Journal of Affective Disorders 202 (2016) 46–52

Contents lists available at ScienceDirect

Journal of Affective Disorders

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

Research paper

Cognitive effects of transcranial direct current stimulation in depression: Results from the SELECT-TDCS trial and insights for further clinical trials

André Russowsky Brunoni [a,b,*], Gabriel Tortella [a,b], Isabela Martins Benseñor [a], Paulo Andrade Lotufo [a], André Ferrer Carvalho [c], Felipe Fregni [d]

[a] Center for Clinical and Epidemiological Research & Interdisciplinary Center for Applied Neuromodulation (CINA), University Hospital, University of São Paulo, São Paulo, Brazil
[b] Service of Interdisciplinary Neuromodulation (SIN), Laboratory of Neurosciences (LIM-27), Department and Institute of Psychiatry, Faculty of Medicine of University of São Paulo, São Paulo, Brazil
[c] Department of Clinical Medicine and Translational Psychiatry Research Group, Faculty of Medicine, Federal University of Ceará, Fortaleza, CE, Brazil
[d] Laboratory of Neuromodulation, Center for Clinical Research Learning, Department of Physical Medicine and Rehabilitation, Harvard University, USA

ARTICLE INFO

Article history:
Received 16 December 2015
Received in revised form
29 February 2016
Accepted 20 March 2016
Available online 21 May 2016

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

ABSTRACT

Background: Cognitive dysfunction treatment remains an unmet clinical need in major depressive disorder (MDD). Transcranial direct current stimulation (tDCS) may improve cognitive symptoms in MDD. Our aim was to investigate the cognitive effects of tDCS in the Sertraline vs. Electric Current Therapy for Treating Depression Clinical Study (SELECT-TDCS). We also explored whether tDCS could have mood-independent cognitive effects.

Methods: One hundred twenty MDD patients aged from 18 to 65 years received 12 sessions of active/sham tDCS (2 mA for 30 min) and real/placebo 50 mg/d sertraline over 6 weeks in a factorial trial. We analyzed whether changes in performance of neuropsychological tests (Trail Making, Digit Span, Stroop Task, Mini-Mental Status Exam and Montreal Cognitive Assessment) occurred over time, according to treatment group and depression improvement. Exploratory analyses were carried out to verify the influence of clinical and demographic variables on the outcomes.

Results: Cognitive improvement was showed in most tests used, although they occurred regardless of intervention type and depression improvement. Further exploratory analyses revealed that clinical response and education level could have mediated pro-cognitive tDCS effects on some of the tests used.

Limitations: The neuropsychological battery used might not have been sensitive to detect tDCS-induced effects on cognition. Lack of simultaneous cognitive training during application may have also limited its cognitive effects.

Conclusions: We found no evidence of beneficial or deleterious cognitive effects of tDCS as a treatment for depression. We discussed clinical trial design considerations for further tDCS studies assessing cognitive effects, including sample and outcomes considerations.

1. Introduction

Major depressive disorder (MDD) is a severe, chronic psychiatric condition with high lifetime prevalence and refractoriness rates (Andrade et al., 2003). Depressed patients present cognitive deficits in several domains such as executive functioning and attention (Wagner et al., 2012). Moreover, a significant proportion of MDD patients persist with cognitive dysfunction even in remitted states (Bora et al., 2013) and there is no antidepressant drug approved for the treatment of cognitive dysfunction in MDD. Thus, this issue is a clear unmet need in the management of MDD, and the search of novel therapeutic strategies is a top priority in the field (Carvalho et al., 2014).

The dorsolateral prefrontal cortex (DLPFC) is associated to cognitive dysfunction in MDD (Long et al., 2015; Roiser et al., 2012). In fact, non-invasive brain stimulation techniques increasing DLPFC activity may improve mood and cognition (Demirtas-Tatlidede et al., 2013). One of these techniques is transcranial

* Correspondence to: Interdisciplinary Center for Applied Neuromodulation, Av. Professor Lineu Prestes, 2565, 3o andar, CEP 05508-000 São Paulo, SP, Brazil.
E-mail address: brunoni@usp.br (A.R. Brunoni).

http://dx.doi.org/10.1016/j.jad.2016.03.066
0165-0327/

direct current stimulation (tDCS), which employs weak direct currents (0.5–2 mA) to modulate brain activity by regulating the frequency of action potentials triggered in the neuronal network (Brunoni et al., 2012). TDCS applied over the DLPFC ameliorates depressive symptoms (Brunoni et al., 2013). Also, a recent meta-analyses showed that single-session tDCS acutely improves working memory in neuropsychiatric patients. Healthy subjects also improved working memory reaction time, although not accuracy (Hill et al., 2015).

However, few sham-controlled studies have evaluated the efficacy of repeated sessions of tDCS in improving cognition over the treatment course of MDD. Fregni et al. (2006) showed, in a pilot study of 18 patients, that 5 active tDCS sessions in depressed patients improved the performance in the digit span forward and backward tasks. Subsequently, Loo et al. (2012), in a larger trial of 64 patients, found a significant performance enhancing effect on the symbol digit modalities test after one tDCS sessions, although no cognitive enhancing effects after 15 sessions of tDCS after controlling for mood effects. Also, case reports showed cognitive improvement after tDCS treatment in post-stroke depression (Bueno et al., 2011) and treatment-resistant depression (Palm et al., 2009). Although these results are promising, the influence of other clinical and demographic variables, including affective improvement, was not explored. In addition, most tDCS clinical trials in depression failed to show cognitive improvement after tDCS treatment (for a recent review, see Tortella et al. (2014)).

Therefore, our aim was investigate whether tDCS would be associated with an independent effect on cognition. Our hypothesis, based on preliminarily reported effects of tDCS on cognition in MDD, was that participants receiving tDCS would present a better performance on neuropsychological tests when the results are adjusted for improvement in depressive symptoms and other covariates. Secondarily, we explored whether baseline characteristics would predict cognitive improvement in patients receiving tDCS as to provide initial data to be used in further studies exploring cognitive effects of tDCS.

