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Cognitive control therapy and transcranial direct current stimulation for depression: a randomized, double-blinded, controlled trial.

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Running title: tDCS and CCT in depression

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Abstract

Background: Based on findings that major depressive disorder (MDD) is associated to decreased dorsolateral prefrontal cortical (DLPFC) activity; interventions that increase DLPFC activity might theoretically present antidepressant effects. Two of them are cognitive control therapy (CCT), a neurobehavioral intervention that uses computer-based working memory exercises, and transcranial direct current stimulation (tDCS), which delivers weak, electric direct currents over the scalp.

Methods: We investigated whether tDCS enhanced the effects of CCT in a double-blind trial, in which participants were randomized to sham tDCS and CCT (n=17) vs. active tDCS and CCT (n=20). CCT and tDCS were applied for 10 consecutive workdays. Clinicaltrials.gov identifier:NCT01434836.

Results: Both CCT alone and combined with tDCS ameliorated depressive symptoms after the acute treatment period and at follow-up, with a response rate of approximately 25%. Older patients and those who presented better performance in the task throughout the trial (possibly indicating greater engagement and activation of the DLPFC) had greater depression improvement in the combined treatment group.

Limitations: Our exploratory findings should be further confirmed in prospective controlled trials.

Discussion: CCT and tDCS combined might be beneficial for older depressed patients, particularly for thosewho have cognitive resources to adequately learn and improve task performance over time. This combined therapy might be specifically relevant in this subgroup that is more prone to present cognitive decline and prefrontal cortical atrophy.

Keywords

Major depressive disorder; transcranial direct current stimulation; control cognitive therapy; non-invasive brain stimulation; randomized clinical trial; geriatric depression.

1. Introduction

Considerable research has been performed on novel treatments for major depression, a chronic, highly prevalent disorder (Kessler et al., 2003) in which antidepressant drugs present modest efficacy (Trivedi et al., 2006) and important adverse effects (Anderson et al., 2008) that limit their use. Some of these novel interventions aim to improve depression symptoms by directly increasing dorsolateral prefrontal cortical (DLPFC) activity, based on the observation of decreased activity of this area and increased activity of subcortical structures observed in MDD, a pattern that is at least partially restored to normal levels after amelioration of depressive symptoms (Mayberg et al., 2000; Pizzagalli, 2011; Siegle et al., 2007). Two of these interventions are particularly appealing considering their low cost, ease of use and applicability in different scenarios: transcranial direct current stimulation (tDCS) and neurobehavioral therapies.

TDCS consists of the induction of a weak, direct electric current through electrodes placed over the scalp that could increase (anode) and decrease (cathode) cortical excitability beyond the period of stimulation(Nitsche and Paulus, 2000). Although the exact mechanisms of action of tDCS are still unclear, it probably operates by inducing small changes (<1mV) in the membrane potential(Datta et al., 2009), thus acting in the frequency of spike timing and modifying net cortical excitability(Purpura and McMurtry, 1965). Compared to repetitive transcranial magnetic stimulation (rTMS), another somatic therapy, tDCS is cheaper, easier to use and a more portable technique with less adverse effects (Priori et al., 2009); characteristics that have motivated further tDCS research in neuropsychiatric disorders, particularly depression. In fact, recent randomized clinical trials demonstrated that daily, repeated sessions of tDCS show clinical efficacy in the treatment of major depression (Brunoni et al., 2013c; Loo et al., 2012). These studies applied anodal tDCS over the left DLPFC, theoretically increasing the activity in this brain area, which is decreased in MDD.

Neurobehavioral therapy is an intervention that addresses the biological mechanisms of psychological disorders (Siegle et al., 2007). For depression, current neurobehavioral interventions consist of tasks focused on working memory and sustained attention training, as these cognitive tasks are associated with DLPFC activity – in fact, patients with depression have poorer performance in many of these tasks (Barch et al., 2003; Gotlib and Joormann, 2010; Jones et al., 2010). In recent studies, Siegle et al. (2007; In press) investigated whether these interventions that increase DLPFC activity could be employed as a depression treatment. The authors compared the outcome of depressed patients that were randomized to receive treatment as usual only vs. combined with cognitive control therapy (CCT) designed to increase DLPFC activity. They showed that the CCT group displayed significantly greater improvements in depression symptoms than those in the treatment as usual group. In another study, Segrave et al. (2013) explored the efficacy of CCT combined with tDCS in a 3-arm trial, randomizing 27 patients to receive CCT + sham tDCS, tDCS + sham CCT and both active therapies combined, finding that only CCT and tDCS combined presented sustained antidepressant response at follow-up. However, the sample size of this study was small (N=9 per condition) andthe number of sessions was limited (5 sessions). These promising results fostered further investigation in this topic.

