1. Depiction of the *n*-back task and internal shift task used in the present study.

interstimulus interval of 3000 ms. A correct response occurs when the subject identified the same stimuli presented two positions before.

The IST stimuli were angry and neutral faces of males and females from the Karolinska Directed Emotional Faces [6]. Participants completed two separate (in counterbalanced order) task conditions: a non-emotional (gender) and an emotional (face). In the former, participants focused on recognizing whether the face was from a male or female, whereas in the latter they identified whether the face was neutral or angry. During each block, they counted and mentally updated the number of faces presented in each category (male/female or angry/neutral). After each face was presented, participants pressed the spacebar when the count was mentally updated. Then, the next face appears after 200 ms. Participants reported the number of faces at the block's end to encourage a consistent counting strategy.

The IST has shift and no-shift trials. In the former case, the target trial is different than the preceding trial (e.g., in the emotion condition an angry face following a neutral face). In the latter case, the target and the preceding trials are similar. The session consisted of 12 blocks of items, each one having a random number of 10–14 trials.

2.4. Transcranial direct current stimulation

We used tDCS devices (Soterix Medical, New York, USA). The anode and the cathode were placed over the left and right DLPFC, respectively. The electrodes were positioned according to the "OLE-system" through the use of a specific headgear [20]. We used a current intensity of 2 mA, electrode size of 25 cm^2 and session duration of 30 min. Sham consisted of a brief period of 2 mA stimulation for 30 s.

2.5. Statistical analysis

Analyses were done with Stata 12 (Statacorp, College Station, TX, USA). Results were significant at $p \leq 0.05$. Effect sizes were Cohen's d (small, medium and large effects correspond to values of 0.2, 0.5, and 0.8, respectively) and ${}_{p}\eta^2$ (0.02, 0.13, and 0.26 to small, medium, and large effects, respectively) [7]. In analyses using ANOVAs, significant interactions were followed by t-tests. Whenever sphericity was violated, the Greenhouse–Geisser correction was applied. Normality of data distribution was verified using the Shapiro–Wilk test. Post-hoc power analysis values (β) are also presented.

Student's-t-tests and Chi-square tests were used to compare characteristics between healthy vs. depressed subjects and between active vs. sham stimulation at baseline.

For the n-back task, the residual score changes in accuracy (i.e., responding to the target or omitting the response to a non-target) and RT were the dependent variables evaluated. Higher accuracy values represent improvement, whereas lower (including negative) RTs represent faster response. The independent variables were: tDCS (active/sham stimulation), group (healthy/depressed subjects), and age (continuous). A mixed-model ANOVA was employed.

For the IST, the RT was obtained after each stimulus. For each participant, the median RT (calculated per trial type: gender/

emotion; shift/no-shift) was used. After, we estimated the changes in performance before to after stimulation using the residual score changes, which is more advantageous to the absolute change (i.e., pre- minus post- RT), as it accounts for issues such as differences in baseline scores (as this variable was not controlled in our study design) and effects of regression to the mean [23]. The residual score change was calculated in two steps: (1) a linear regression between post- and pre-RT was performed and the predicted scores were obtained; (2) the difference between the observed and predicted values were obtained.

In the next step, we calculated the switch costs, which index the efficiency of switching between mental representations held in working memory [8], between each condition (e.g., emotional switch cost = emotion/shift minus emotion/no-shift). As we calculated the switch cost as the difference between residual score changes of shift minus no-shift trials, positive values represent faster response, whereas negative values represent slower response.

Finally, the dependent variable was the changes in switch cost and the independent variables were tDCS, group, condition (within-subjects: gender/face conditions) and age (continuous). A repeated-measures, mixed-model ANOVA was employed. According to previous literature, all responses (whether correct or incorrect) were included [8,9].

In exploratory analyses, we introduced gender as a factor in our ANOVA models. Also, we performed regression analyses to investigate whether depression scores were associated to cognitive performance in the performed tasks.