2. Methods

2.1. Design

The SELECT-TCS was a factorial, double-blind, sham-controlled trial that enrolled 120 participants with MDD who were randomized for placebo, sertraline, tDCS or the combined treatment, as described in detail elsewhere (Brunoni et al., 2011a). We conducted the study at the University Hospital, University of São Paulo, Brazil. The study was registered in clinicaltrials.gov (NCT01033084) and was approved by the Local and National Ethics Committee. All participants provided written, informed consent.

The trial duration was 6 weeks, which included an acute treatment period when ten consecutive weekday sessions of active/sham tDCS were performed, followed by two extra tDCS sessions delivered every other week. This treatment protocol was defined in 2009, when our study was designed. The evidence that was available then suggested that 10 tDCS sessions could be more effective than 5 sessions (Brunoni et al., 2011b). More sessions were not applied as we considered that this would increase dropout rate, as patients needed to return daily to our clinical center, which was not easily assessable by public transportation. The endpoint at week 6 was chosen to compare tDCS efficacy with sertraline, whose clinical effects manifest gradually over time.

Sertraline (or placebo), a selective serotonin reuptake inhibitor (SSRI), was used in a fixed dose of 50 mg/day, starting and ending simultaneously with tDCS.

2.2. Participants

We enrolled patients aged from 18 to 65 years diagnosed with unipolar, non-psychotic MDD according to DSM-IV criteria and confirmed by the Mini-International Neuropsychiatric Interview (M.I.N.I.). Subjects were required to have a Hamilton Depression Rating Scale (17-itens) (HDRS17) > 18 and low suicidal ideation. Exclusion criteria were other axis I disorders such as bipolar disorder, schizophrenia, alcohol and substance use disorders; and any axis II (personality and developmental) disorders. Patients who presented severe, life-threatening medical conditions and concomitant neuropsychiatric disorders such as dementia, epilepsy and stroke were also excluded. We also excluded subjects using or who used sertraline in the current acute depressive episode. However, those who had used sertraline in previous episodes and presented clinical response could be included. Patients were gradually tapered off any psychotropic medications except benzodiazepine drugs that remained constant throughout the entire study and at a maximum dose of 20 mg/day (diazepam-equivalent).

2.3. Procedures

We used standard, commercial tDCS devices (Chattanooga Ionto™ Dual Channel Devices, Chattanooga Group, Hixson, TN, USA). The anode and the cathode were respectively placed over the left and the right DLPFC. Brain areas were localized using the EEG 10/20 system. The rubber electrodes were involved in 25 cm^2 saline-soaked sponges and fixed with a headband. We used a direct current of 2 mA for 30 min For sham tDCS, the device was turned on for only 1 min Trained nurses applied all sessions, thus ensuring patients' blinding. Raters were blind to the procedure being administered and raters and nurses were blind to study medication.

2.4. Assessments

The neuropsychological assessments were applied at baseline and at endpoint (i.e., week 6, before the last tDCS session), in a quiet room by a trained psychologist or psychiatrist. They were:

(1) The Montreal Cognitive Assessment (MOCA) (Nasreddine et al., 2005), which assesses global cognitive functioning and is used for rapid detection of cognitive impairments;
(2) The Mini-Mental State Exam (MMSE) (Fuentes et al., 2000), another tool used for global cognitive assessment;
(3) The Wechsler Adult Intelligence Scale-III (WAIS-III) digit span forward (DSF) and backward (DSB) (Wechsler, 1997). These tests consist of seven pairs of random number sequences of increasingly longer sequences that the examiner reads and the patient repeats each sequence as it given (DSF) or in the inverse order (DSB). DSF is related to the efficiency of attention, whereas DSB, which demands storage of a few data bits, assesses working memory (Lezak et al., 2004);
(4) The Stroop Test (color, word, and interference; StC, StW and StIC) (Golden, 1976), which consists in presenting colored word cards in which the subject, as fast and accurate as possible, has (1) to say the name of the color (StC); (2) to say the word's color, being the word "neutral" (StW, e.g., 'home' printed in blue color); (3) to say the word's color, being the word a color name (StIC, e.g., 'green' printed in blue color). The Stroop test measures executive functions such as attention, concentration and inhibitory control;
(5) The Trail Making Test parts A (TMT-A) and (TMT-B) (Moses, 2004), in which the subject is instructed to connect a set of the 25 dots sequentially and as fast as possible; part A contains

only numbered circles and part B has numbered and lettered circles that need to be connected in an alternate order. Thus, this test involves not only attention (TMT-A and -B) and working memory (TMT-B) but also visual perception, decision-making, and motor speed (Lezak et al., 2004).

The tests applied in SELECT-TDCS were chosen because they are easily and relatively fast to apply. MOCA and MSSE were used as screening tests for global cognitive functioning and safety. Stroop, Digit Span and Trail Making tasks were used to provide a quick assessment of working memory and attention, functions related to the DLPFC, the target region stimulated. Moreover, a previous study from our group with a small sample size had shown that several of these tests presented a trend for improvement after tDCS in depressed patients (Fregni et al., 2006). All assessments were performed in their Portuguese, validated versions. For the MOCA, MSSE and Digit Span tests, *higher* scores indicate better performance whereas for the Stroop and Trail Making tests, *lower* scores are indicative of better performance.

Finally, the Montgomery–Åsberg Depression Rating Scale (MADRS) was used for assessing depression assessment.

2.5. Statistical analysis

The software Stata 12 (Statacorp, College Station, TX, USA) was employed for all analyses, with 2-sided significance tests at the 5% significance level. As this was an exploratory study, we did not correct for multiple comparisons. We described clinical and demographic variables across groups using one-way analysis of variance (ANOVA), $\chi 2$ tests or Fisher's exact tests, when necessary. ANOVAs were corrected using the Greenhouse-Geisser correction if sphericity was violated. Whether the result of an interaction was significant, post-hoc pairwise comparisons were carried out.