Both tDCS and CCT might act in depression improvement via enhancement of DLPFC activity. Theoretically, tDCS could enhance - i.e., present synergistic effects – the influence of CCT, based on previous studies that showed that tDCS increases WM performance in healthy and depressed volunteers (Brunoni and Vanderhasselt, in press; Fregni et al., 2005; Oliveira et al., 2013). We examined whether tDCS, by increasing cortical activity in the DLPFC, could enhance performance and therefore the effects of CCT, which actively recruits similar brain areas, thus ameliorating depression. Importantly, we used the Paced Auditory Serial Addition Task (PASAT) training alone (and not combined to the computer-based attention training part as used in the Segrave et al. study) for CCT, because by using two tasks it is impossible to disentangle the specific contribution of each task. We used the PASAT because this task is already known to activate the

left middle frontal gyrus, including the DLPFC (Lazeron et al., 2003). The importance of this study is both mechanistic – i.e., to increase the understanding of the pathophysiological mechanisms involved in depression – and clinical, as we investigated whether the combination of two non-pharmacological, affordable therapies presented clinical gains in depressed subjects.

2. Methods

The study was approved by the Local and National Ethics Committee and is registered in clinicaltrials.gov (NCT01434836). All patients provided written, informed consent. The trial was conducted in the University Hospital, University of São Paulo, Brazil and in the Mackenzie Presbyterian University, also situated in São Paulo, Brazil from September 2011 to May 2013.

Subjects

We enrolled patients from both genders with acute depressive disorder according to the evaluation of board-certified psychiatrists (ARB and LCLV) who confirmed the diagnosis using the Portuguese-validated version of the Mini International Neuropsychiatric Inventory (Amorim, 2000). Only those with a 24-item Hamilton Depression Rating Score (HDRS) greater than 21, with low suicide risk and aged between 18 and 65 years were included. We did not include patients who presented any of the following: (1) other psychiatric disorders, notably bipolar disorder, substance use disorders and schizophrenia, except for anxiety disorders whencomorbid with depression; (2) personality disorders; (3) previous neurologic conditions (i.e., stroke, post-stroke depression, dementias); (4) severe, life threatening conditions; (5) specific contraindications to tDCS, such as metallic plates in the head; (6) did not complete at least 2 visits to our research center; and (7) less than 8 years of schooling and/or difficulties in performing arithmetic operations, due to the nature of the CCT intervention performed, as described below.

Regarding pharmacotherapy, we did not include patients taking antipsychotics and tricyclic antidepressants, as to avoid confounding factors and also because these treatments can interfere in other measurements we performed, such as heart rate variability and pupil dilation. All participants were in a stable drug dose regimen for at least 6 weeks - i.e. either based on Selective Serotonin Reuptake Inhibitors (SSRI) or Selective Noradrenalin Reuptake Inhibitors (SNRI). Benzodiazepine drugs were tolerated but tapered to a maximum of 20mg/d diazepam (or equivalent) according to previous findings suggesting that benzodiazepines could interfere in tDCS antidepressant mechanisms (Brunoni et al., 2013a; Brunoni et al., 2013c).

2.1 Design

Participants were randomized to (1) CCT with sham tDCS and (2) CCT with active tDCS (i.e., all participants received CCT). The trial duration was 4 weeks, entailing a short treatment period of 10 daily, consecutive tDCS and CCT sessions (first two weeks, except weekends) and the endpoint assessment two weeks after the end of the treatment period (i.e., week 4). The primary endpoint at week 4 was chosen *a priori* according to prior tDCS studies showing that greater tDCS effects are usually observed in this time frame. Also, amelioration of depressive symptoms usually occurs in this time frame. Participants were allowed 2 nonconsecutive missed visits; in such cases extra tDCS sessions were performed to complete the total number of sessions.