3. Results

3.1. Non-emotional (cold) working memory task

At baseline, controls outperformed patients in the accuracy of the *n*-back task (mean difference = 0.078, SD = 0.11, Cohen's $d = 0.69$, $p = 0.02$, $\beta = 0.77$), confirming the cognitive deficits observed in non-emotional working memory tasks observed in depression. We also observed a trend for MDD patients being slower than controls (mean difference = 112 ms, SD = 205, $p = 0.06$, $\beta = 0.46$).

The mixed-model ANOVA for accuracy revealed significant main effects for tDCS ($F_{1,37} = 4.6$, $p = 0.04$, ${}_p\eta^2 = 0.09$, $\beta = 0.55$) but not for group or the two-way interaction (Fs > 0.04, ps < 0.84). We exploratory analyzed the contrasts of the interaction, finding no significant differences in the active vs. sham group in depressed patients ($p = 0.09$, $\beta = 0.31$).

The mixed-model ANOVA for RT revealed similar results, with a main effect of tDCS ($F_{1,37} = 6.4$, $p = 0.02$, ${}_p\eta^2 = 0.106$, $\beta = 0.7$), but not for group or the two-way interaction (Fs > 0.09, ps < 0.76) – i.e., healthy and depressed subjects receiving active tDCS presented an improvement in accuracy and RT during the *n*-back, compared to those receiving sham tDCS (Fig. 2). We exploratory analyzed the contrasts of the interaction, finding no significant differences in the active vs. sham group in depressed patients ($p = 0.14$, $\beta = 0.32$).

3.2. Emotional (hot) working memory task

At baseline, patients present non-significant numerically higher switch costs than controls ($ps > 0.38$).