We had 9 dependent variables, corresponding to the neuropsychological scales (or its subtypes, when applicable) previously described. Although these variables were not normally distributed, we applied parametric tests according to the Central Limit Theorem that authorizes this approach for larger sample sizes, particularly for more than 30 observations (Portney and Watkins, 2008).

Our first step was to perform several repeated-measures ANOVAs (one for each dependent variable) with time (baseline and endpoint) as the within-subject, independent variable and tDCS (active/sham), sertraline (verum/placebo) and their interaction as between-subject, independent variables. Therefore, we analyzed the influence of time and treatment on neuropsychological performance. We also performed additional analyses comparing placebo vs. tDCS-only and placebo vs. combined treatment to further explore the putative effects of tDCS on cognitive improvement.

Clinical response was explored as a moderator and mediator of cognitive improvement. According to (Papakostas and Fava, 2008), a *moderator* is a variable that influences the relative likelihood of an outcome according to the type of the clinical intervention whereas a *mediator* is a measurable change that occurs vis-à-vis treatment outcome. Therefore, to explore clinical response as a moderator we introduced this variable as an independent variable in the abovementioned models. To test clinical response as a mediator, we used Pearson's correlations to explore the association of changes in depression scores with changes in task performance, for each intervention.

In addition, we investigated whether performance in neuropsychological tasks at baseline is a moderator of clinical response, using changes in depression scores as the dependent variables and the task scores at baseline and interventions (tDCS and sertraline) as independent variables, in several general linear models. The interaction between the interventions and each neuropsychological task was evaluated to identify whether they were moderators.

Finally, we explored whether variables associated to cognitive performance such as college degree (dichotomized in 15 years of schooling), age (dichotomized in 40 years-old) and use of benzodiazepines were moderators of changes in neuropsychological performance. Statistically, we performed these analyses by assessing the interaction between each abovementioned variable with time and tDCS. Each variable was explored separately in a distinct repeated-measures ANOVA model.

3. Results

3.1. Overview

Data from the 103 participants who completed the study were analyzed (Supplementary material). Main trial results are described elsewhere (Brunoni et al., 2013). In summary, it was observed clinical improvement of the combined treatment over the other groups, increased improvement of tDCS-only and sertraline-only over placebo and similar antidepressant effects of tDCS-only compared to sertraline-only.

The four groups were similar in clinical and demographic variables, except for the StW, which was slightly higher (worse performance) in the placebo group. At endpoint, patients in the sertraline group present lower scores (better performance) in the StW and StC (Table 1). Also, no patient was color-blind.

3.2. Changes in neuropsychological performance over time and tDCS and sertraline use

There was a significant ($p \leq 0.02$) main effect of time for most cognitive tests, except for StC (non significant trend of $p=0.06$), TMT-B ($p=0.15$) and MMSE ($p=0.1$) (Table 2). This indicates that all patients, regardless of intervention group, overall improved in most neuropsychological tasks when comparing baseline and endpoint performance.

Conversely, we found no interaction effects of time with tDCS, sertraline or the triple interaction. The single exception was the model using MOCA as the dependent variable, in which patients receiving sertraline improved more than those not receiving the drug ($p=0.02$, difference in means [SE] of 1.48 [0.43] vs. −0.03 [0.43], respectively). In sum, treatment did not have an overall influence on neuropsychological improvement.

Further models using time with placebo vs. tDCS-only and placebo vs. combined treatment showed no influence of treatment on cognitive performance, expect for MOCA, in which patients receiving combined treatment performed better than those receiving placebo at endpoint (M=24.4, SE=0.66 vs. M=26, SE=0.63, respectively, $p=0.02$) (Table 3).

3.3. Depression improvement and neuropsychological performance

Depression improvement and neuropsychological changes were not correlated according to Pearson's analyses performed separately for each group (data not shown). This means that depression improvement was not a mediator of changes in cognitive performance.

We also evaluated whether clinical response as an independent variable was associated with neuropsychological performance. As treatment variables, we used two distinct models to test placebo vs. tDCS-only and placebo vs. combined treatment separately. For the placebo vs. tDCS-only analyses, we found a significant interaction for StC ($F=5.7$, $p<0.01$) – in this analysis, responders who received tDCS performed significantly better than the other groups

Table 1
Clinical and demographic characteristics of the sample.