The sample size was estimated based on previous findings from our group at the time of study design (Boggio et al., 2008), in which a 6-point difference in the HDRS scores between active vs. sham tDCS (SD=6) was observed. Therefore, with two-sided $\alpha=0.05$ and $\beta=0.2$, we calculated that it would be necessary to enroll 32 patients to detect this 6-point difference between groups. Considering an attrition rate of 10-20%, we aimed to recruit 36 to 40 patients for this study.

2.2 Procedures

TDCS was administered using commercial devices (Chattanooga Ionto Device; Chattanoga group), which deliver a constant, fixed current by varying the voltage output according to resistance changes and turning off the current when the resistance is too high. For each active tDCS session, we applied a direct current of 2mA through 25cm^2 saline-soaked rubber sponges for 30min/d. The anode and the cathode were respectively placed over F3 and F4 that correspond to the left and the right DLPFC. This montage, as described by Ferrucci et al. (2009), is advantageous to the placement of the cathode over the right supraorbital area as it simultaneously increases the left and decreases the right DLPFC activity, which are respectively hypo- and hyperactive in depression. The sham procedure consisted of an initial 30-second ramp-in phase, 30 seconds of active stimulation and a ramp-out phase of 15 seconds, a reliable sham method (Gandiga et al., 2006), with similar efficacy to placebo-pill blinding (Brunoni et al., 2013b). The electrode position and all other procedures were performed identically to the active tDCS. Trained nurses were responsible to deliver the tDCS sessions and were instructed to adopt the same procedures for both sham and active stimulation. They were also trained to turn off the device outside patient's eyesight.

The CCT was a modified version of thePaced Auditory Serial Addition Task(PASAT, for a detailed description see (Siegle et al., 2007; Siegle et al., In press)). The original PASAT (Gronwall, 1977) consists in successively presenting numeric digits, the participants were being asked to continuously sum the new digit to the digit that was just presented. This task activates the left prefrontal cortex (Audoin et al., 2005) and reflects multiple cognitive abilities, such as sustained attention, working memory, inhibitory control and processing speed (Gonzalez et al., 2006). As suggested by Siegle et al. (2007), who considered that the original PASAT could be frustrating for depressed subjects, we used an "adaptive", slower version, which starts with a 3000ms inter-stimulus interval and speeds up by 100ms when participants get four consecutive items correct. Conversely, it slows down by 100ms when participants miss four consecutive items, therefore

keeping the performance relatively constant and equating the task for difficulty across participants and sessions. CCT was delivered in the last 15 minutes of each active/sham tDCS session.

For the CCT, the numbers (1 to 9) were recorded in Portuguese and presented in a random order to the participants, who had to perform the sum of the last two digits by selecting the correct response on the screen. Participantscompletedthree5-minblockspersession,andtheywereinstructedtoconcentrateonthetaskandgetasmanyitemscorrectandtoresumethetaskasquicklyaspossiblewhentheymadeanerror.

2.3 Assessments

The primary efficacy outcome was the HDRS score throughout the trial. Secondary outcome was the Beck Depression Inventory (BDI) scores. Treatment-resistant depression was defined as failure to achieve clinical response after at least two antidepressant drug trials of adequate dose and duration (Berlim and Turecki, 2007).

This study also assessed several other outcomes such as salivary cortisol response, heart rate variability, electroencephalography, pupil dilation and rumination that could be reported in upcoming publications.

2.4 Statistical analysis

All analyses were performed using Stata 12 (Statacorp LP), with 2-sided significance tests at the 5% significance level. Analyses were conducted in the sample of completers and in the intention-to-treat sample, in which missing data were considered to be at random and imputed according to the last observation carried forward. Missing data were considered to be missing at random.

As previously defined per protocol (and registered in clinicaltrials.gov) our main analysis was performed in the intention-to-treat (ITT) sample, using the method of the last-observation carried forward (LOCF), in which missing observations are imputed with the last observed known values. Since the dropout rate was high, we also explored our results by using a dataset in which missing data were imputed using the multiple imputation predictive mean matching (PMM) technique using 10 imputations (M=10). We tested this approach because it might be better than the LOCF method to recover lost information due to missing data (Barnes et al., 2006). We also performed complete-case (CC) analysis (or listwise deletion, in which all cases without complete observations are not included in the analysis) for the main outcomes.