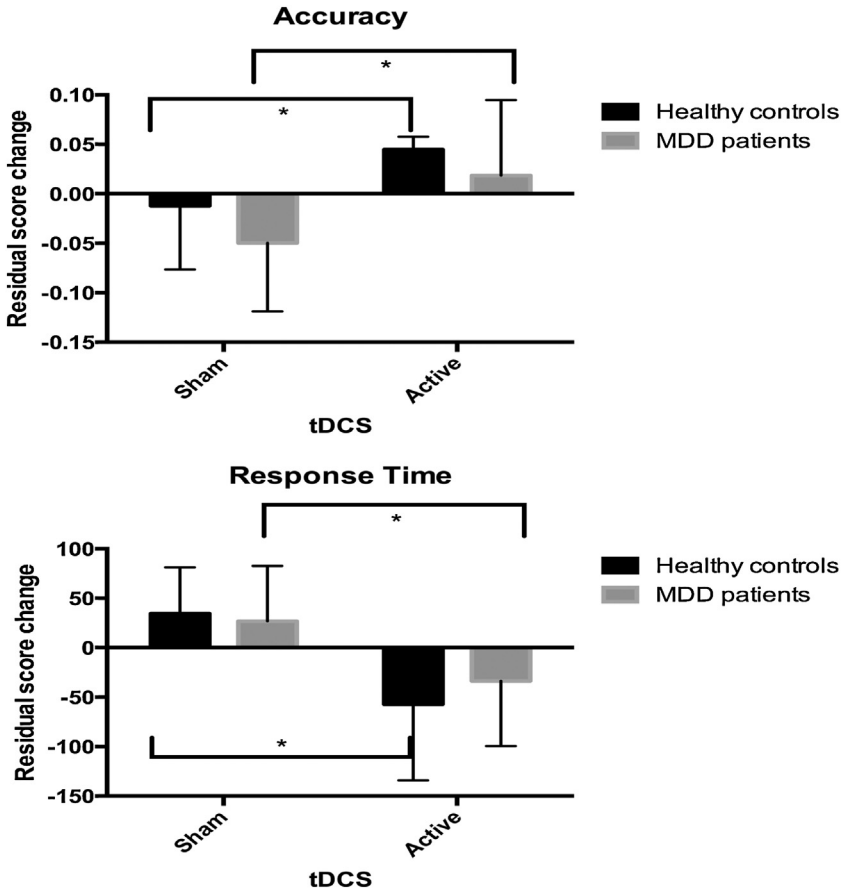

Fig. 2. Performance in the *n*-back task.
Improvement in accuracy and response time after active tDCS compared to sham. (*) represent significant differences at $p < 0.05$. Values > 0 indicate improvement for accuracy whereas values < 0 indicate faster response times. Bars represent 95% confidence interval.

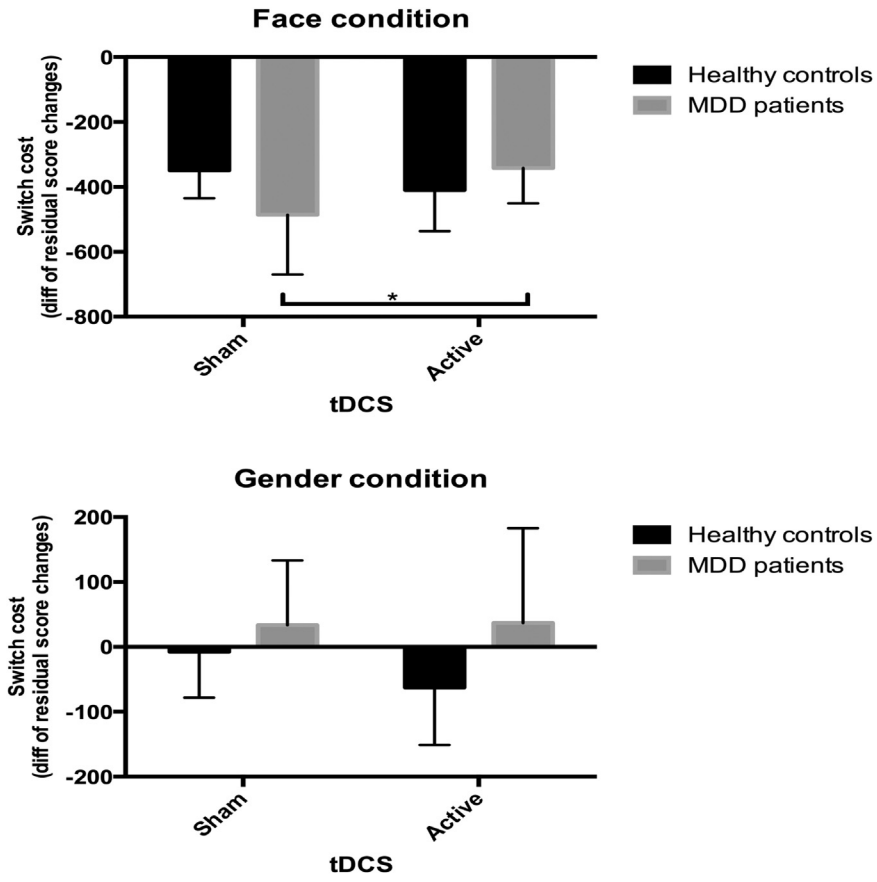

Fig. 3. Performance in the Internal Shift task.
Improvement after active tDCS compared to sham for the face (emotional) condition but not for the gender (non-emotional) condition. (*) represent a significant difference at $p < 0.05$. Values > 0 indicate faster response times. Bars represent 95% confidence interval.