		Sham tDCS – placebo	Sham tDCS – sertraline	Active tDCS – placebo	Active tDCS – sertraline	*p*	Total
Age, years		46.4 (14)	41 (12)	41 (12)	41 (13)	0.24	42 (12)
Women, n (%)		20 (67)	17 (56)	21 (70)	24 (80)	0.28	82 (68)
Years of study		13 (4)	14.6 (4)	13.5 (3)	14 (4)	0.51	13.7 (4)
On benzodiazepines, n (%)		5 (4.2)	6 (5)	4 (3.3)	8 (6.7)	0.6	23 (19)
Melancholic depression, n (%)		13 (10.8)	14 (11.7)	17 (14.2)	19 (15.8)	0.38	63 (52.5)
Refractory depression, n (%)		11 (9.2)	14 (11.7)	13 (10.9)	12 (10.1)	0.82	50 (42)
Recurrent depression, n(%)		9 (7.5)	8 (6.7)	8 (6.7)	7 (5.8)	0.95	32 (26.7)
Chronic depression, n (%)		13 (10.8)	12 (10)	15 (12.5)	8 (6.7)	0.3	48 (40)
Severe depression, n (%)		17 (14.2)	17 (14.2)	20 (16.7)	16 (13.3)	0.74	70 (59.3)
MADRS	Baseline	31 (5.3)	30.5 (6)	31 (5.8)	30.7 (7)	0.99	30.6 (6)
	Endpoint	24.7 (8.6)	21.6 (13.1)	19 (12.2)	13.1 (8.5)	< **0.01**	19.6 (11.5)
MOCA	Baseline	24.9 (4.3)	24.9 (3)	25(3.2)	24.9 (3.1)	1	24.9(3.4)
	Endpoint	24.9 (3)	26.5 (2.8)	25.5 (3.8)	26 (2.4)	0.31	25.7 (3)
MMSE	Baseline	28.4 (1.5)	28.9 (1.6)	28.6 (1.3)	28.6 (1.8)	0.7	28.6 (1.6)
	Endpoint	28.4 (1.5)	27.4 (5.6)	28.6 (1.7)	28.3 (2)	0.58	28.2 (3.1)
TMT-A	Baseline	50.1(17.9)	42.8(13.7)	42.4(16.6)	49.6(24.4)	0.21	46.2(18.7)
	Endpoint	42 (14)	34 (15.6)	39.2 (12.2)	39.4 (12)	0.22	38.7 (13.6)
TMT-B	Baseline	94.5(47)	72.4(24.8)	79.6(32.5)	90.8(51)	0.13	84.2(40.6)
	Endpoint	81.8 (46.3)	69.2 (27.2)	82.4 (47.7)	80.5 (51.3)	0.7	78.8 (44)
DSF	Baseline	8.4 (2.3)	9.8 (3)	8.7 (2.5)	8.9 (2.7)	0.21	8.9(2.6)
	Endpoint	9.4 (2)	10.6 (2.8)	9.2 (2.3)	9.5 (2.8)	0.2	9.7 (2.5)
DSB	Baseline	5.6 (1.8)	5.8 (2.2)	5.4 (1.8)	5.6 (2)	0.9	5.6(1.9)
	Endpoint	5.8 (2.3)	6.8 (2)	5.4 (1.6)	6.2 (2.4)	0.14	6 (2.1)
StW	Baseline	19.7(7.3)	14.9 (2.8)	16.3(4.3)	17(5.1)	< **0.01**	17(5.4)
	Endpoint	17.1 (4.7)	13.9 (2.1)	15.9 (4.5)	15 (3.3)	**0.03**	17.5 (3.9)
StC	Baseline	22.7(8.4)	19(5.6)	19.9(6.1)	19.6(5.1)	0.12	20.2(6.5)
	Endpoint	22 (10)	16.8 (3.6)	19.4 (5.1)	18 (4.3)	**0.02**	19.1 (6.4)
StIC	Baseline	34.9(14.7)	29.5(10.9)	32(11.8)	33(14)	0.49	32.3(12.9)
	Endpoint	27.6 (8.8)	24.2 (6.7)	28.4 (7.9)	27.4 (9.9)	0.3	26.9 (8.5)

All values represent mean (SD) unless otherwise noted. MADRS=Montgomery-Åsberg depression rating scale; MOCA=Montreal Cognitive Assessment; MMSE, Mini-Mental Status Evaluation; TMT=Trail Making Test; DSF and DSB, Digit Span Forward and Backward; StW, StC, StIC; Stroop test – Word, color and interference. Significant results ($p \leq 0.05$) are highlighted in bold. For MADRS endpoint scores, scores were significantly lower in the combined treatment group, compared to all other groups, and significantly lower in the tDCS-only and sertraline-only groups, when compared to placebo. For StW baseline scores and StW and StC endpoint scores, scores were lower in sertraline-only group, compared to placebo group.

Table 2
Repeated-measures ANOVA results for the main and interaction effects of the factors time and treatment.

	Time			Time × tDCS			Time × sertraline			Time × tDCS × sertraline		
	F	d.f.	*p*	F	d.f.	*p*	F	d.f.	*p*	F	d.f.	*p*
MOCA	5.37	1, 95	**0.02**	1.21	1, 95	0.27	6.3	1, 95	**0.01**	13.3	1, 95	0.1
MMSE	2.4	1, 96	0.12	1.47	1, 96	0.22	1.66	1, 96	0.2	0.46	1, 96	0.5
TMT-A	24.2	1, 97	< **0.01**	0.1	1, 97	0.77	3.2	1, 97	0.07	0.4	1, 97	0.53
TMT-B	2	1, 96	0.15	0.5	1, 96	0.48	0.03	1, 96	0.86	1.89	1, 96	0.17
DSF	27.2	1, 97	< **0.01**	0.03	1, 97	0.85	0.15	1, 97	0.7	0.2	1, 97	0.65
DSB	5.76	1, 97	**0.02**	< 0.01	1, 97	0.23	1.42	1, 97	0.23	0.29	1, 97	0.58
StW	10.6	1, 97	< **0.01**	0.17	1, 97	0.68	< 0.01	1, 97	0.96	2.27	1, 97	0.13
StC	3.5	1, 97	0.06	0.5	1, 97	0.48	2.7	1, 97	0.1	1.3	1, 97	0.25
StIC	43.9	1, 97	< **0.01**	0.35	1, 97	0.55	0.15	1, 97	0.7	< 0.01	1, 97	0.97

The table represents the analysis of each cognitive assessment according to time and treatment. MOCA=Montreal Cognitive Assessment; MMSE, Mini-Mental Status Evaluation; TMT=Trail Making Test; DSF and DSB, Digit Span Forward and Backward; StW, StC, StIC; Stroop test – Word, color and interference; d.f.=degrees of freedom. Significant results ($p \leq 0.05$) are highlighted in bold.

($p < 0.01$). For the placebo vs. combined treatment analyses, we found no significant interactions.

Finally, baseline neuropsychological scores were not moderators of clinical response for either tDCS or sertraline interventions and also considering the main effects of clinical response (data not shown). In other words, neuropsychological performance at baseline was not associated with depression improvement or intervention.

3.4. Influence of clinical and demographic variables on neuropsychological performance

We explored whether age, educational level and benzodiazepine use were moderators of cognitive performance by assessing, in different repeated-measures ANOVA models, their interaction with time and tDCS.

We found that age was a moderator for TMT-A. Post-hoc tests revealed that older patients receiving tDCS improved more than younger patients (10.1[3.6] vs. 4.5[1.8] s, respectively), although this difference was not significant ($p=0.17$).