Clinical and demographic characteristics between groups were compared using t-tests and chi-square tests for continuous and categorical variables, respectively. For the primary outcome, we employed a mixed 2x3 analysis of variance (ANOVA), using HDRS scores as the dependent variable, Group (two levels: active tDCS with CCT; sham tDCS with CCT) as the between-subjects independent variable and Time (3 levels: baseline; 2 weeks; 4 weeks) as the within-subjects, repeated measures independent variable. The Mauchly's sphericity test was applied to check for violations of sphericity. We performed follow-up independent *t*-tests to test differences between groups at each time point and paired *t*-tests to test the within group changes over time.

The BDI scale and other time points were also analyzed as secondary outcomes. We also described response and remission rates at endpoint. Response was defined as a ≥50% of depression improvement from baseline and remission as an endpoint HDRS score ≤7.

In the exploratory analysis, we first performed several simple general linear regression analyses to identify whether the predictors age, gender, length of depressive episode, age of depression onset, number of depressive episodes, treatment-resistant depression, benzodiazepine use, improvement in the task performance throughout the stimulation period (hereby referred as "PASAT improvement") and baseline inter-stimulus interval (ISI) on the PASAT were associated

with depression improvement.In this model, the dependent variable was the HDRS score change between baseline and week 4. The independent variables were group (dummy-coded in 0 and 1), the predictor and the interaction between group and the predictor.

Of note, inpriorstudies(Siegle et al.; Siegle et al., In press), the median inter-stimulus interval (ISI) onthePASAT was computedforeachparticipant,and the mean of the median was examinedacrossparticipants. Here, our aim was to take into account the sequential adaptation in performance over each day of the training as to assess the progressive gains in cognitive performance throughout the trial.Therefore,inthecurrentstudy, the regression slope was used to assess PASAT improvement. In order to compute this variable, we first extracted the median ISI of each session (total of 10 sessions). After that, we performed a linear regression using the median ISI and day of training as dependent and independent variables, respectively. The slope of the model was used as an index of PASAT improvement throughout the trial. For visualization purposes, themore*positive*theslope,the*faster*theparticipantsexecutedthePASATwithouterrors,andthusthebettert heimprovementoverthecourseofthetraining.

In a final step, we also performedmultiple regression analysis using different *p* cut-offs for variable inclusion (≤0.05, ≤0.1 and ≤0.15). In this method, only significant (according to the *p* cut-off) predictors in the simple regression analysis are included in the multiple regression analyses. We used similar methodology in a previous study (Brunoni et al., 2013a).

3. Results

Approximately 200 potential volunteers were screened to participate in the study. Of them, 160 were excluded, as they did not attend to the eligibility criteria. The included patients were randomized to the active tDCS + CCT and sham tDCS + CCT groups. The groups were similar in clinical and demographic characteristics at baseline (Table 1). Importantly, 3 of the 40 participants were not included in our analyses due to trial abandonment (i.e., did not complete at least 2 visits to

our research center, n=2) and technical reasons (n=1, one participant with bipolar depression who was mistakenly diagnosed as unipolar depression during trial enrollment).

Four patients dropped-out at week 2 and 13 patients dropped-out at week 4. The dropouts were evenly distributed between groups (Figure 1). All patients tolerated tDCS well, without adverse effects.

(Table 1)

(Figure 1)

3.1 Main outcomes

No violations of sphericity were observed in all analyses. In the ITT analysis, we observed significant main effects of time ($F_{2,110}$=12.21, p<0.01) but no significant main effects of group ($F_{1,110}$=0.19, p=0.66) and of the interaction of time x group ($F_{2,110}$=0.05, p=0.94). Follow-up independent *t*-tests showed that the groups presented no significant differences at any time point (Table 1). Moreover, paired *t*-tests revealed that depression significantly improved from baseline to week 2 and week 4 (t=2.7, p=0.01 and t=2.77, p<0.01, respectively) in the sham tDCS + CCT and also in the active tDCS + CCT (t=2.35, p=0.02 and t=2.85, p<0.01, respectively). In other words, there were no baseline depression differences between groups, and both groups showed similar depression improvement.

Similar results were observed with the BDI scale and for the ITT and CC analyses (Table 2). Finally, the analysis using the multiple imputation PMM approach also yielded similar results (data not shown).