The mixed-model ANOVA observed no significant main effects for tDCS and group (Fs > 0.34, ps < 0.56) and a significant main effect for condition ($F_{1,72} = 167.59$, $p < 0.01$, $_p\eta^2 = 0.396$, $\beta = 0.95$), i.e., patients were overall slower in the face (vs. gender) tasks. A significant interaction was observed between group and condition ($F_{1,72} = 4.62$, $p = 0.04$, $\beta = 0.52$), showing that both patients and controls were overall slower in the face vs. gender conditions. Finally, the three-way ANOVA (tDCS, group, condition) was significant ($F_{1,72} = 4.64$, $p = 0.03$, $\beta = 0.56$). Follow-up tests revealed that depressed patients receiving active tDCS were faster over time for the face (emotional) condition ($t = 2.16$, Cohen's $d = 0.53$, $p = 0.03$, $\beta = 0.57$) only (Fig. 3).

3.3. Exploratory analyses

Additional exploratory analyses did not reveal a relationship between depression scores and cognitive performance in the depressed patients in the sham and active groups (ps > 0.05). Also, the factor gender was not significant in our ANOVA models (ps > 0.05).

4. Discussion

In this first sham-controlled study evaluating immediate tDCS changes in antidepressant-free MDD patients and healthy controls; a single, sham-controlled session of bifrontal tDCS over the DLPFC acutely improved (1) a "cold" working memory task (*n*-back) in healthy subjects and depressed patients; (2) a "hot" working memory task (IST) only in depressed patients. Furthermore, at baseline, depressed patients performed worse in the *n*-back task compared to healthy controls. Also, we did not observe a worse performance for depressed patients in the IST task at baseline as predicted.

Our findings are in accordance to previous literature showing that tDCS increased performance in the *n*-back task [15], ameliorated emotional inhibitory control [25], enhanced performance in the Emotional Stroop Task [5] and in the affective go/no-go task [1] in depression. Thus, tDCS effects might not be limited to the DLPFC, but also extends to the broader cortico-subcortical network associated with cognitive dysfunction in MDD and regulation of emotionally loaded information processing.

Previous studies suggested that tDCS has pro-cognitive effects in MDD, although they were hindered by different methodological issues such as absence of control group, concomitant antidepressant use and lack of sensitivity for detecting cognitive changes due to task choice [22]. Therefore, our findings confirm and expand the evidence regarding the potential benefits of tDCS on cognitive amelioration in MDD.

In healthy subjects, we found tDCS effects only after the non-emotional but not the emotional task. The lack of effects in the hot working memory task might be explained by a "ceiling" effect in healthy samples that already adequately process emotional content, leaving little room for improvement for the task. It is also possible that subjective (self-report) mood evaluation is not sensible enough, at least in healthy volunteers, to index tDCS effects. For instance, in a previous study we observed [4] that tDCS did not change mood in healthy individuals, although cortisol levels and heart rate variability changed in a polarity- and valence-specific manner. Nonetheless, in the present study we did not examine the acute effects of tDCS on HDRS scores–future studies in

depression could examine whether tDCS has fast antidepressant effects as observed for other novel therapies, such as ketamine.

Notwithstanding the enrollment of only antidepressant-free MDD subjects and its sham-controlled design, our study has some limitations. First, no neuroimaging assessment was performed and therefore we could not delimit which brain structures were affected by tDCS. Second, we could not test different montages as this protocol used participants recruited for a larger study. Finally, the study sample was relatively small; therefore some analyses might be underpowered, particularly the lack of significant differences between patients and controls in the IST task at baseline and between type of stimulation in depressed patients in the *n*-back task. In fact, post-hoc power analyses revealed that some analyses, particularly for estimating small and medium effect sizes, were underpowered.

In summary, bifrontal tDCS increased performance in "hot" and "cold" working memory tasks in depressed patients and in "cold" cognition in controls. This suggests that tDCS (1) improves cognitive functions associated with key circuits involved in MDD pathophysiology and, therefore, its putative procognitive mechanisms in MDD may involve modulation of these pathways and (2) exerts modulatory top-down effects, probably by primary DLPFC activation. Our findings should be integrated with other biological markers to assess the putative mechanisms of tDCS for cognitive amelioration in depression.

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