Also, college degree was a moderator for MOCA: patients presenting a college degree had increased cognitive performance when receiving active compared to sham tDCS (mean diff=1.96 [0.8] points, $p=0.01$) whereas no tDCS effects were observed for those without a college degree. This finding was reproduced when using years of schooling (a continuous variable) instead of college degree. In fact, the higher the educational level, the greater the difference in MOCA improvement between active and sham tDCS

Table 3
Repeated-measures ANOVAs results for the main and interaction effects of the factors time and placebo vs. tDCS-only, and time and placebo vs. combined treatment.

	Placebo vs. tDCS-only						Placebo vs. combined treatment					
	Time			Time × tDCS			Time			Time vs. Combined treatment		
	F	d.f.	p	F	d.f.	p	F	d.f.	p	F	d.f.	p
MOCA	0.02	1, 107	0.86	3.63	1, 107	0.06	0.2	1, 108	0.66	6.34	1, 108	**0.01**
MMSE	0.15	1, 107	0.15	0.57	1, 107	0.45	1.63	1, 109	0.2	0.01	1, 109	0.91
TMT-A	7.38	1, 109	< **0.01**	0.08	1, 110	0.77	11.15	1, 111	< **0.01**	1.57	1, 111	0.21
TMT-B	0.49	1, 107	0.48	1.35	1, 107	0.25	3.78	1, 109	0.06	0.14	1, 109	0.7
DSF	3.54	1, 109	**0.01**	0.2	1, 109	0.65	5.42	1, 111	**0.02**	0.03	1, 111	0.87
DSB	0.65	1, 109	0.42	0.13	1, 109	0.71	1.62	1, 111	0.2	0.67	1, 111	0.41
StW	3.69	1, 110	0.06	0.43	1, 110	0.51	9.47	1, 109	< **0.01**	0.09	1, 109	0.76
StC	0.02	1, 110	0.89	1.18	1, 110	0.28	0.21	1, 109	0.65	2.09	1, 109	0.15
StIC	25.3	1, 110	< **0.01**	0.2	1, 110	0.65	20.7	1, 109	< **0.01**	0.44	1, 109	0.51

MOCA = Montreal Cognitive Assessment; MMSE, Mini-Mental Status Evaluation; TMT = Trail Making Test; DSF and DSB, Digit Span Forward and Backward; StW, StC, StIC; Stroop test – Word, color and interference; d.f. = degrees of freedom. Significant results ($p \leq 0.05$) are highlighted in bold.

(data not shown).

In addition, college degree was also a moderator for TMT-A, although post-hoc analyses did not reveal any significant comparison. Finally, benzodiazepine use and refractory depression were moderators for TMT-A and TMT-B, respectively, although post-hoc analyses did not reveal any significant comparison (Table 4).

4. Discussion

In this exploratory study, we evaluated neuropsychological performance of a depressed sample from the SELECT-TDCS trial. We observed cognitive improvement in most tests applied. However, such improvement occurred over time for all patients, irrespectively of the treatment condition. We also explored the relationship between depression and neuropsychological performance, although we found that changes in depression and task performance were not correlated, and also that neither baseline task performance was a moderator of depression improvement nor clinical response was a moderator of cognitive changes (except in the StW task for tDCS). Finally, we evaluated whether clinical and demographic variables moderated cognitive improvement according to the intervention. Although several interactions were observed, significant results in post-hoc analyses were only observed for some tests and variables. These findings are further discussed.

Table 4
Evaluation of a moderation effect between several variables with time and tDCS treatment.

		Age	College degree	BZD use
MOCA	F	3.4	6.37	< 0.01
	p	*0.06*	***0.01***	*0.96*
MMSE	F	1.68	0.17	0.04
	p	*0.19*	*0.67*	*0.83*
TMT-A	F	4.05	3.64	4.06
	p	***0.04***	***0.05***	***0.04***
TMT-B	F	0.1	0.17	1.15
	p	*0.75*	*0.68*	*0.28*
DSF	F	0.28	0.16	0.2
	p	*0.59*	*0.69*	*0.65*
DSB	F	0.18	0.08	0.05
	p	*0.67*	*0.77*	*0.82*
StW	F	0.09	0.28	0.79
	p	*0.76*	*0.59*	*0.37*
StC	F	2.25	0.29	0.05
	p	*0.13*	*0.58*	*0.83*
StIC	F	0.38	1.24	0.01
	p	*0.53*	*0.26*	*0.91*

The table shows the results of the interaction of each variables (columns) with time and tDCS treatment, using mixed-models. MOCA = Montreal Cognitive Assessment; MMSE, Mini-Mental Status Evaluation; TMT = Trail Making Test; DSF and DSB, Digit Span Forward and Backward; StW, StC, StIC; Stroop test – Word, color and interference; d.f. = degrees of freedom. Significant results ($p \leq 0.05$) are highlighted in bold.

4.1. Practice effects

Neuropsychological performance improved in all treatment groups for almost all tasks. In fact, we used tests vulnerable to practice effects as they are relatively simple and patients were retested in a short time interval. Moreover, we did not use different versions of the same test, which further increases practice effects. For instance, Bartels et al. (2010) observed an important performance improvement in healthy subjects who were continuously tested over a prolonged period of time with a standard neuropsychological battery. Moreover, tasks such as the Trail Making, the Digit Span and the Stroop Task, are influenced by anxiety (Lezak et al., 2004). Therefore, it is possible that participants were more anxious at the trial onset than at the study endpoint, which could have caused cognitive improvement over time.

4.2. Impact of depression improvement on cognitive performance

Although patients significantly presented robust depression improvement, clinical response did not influence tDCS effects on cognition – i.e., changes in depressive symptoms associated with tDCS were not related to changes in cognitive performance. Thus, it is unlikely that alleviation of depressive symptoms after tDCS treatment would explain possible improvements in cognitive performance. In fact, our results showed overall no evidence of pro-cognitive tDCS effects in depression. In contrast, a recent meta-analysis of single-session, sham-controlled tDCS studies in neuropsychiatric samples have found significant effects of anodal tDCS over the left DLPFC in improving accuracy of working memory tasks (Hill et al., 2015). Nevertheless, that meta-analysis only observed effects for online tDCS (i.e., the task being applied simultaneously to tDCS) and not for offline stimulation (i.e., the task applied after tDCS). In our study we applied the tasks before tDCS as to avoid its acute effects, which could also explain why our findings differ from single-session tDCS studies.