(Table 2)

3.2 Simple linear regression analysis

In the simple linear regression analysis only age ($F_{1,34}$=5.82, p=0.02) was significantly associated with the outcome, with a superior improvement in younger patients. (Table 3)

(Table 3)

3.3 Multiple linear regression analysis

Only age was significantly associated with the outcome for all *p* cut-offs and only "PASAT improvement" was associated with the outcome at the *p* cut-off of ≤0.15. Therefore, we performed only one analysis, which explored the influence of age and PASAT improvement with the outcome. In the exploratory model, we found no main effects of PASAT improvement ($F_{1,29}$=2.29, p=0.14), age ($F_{1,29}$=0.19, p=0.66) and the interaction of age with PASAT improvement ($F_{1,29}$=1.65, p=0.2). Nonetheless, we found trends for the main effects of tDCS ($F_{1,29}$=3.73, p=0.06), with a trend of superior improvement in the active tDCS + CCT vs. sham tDCS + CCT groups; and of the interaction of tDCS with age ($F_{1,29}$=3.84, p=0.06), with a trend of superior improvement in the active vs. sham groups with increasing age. We found significant effects of the interaction of tDCS with PASAT improvement ($F_{1,29}$=6.51, p=0.02), with superior improvement in the active vs. sham groups directly associated with task performance. Finally, the triple interaction of tDCS, age and PASAT improvement ($F_{1,29}$=7.18, p=0.01) was significant, with a greater difference in the active tDCS + CCT vs. sham tDCS + CCT groups directly associated with age and task improvement, as depicted in Figure 2. In other words, PASAT improvement and age influenced the effects of active tDCS + CCT in depression, with older age and greater PASAT improvement being associated with increased difference in depression improvement in active vs. sham groups.

(Figure 2)

4. Discussion

In this randomized, double-blinded trial assessing the efficacy of cognitive control therapy alone (n=17) and combined with tDCS (n=20) in major depression; CCT alone and combined with tDCS ameliorated depressive symptoms immediately after the acute treatment period (week 2) and at endpoint (week 4). Exploratory analyses revealed a superior improvement in depressive symptoms for the combined therapy when taking into account age and improvement in the PASAT performance throughout the trial. Specifically, older age was associated with greater enhancement of tDCS on CCT, and patients who presented greater PASAT improvement during the task were those who improved more in their depressive symptoms. These findings are discussed below.

To the best of our knowledge, only Segrave et al. (2013) had previously explored the efficacy of CCT combined with tDCS. In a 3-arm, double-blinded, sham-controlled trial, they randomized 27 patients to receive CCT with sham tDCS, tDCS with sham CCT and both therapies combined. Similarly to our study, all groups presented improvement in depressive symptoms after 5 days of tDCS and/or CCT therapy. However, they found that only the tDCS + CCT group presented a sustained depression improvement at follow-up; whereas we found that both groups, including the sham tDCS + CCT group, also sustained improvement during follow-up. However, their study and ours have several methodological differences that might explain these contrasting outcomes, such as: (1) we performed more tDCS/CCT sessions (5 vs. 10 days) and we used only one (vs. two) training task and (2) our follow-up period was relatively shorter (2 vs. 3 weeks) and had more dropouts than theirs.

In addition, we might have not identified a superior synergistic effect of tDCS with CCT – as found in Segrave et al. – for some methodological reasons, which include:

(1) a ceiling effect of the CCT intervention, which could have impaired the signal detection between active vs. sham groups;

(2) the high number of dropouts between weeks 2 and 4 that could have also converged the mean depression scores of the groups – although we cannot explain the high dropout rate at week 4, we anecdotally observed that patients complained to perform the EEG sessions, which were very time consuming. As the second EEG was scheduled at week 4, they could have not returned to the session for this reason; and

(3) the high variance in the final HDRS scores (as observed in SD scores around 10, much higher than initially predicted in our power analyses), which suggested an unexplained source of heterogeneity influencing the outcomes.

Therefore, in order to identify variables associated with heterogeneity, we performed simple and multiple linear regression exploratory models. We found that PASAT improvement and age wererelated tothe outcome. From a biological perspective, this model is interesting because PASAT performance decreases with age (Tombaugh, 2006) and tDCS effects in cognitive processing are also influenced by age (Berryhill and Jones, 2012; Meinzer et al., 2013). Furthermore, cognitive processing - the basis of the clinical effects of CCT (Siegle et al., 2007; Siegle et al., In press) - decreases with age and can be enhanced by tDCS in older individuals (Berryhill and Jones, 2012; Holland et al., 2011; Meinzer et al., 2013); and prefrontal atrophy is observed with ageing (Lemaitre et al., 2012).

