Neuroscience Letters 591 (2015) 126–131

Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Research article

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

Marina L. Moreno[a], Marie-Anne Vanderhasselt[b], Andre F. Carvalho[c], Adriano H. Moffa[a], Paulo A. Lotufo[a], Isabela M. Benseñor[a], Andre R. Brunoni[a,d,*]

[a] Interdisciplinary Center for Applied Neuromodulation (CINA), University Hospital, University of São Paulo, São Paulo, Brazil
[b] Department of Experimental Clinical and Health Psychology, Ghent University, Ghent, Belgium
[c] Department of Clinical Medicine and Translational Psychiatry Research Group, Faculty of Medicine, Federal University of Ceará, Fortaleza, Brazil
[d] Service of Interdisciplinary Neuromodulation (SIN), Laboratory of Neurosciences (LIM-27), Department and Institute of Psychiatry, University of São Paulo, São Paulo, Brazil

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.

ARTICLE INFO

Article history:
Received 19 December 2014
Received in revised form 5 February 2015
Accepted 17 February 2015
Available online 20 February 2015

Keywords:
Transcranial direct current stimulation
Major depressive disorder
Working memory
Cognition

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.

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.

* Corresponding author at: Interdisciplinary Center for Applied Neuromodulation, Av. Professor Lineu Prestes, 2565, 3o andar, CEP 05508-000, São Paulo (SP), Brazil. Tel.: +55 11 3091 9241; fax: +55 11 3091 9241.
E-mail address: brunoni@usp.br (A.R. Brunoni).

http://dx.doi.org/10.1016/j.neulet.2015.02.036
0304-3940/

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