4.3. Limitations

It is important to consider some aspects of the original design of SELECT-TDCS that could have influenced the results of this

present analysis. First, we employed neuropsychological tests primarily used to show *safety* of tDCS. Some of these tests might have generally poor sensitivity to detect cognitive improvement. Future studies could apply more sensible, computerized tests to evaluate cognitive performance. For instance, in a study in healthy volunteers applying 10 repeated, daily tDCS sessions, Martin et al. (2013b) observed an improvement in the dual n-back task. This task is also more specific for a cognitive domain (in this case, working memory) than some of the neuropsychological tasks applied that other functions such as global functioning (e.g., MMSE and MOCA) (Lezak et al., 2004). Second, our sample had a high education level (most of them were recruited among the staff, faculty or were students from the university), was non-geriatric and presented moderate depression severity; presenting neuropsychological scores in the normal (or even upper) range at baseline, favoring a possible "ceiling effect". Thus, in this depressed sample effects of tDCS on cognition might have been subtler to detect. For instance, in healthy samples, despite some initial positive findings (Fregni et al., 2005), a recent meta-analysis found no evidence of working memory accuracy improvement after anodal tDCS over the DLPFC (Hill et al., 2015). Conversely, in populations with more severe cognitive deficits, the pro-cognitive tDCS effects might be more noted. For instance, in a sham-controlled trial in schizophrenia, a psychiatric disorder with marked cognitive deficits, 5 sessions of active tDCS significantly improved several working memory tasks (Smith et al., 2015). Third, an important difference between our results compared to the significant effects of tDCS on cognition observed in two previous MDD trials (Fregni et al., 2006; Loo et al., 2012). Here, we applied 10 tDCS sessions consecutively and then only one session every fortnight, measuring endpoint neuropsychological assessments after 6 weeks of treatment. In contrast, Fregni et al. observed improvement after 5 sessions whereas Loo et al. observed cognitive improvement after one session, but not after 15 sessions. It is thus possible that a cognitive improvement occurred immediately after or during the daily tDCS phase and faded away afterwards. We only assessed cognitive performance at endpoint considering that performing three or more assessments in 6 weeks would increase practice effects bias. Finally, we did not test alternative montages. Although virtually all studies evaluating pro-cognitive working memory effects of tDCS placed the anode over the left DLPFC; the cathode is usually placed over the right supra-orbital area. Theoretically, cathodal DLPFC over the right DLPFC could decrease cortical excitability and thus cognitive performance. Nonetheless, tDCS has poor spatial resolution – for instance, a computer simulation modeling showed that current distribution in the right DLPFC does not substantially differ when comparing cathode positioning over right supraorbital area vs. right DLPFC (Bai et al., 2014). Also, cathodal stimulation is not necessarily inhibitory when evaluating cognition (Parkin et al., 2015).

4.4. Influence of baseline characteristics on tDCS effects

We also evaluated whether clinical and demographic variables were moderators of cognitive changes. First, it should be underscored that significant results must be interpreted with caution, as several tests were performed, increasing the probability of a type I error. Notwithstanding, we found evidence that the presence of college degree (or more years of schooling) predicted a greater difference in MOCA improvement between active and sham tDCS. A previous study also found that, in older adults, anodal tDCS only improved working memory in individuals with higher education, providing no benefits in the less educated group (Berryhill and Jones, 2012).

Finally, for the StW, we found that clinical responders receiving active tDCS showed greater cognitive improvement than those receiving sham tDCS. Indeed, immediate improvement in the Stroop task following tDCS was demonstrated in healthy volunteers (Jeon and Han, 2012; Ouellet et al., 2015). The fact that only responders presented this finding could suggest that improvement in the StW might be related to depression improvement associated to tDCS treatment.

4.5. Insights for designing further trials assessing cognitive effects on depression

Based on our findings, we suggest the following design considerations to assess whether tDCS has cognitive effects in patients with depression:

(1) Using more sensitive and specific instruments to detect cognitive changes such as computerized cognitive tasks, particularly tasks associated to DLPFC activity, for instance, the n-back task (Owen et al., 2005) – also, both accuracy and reaction time should be collected, as it is not clear if tDCS improves only reaction time (Brunoni and Vanderhasselt, 2014) or accuracy (Hill et al., 2015);
(2) Nonetheless, at least a brief assessment of other cognitive functions should be performed to investigate changes in other cognitive tasks – for instance, a recent study found that tDCS decreased performance in some tasks of the WAIS-IV (Sellers et al., 2015);
(3) Selecting specific populations that would have a greater likelihood of improvement, as cognitive deficits in moderate depressive episodes are subtle. Therefore, patients who are more severe, refractory or older – i.e., those presenting more prominent cognitive deficits – could present a greater cognitive improvement receiving active compared to sham tDCS and;
(4) Performing studies using online administration of cognitive training with tDCS, which could enhance tDCS cognitive. According to the neurocognitive model of depression, a dysfunctional top-down functioning, characterized by DLPFC hypoactivity and amygdala hyperactivity, is associated to poor cognitive control, leading to affective and attentional biases toward negative information, which, in turn, reinforces the depressive symptoms (Plewnia et al., 2015). TDCS and working memory tasks, by increasing DLPFC activity, could therefore enhance cognitive control (De Raedt et al., 2015). Studies using repeated tDCS sessions combined to cognitive training showed cognitive performance enhancement in healthy volunteers (Martin et al., 2013a) and a sustained antidepressant response in depressed patients (Segrave et al., 2013). In this context, "online" (vs. "offline") administration of the task seems to induce better effects (Hill et al., 2015; Martin et al., 2014).