The findings of our exploratory analyses (Figure 2) showed that for older patients the clinical effects of active tDCS + CCT were observedaccording to task improvement throughout the trial. This suggests that this combined intervention might be particularly effective in older individuals who still have cognitive resources to adequately learn and improve task performance over time. In fact, the ceiling effect of CCT could be more important in younger compared to older patients who have (even in the absence of degenerative diseases) volume reduction in several brain areas, particularly the prefrontal cortex (Lemaitre et al., 2012).

The specific mechanisms of action of tDCS in older adults are still being investigated in literature, however our hypothesis is that some of these individuals, with decreased cognitive resources due to cortical atrophy and cognitive decline, can particularly benefit from focal (CCT) and non-focal (tDCS) interventions aiming to increase prefrontal cortical activity compared to younger adults. Although our exploratory findings should be confirmed in future studies specifically targeting older adults; they are clinically relevant considering the worldwide ageing of population and the limited efficacy of pharmacotherapy in this group, in which adverse effects are an important issue(Sanglier et al., 2011). In this regard, the development of effective therapies without clinical adverse effects is particularly relevant.

4.1 Limitations

Some limitations of our study should be underscored. First, the higher number of dropouts could have lead to false-negative findings. Although we performed our data analysis with different approaches (ITT, CC and multiple imputation PMM), the results were similar. Another limitation is that we did not have a pure placebo arm, therefore we were not able to examine directly whether the treatment groups would have presented a superior response than a placebo group – although we observed a response rate of 25%, which is a similar magnitude than found in single- and double-blind tDCS studies(Berlim et al., 2013; Brunoni et al., 2012).

5. Conclusion

In this randomized, double-blind, sham-controlled trial we investigated whether tDCS could enhance the efficacy of CCT in the treatment of depression. Our main outcome showed that both groups similarly improved over time. However, exploratory analyses revealed that tDCS augmented the clinical effects of CCT in older individuals, particularly in those who presented improvement in

the cognitive task performed throughout the trial. We hypothesize that this combined therapy might be particularly relevant in this subgroup that is more prone to present cognitive decline and prefrontal cortical atrophy. Nonetheless, confirmatory trials exploring the effects of CCT with tDCS in geriatric depression are warranted.

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Conflicts of Interest

None.

Role of the funding source

None.

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Table 1. Clinical and demographic characteristics at baseline.

	Sham tDCS + CCT	Active tDCS + CCT	p
Male / Female	13/4	13/7	0.45
Age, years (SD)	41.5 (10.6)	46.1 (10.4)	0.2
N (SD) previous depressive episodes	6.3 (6.2)	4.4 (4.3)	0.44
Duration of current episode, months (SD)	9.2 (9.2)	17.4 (15.8)	0.09
Age of depression onset, year (SD)	23.5 (12.2)	29.6 (11.7)	0.15
Treatment resistant depression, n (%)	7 (41)	7 (35)	0.7
Benzodiazepine-use, n (%)	6 (35)	4 (20)	0.3
HAMD-21, mean (SD)	27 (5.7)	25.6 (5.8)	0.5
BDI, mean (SD)	34 (8.2)	30.8 (7.4)	0.25
ISI, ms (SD)	4088 (744)	3957 (913)	0.64

HDRS-21, Hamilton Depression Rating Score, 21-items; BDI, Beck Depression Inventory, ISI, interstimulus interval (from the PASAT test). Values represent mean (standard deviation) for continuous variables and number (%) of cases for categorical variables.

Table 2. Depression scores during the trial.

	Intention-to-treat				Completers			
	n	Sham tDCS + CCT	Active tDCS + CCT	p	n	Sham tDCS + CCT	Active tDCS + CCT	p
HDRS-21								
Baseline	17 / 20	27 (5.7)	26 (5.8)	0.5	17 / 20	27 (5.7)	26 (5.8)	0.5
Week 2	17 / 20	20 (9)	20 (9.8)	0.91	14 / 19	19 (10)	20 (10)	0.89
Week 4	17 / 20	20 (8.7)	19 (9.3)	0.71	7 / 13	20 (10)	16 (8)	0.28
Responders (week 4)	--	4 (23)	5 (25)	0.9	--	1 (14)	5 (38)	0.26
Remitters (week 4)	--	2 (11)	1 (5)	0.4	--	1 (14)	1 (7)	0.64
BDI								
Baseline	15 / 18	34 (8)	31 (7.5)	0.25	15 / 18	34 (8)	31 (7.5)	0.25
Week 2	15 / 18	23 (12)	23 (12)	0.97	13 / 17	22 (13)	21 (11)	0.82
Week 4	15 / 18	24 (11.4)	21 (10.3)	0.54	10/12	24 (12)	20 (10)	0.35

HDRS-21, Hamilton Depression Rating Score, 21-items; BDI, Beck Depression Inventory. Values represent mean (standard deviation) scores except for responders and remitters, in which the values represent number (%) of cases.

Table 3. Analysis of predictors of response.

Variable	F	Degrees of freedom	p
Age	5.82	1,34	0.02
Gender	0.52	1,34	0.47
Number of depressive episodes	1.23	1,34	0.28
Duration of current episode	0.01	1,34	0.98
Age of depression onset	1.24	1,34	0.27
Treatment-resistant depression	0.07	1,34	0.78
Benzodiazepine use	1.78	1,34	0.2
PASAT improvement	2.15	1,34	0.15
Baseline ISI	0.08	1,34	0.78

ISI, inter-stimulus interval. PASAT, Paced Auditory Serial Addition Task.

Figure 1. Flow chart of the study.

Figure 2. Depression improvement (y axis, higher scores indicating improvement) vs. Cognitive task ("PASAT") improvement (x axis, higher scores indicate better performance) in patients younger and older than 50 years-old. In younger patients, active vs. sham tDCS present similar scores regardless of PASAT improvement. In older patients, active vs. sham tDCS are different according to PASAT improvement, with greater depression improvement in those who presented better performance in the task, for the active tDCS group. Error bars indicate standard deviation.

Figure 1.