5. Conclusion

To conclude, we did not observe pro-cognitive effects of tDCS in cognition in a large depressed sample. Nonetheless, our exploratory findings suggested that some neuropsychological variables could be influenced by education, gender and depression improvement; results that should be confirmed in further studies. Also, future studies should aim to explore tDCS effects of cognition using more sensible and specific neuropsychological tests associated to the DLPFC and enrolling samples with more prominent cognitive deficits.

Acknowledgements

ARB receives Young Investigator grants from the Brain & Behavior Research Foundation (NARSAD, YI 2013), São Paulo Research State Foundation (FAPESP

2012/20911-5) and the National Council for Scientific and Technological Development (CNPq, 455157/2013-8). This work was supported by a FAPESP Grant (2009/05728-7). The authors have no conflicts of interest to disclose.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.jad.2016.03.066.

References

Andrade, L., Caraveo-Anduaga, J.J., Berglund, P., Bijl, R.V., De Graaf, R., Vollebergh, W., Dragomirecka, E., Kohn, R., Keller, M., Kessler, R.C., Kawakami, N., Kilic, C., Offord, D., Ustun, T.B., Wittchen, H.U., 2003. The epidemiology of major depressive episodes: results from the international consortium of psychiatric epidemiology (ICPE) surveys. Int. J. Methods Psychiatr. Res. 12, 3–21.

Bai, S., Dokos, S., Ho, K.A., Loo, C., 2014. A computational modelling study of transcranial direct current stimulation montages used in depression. NeuroImage 87, 332–344.

Bartels, C., Wegrzyn, M., Wiedl, A., Ackermann, V., Ehrenreich, H., 2010. Practice effects in healthy adults: a longitudinal study on frequent repetitive cognitive testing. BMC Neurosci. 11, 118.

Berryhill, M.E., Jones, K.T., 2012. tDCS selectively improves working memory in older adults with more education. Neurosci. Lett. 521, 148–151.

Bora, E., Harrison, B.J., Yucel, M., Pantelis, C., 2013. Cognitive impairment in euthymic major depressive disorder: a meta-analysis. Psychol. Med. 43, 2017–2026.

Brunoni, A.R., Nitsche, M.A., Bolognini, N., Bikson, M., Wagner, T., Merabet, L., Edwards, D.J., Valero-Cabre, A., Rotenberg, A., Pascual-Leone, A., Ferrucci, R., Priori, A., Boggio, P.S., Fregni, F., 2012. Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions. Brain Stimul. 5, 175–195.

Brunoni, A.R., Valiengo, L., Baccaro, A., Zanao, T.A., de Oliveira, J.F., Goulart, A., Boggio, P.S., Lotufo, P.A., Bensenor, I.M., Fregni, F., 2013. The sertraline vs. electrical current therapy for treating depression clinical study: results from a factorial, randomized, controlled trial. JAMA Psychiatry 70, 383–391.

Brunoni, A.R., Valiengo, L., Baccaro, A., Zanao, T.A., de Oliveira, J.F., Vieira, G.P., Bueno, V.F., Goulart, A.C., Boggio, P.S., Lotufo, P.A., Bensenor, I.M., Fregni, F., 2011a. Sertraline vs. electrical current therapy for treating depression clinical trial – SELECT TDCS: design, rationale and objectives. Contemp. Clin. Trials 32, 90–98.

Brunoni, A.R., Valiengo, L., Baccaro, A., Zanao, T.A., de Oliveira, J.F., Vieira, G.P., Bueno, V.F., Goulart, A.C., Boggio, P.S., Lotufo, P.A., Bensenor, I.M., Fregni, F., 2011b. Sertraline vs. electrical current therapy for treating depression clinical trial – SELECT TDCS: design, rationale and objectives. Contemp. Clin. Trials 32, 90–98.

Brunoni, A.R., Vanderhasselt, M.A., 2014. Working memory improvement with non-invasive brain stimulation of the dorsolateral prefrontal cortex: a systematic review and meta-analysis. Brain Cogn. 86, 1–9.

Bueno, V.F., Brunoni, A.R., Boggio, P.S., Bensenor, I.M., Fregni, F., 2011. Mood and cognitive effects of transcranial direct current stimulation in post-stroke depression. Neurocase 17, 318–322.

Carvalho, A.F., Miskowiak, K.K., Hyphantis, T.N., Kohler, C.A., Alves, G.S., Bortolato, B., PM, G.S., Machado-Vieira, R., Berk, M., McIntyre, R.S., 2014. Cognitive dysfunction in depression - pathophysiology and novel targets. CNS Neurol. Disord. Drug Targets 13, 1819–1835.

De Raedt, R., Vanderhasselt, M.A., Baeken, C., 2015. Neurostimulation as an intervention for treatment resistant depression: from research on mechanisms towards targeted neurocognitive strategies. Clin. Psychol. Rev. 41, 61–69.

Demirtas-Tatlidede, A., Vahabzadeh-Hagh, A.M., Pascual-Leone, A., 2013. Can non-invasive brain stimulation enhance cognition in neuropsychiatric disorders? Neuropharmacology 64, 566–578.

Fregni, F., Boggio, P.S., Nitsche, M., Bermpohl, F., Antal, A., Feredoes, E., Marcolin, M. A., Rigonatti, S.P., Silva, M.T., Paulus, W., Pascual-Leone, A., 2005. Anodal transcranial direct current stimulation of prefrontal cortex enhances working memory. Exp. Brain Res. 166, 23–30.

Fregni, F., Boggio, P.S., Nitsche, M.A., Rigonatti, S.P., Pascual-Leone, A., 2006. Cognitive effects of repeated sessions of transcranial direct current stimulation in patients with depression. Depress Anxiety 23, 482–484.

Fuentes, D., Tavares, H., Camargo, C., Gorenstein, C., 2000. Inventário de Temperamento e de Carater de Cloninger – Validação da Versão em Português. In: Gorenstein, C., Andrade, L.H.S.G., Zuardi, A.W. (Eds.), Escalas De Avaliação Clínica Em Psiquiatria e Psicofarmacologia. Lemos-Editorial, Sao Paulo, pp. 363–376.

Golden, C.J., 1976. Identification of brain disorders by the stroop color and word test. J. Clin. Psychol. 32, 654–658.

Hill, A.T., Fitzgerald, P.B., Hoy, K.E., 2015. Effects of anodal transcranial direct current stimulation on working memory: a systematic review and meta-analysis of findings from healthy and neuropsychiatric populations. Brain Stimul.

Jeon, S.Y., Han, S.J., 2012. Improvement of the working memory and naming by transcranial direct current stimulation. Ann. Rehabil. Med. 36, 585–595.

Lezak, M.D., Howieson, D.B., Loring, D.W., 2004. Neuropsychological Assessment. Oxford University Press, New York.

Long, Z., Duan, X., Wang, Y., Liu, F., Zeng, L., Zhao, J.P., Chen, H., 2015. Disrupted structural connectivity network in treatment-naive depression. Prog. Neuropsychopharmacol. Biol. Psychiatry 56, 18–26.

Loo, C.K., Alonzo, A., Martin, D., Mitchell, P.B., Galvez, V., Sachdev, P., 2012. Transcranial direct current stimulation for depression: 3-week, randomised, sham-controlled trial. Br. J. Psychiatry 200, 52–59.

Martin, D.M., Liu, R., Alonzo, A., Green, M., Loo, C.K., 2014. Use of transcranial direct current stimulation (tDCS) to enhance cognitive training: effect of timing of stimulation. Exp. Brain Res. 232, 3345–3351.

Martin, D.M., Liu, R., Alonzo, A., Green, M., Player, M.J., Sachdev, P., Loo, C.K., 2013a. Can transcranial direct current stimulation enhance outcomes from cognitive training? A randomized controlled trial in healthy participants. Int. J. Neuropsychopharmacol. Off. Sci. J. Coll. Int. Neuropsychopharmacol. 16, 1927–1936.

Martin, D.M., Liu, R., Alonzo, A., Green, M., Player, M.J., Sachdev, P., Loo, C.K., 2013b. Can transcranial direct current stimulation enhance outcomes from cognitive training? A randomized controlled trial in healthy participants. Int. J. Neuropsychopharmacol. 16, 1927–1936.

Moses Jr., J.A., 2004. Test review – comprehensive trail making test (CTMT). Arch. Clin. Neuropsychol. 19, 703–708.

Nasreddine, Z.S., Phillips, N.A., Bedirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J.L., Chertkow, H., 2005. The montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment. J. Am. Geriatr. Soc. 53, 695–699.

Ouellet, J., McGirr, A., Van den Eynde, F., Jollant, F., Lepage, M., Berlim, M.T., 2015. Enhancing decision-making and cognitive impulse control with transcranial direct current stimulation (tDCS) applied over the orbitofrontal cortex (OFC): a randomized and sham-controlled exploratory study. J. Psychiatr. Res. 69, 27–34.

Owen, A.M., McMillan, K.M., Laird, A.R., Bullmore, E., 2005. N-back working memory paradigm: a meta-analysis of normative functional neuroimaging studies. Hum. Brain Mapp. 25, 46–59.

Palm, U., Keeser, D., Schiller, C., Fintescu, Z., Reisinger, E., Baghai, T.C., Mulert, C., Padberg, F., 2009. Transcranial direct current stimulation in a patient with therapy-resistant major depression. World J. Biol. Psychiatry: Off. J. World Fed. Soc. Biol. Psychiatry 10, 632–635.

Papakostas, G.I., Fava, M., 2008. Predictors, moderators, and mediators (correlates) of treatment outcome in major depressive disorder. Dialog. Clin. Neurosci. 10, 439–451.

Parkin, B.L., Ekhtiari, H., Walsh, V.F., 2015. Non-invasive human brain stimulation in cognitive neuroscience: a primer. Neuron 87, 932–945.

Plewnia, C., Schroeder, P.A., Wolkenstein, L., 2015. Targeting the biased brain: non-invasive brain stimulation to ameliorate cognitive control. Lancet Psychiatry 2, 351–356.

Portney, L.G., Watkins, M.P., 2008. Foundations of Clinical Research: Applications to Practice, 3rd ed. Prentice Hall, Philadelphia, PA.

Roiser, J.P., Elliott, R., Sahakian, B.J., 2012. Cognitive mechanisms of treatment in depression. Neuropsychopharmacology 37, 117–136.

Segrave, R.A., Arnold, S., Hoy, K., Fitzgerald, P.B., 2013. Concurrent cognitive control training augments the antidepressant efficacy of tDCS: a pilot study. Brain Stimul.

Sellers, K.K., Mellin, J.M., Lustenberger, C.M., Boyle, M.R., Lee, W.H., Peterchev, A.V., Frohlich, F., 2015. Transcranial direct current stimulation (tDCS) of frontal cortex decreases performance on the WAIS-IV intelligence test. Behav. Brain Res. 290, 32–44.

Smith, R.C., Boules, S., Mattiuz, S., Youssef, M., Tobe, R.H., Sershen, H., Lajtha, A., Nolan, K., Amiaz, R., Davis, J.M., 2015. Effects of transcranial direct current stimulation (tDCS) on cognition, symptoms, and smoking in schizophrenia: a randomized controlled study. Schizophr. Res. 168, 260–266.

Tortella, G., Selingardi, P.M.L., Moreno, M.L., Veronezi, B.P., Brunoni, A.R., 2014. Does non-invasive brain stimulation improve cognition in major depressive disorder? A systematic review. CNS Neurol. Disord. Drug. Targets 13, 1759–1769.

Wagner, S., Doering, B., Helmreich, I., Lieb, K., Tadic, A., 2012. A meta-analysis of executive dysfunctions in unipolar major depressive disorder without psychotic symptoms and their changes during antidepressant treatment. Acta Psychiatr. Scand. 125, 281–292.

Wechsler, D., 1997. WechslerAdult Intelligence Scale – Administration and scoring Manual. TX, San Antonio.