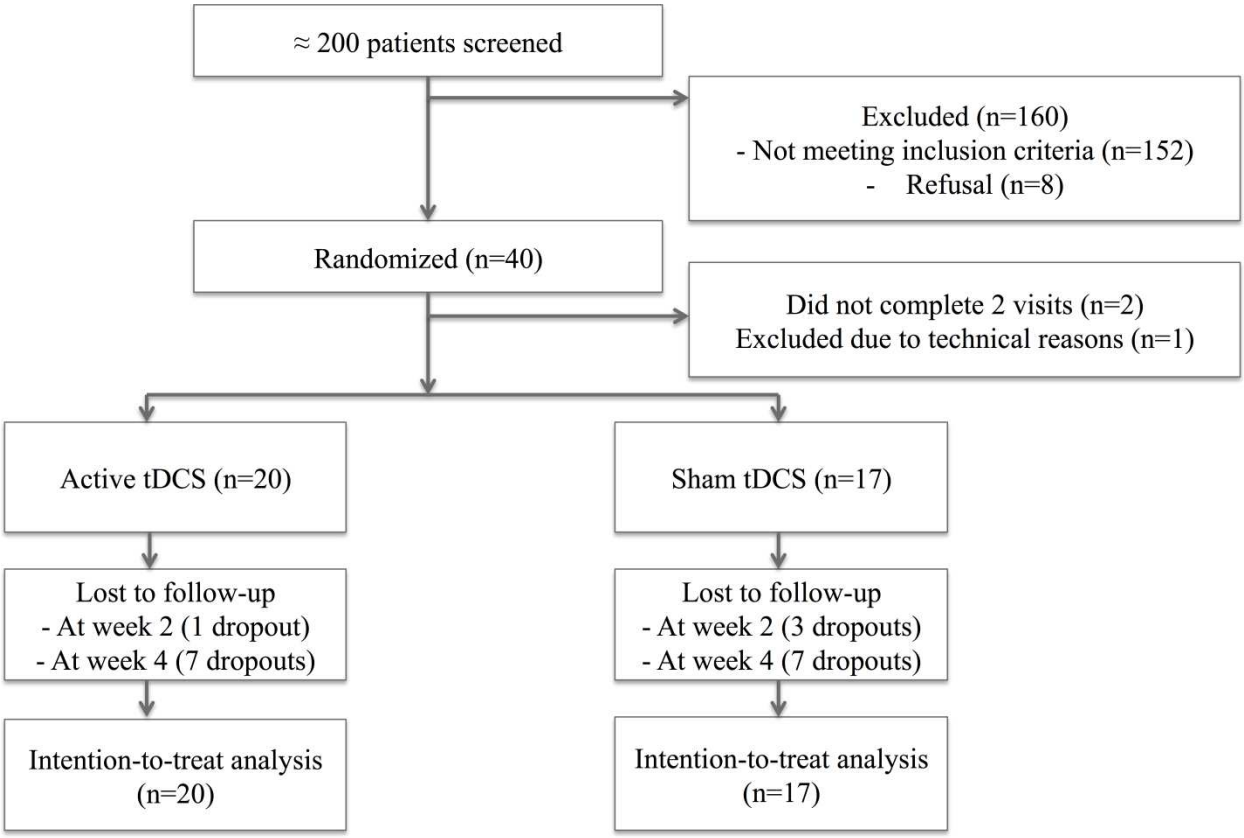
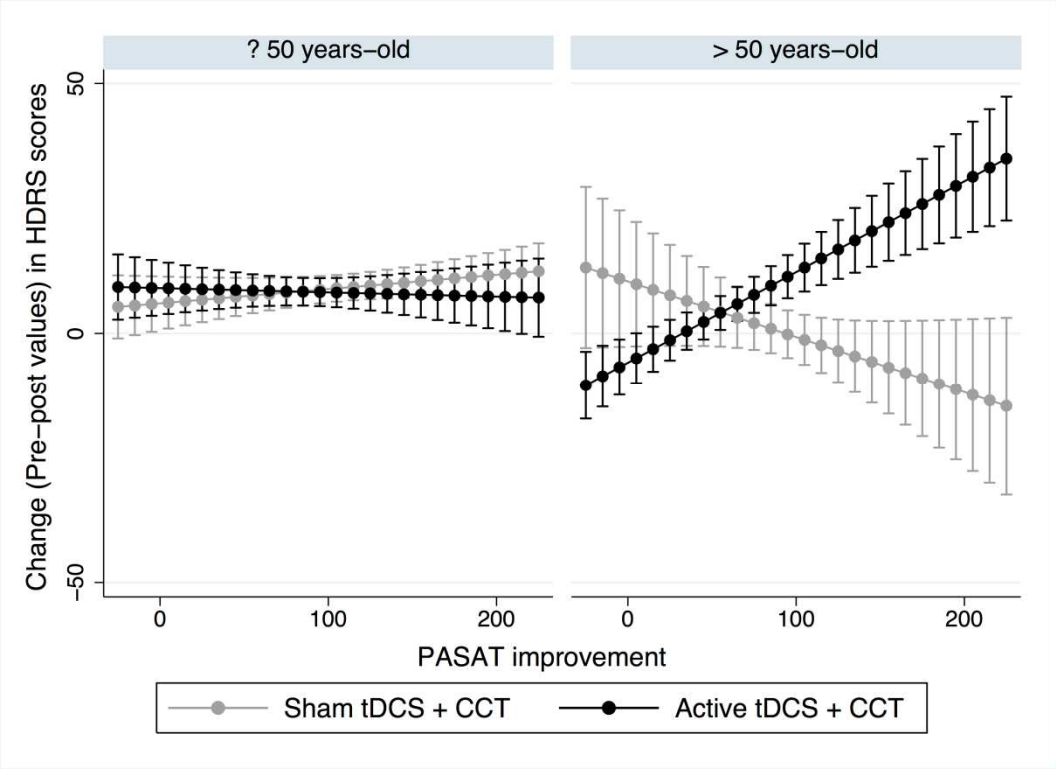

≈ 200 patients screened
Excluded (n=160)
- Not meeting inclusion criteria (n=152)
- Refusal (n=8)
Randomized (n=40)
Did not complete 2 visits (n=2)
Excluded due to technical reasons (n=1)
Active tDCS (n=20)
Sham tDCS (n=17)
Lost to follow-up
- At week 2 (1 dropout)
- At week 4 (7 dropouts)
Lost to follow-up
- At week 2 (3 dropouts)
- At week 4 (7 dropouts)
Intention-to-treat analysis
(n=20)
Intention-to-treat analysis
(n=17)

Figure 2.


? 50 years–old
> 50 years–old
Change (Pre–post values) in HDRS scores
50
0
–50
0
100
200
0
100
200
PASAT improvement
Sham tDCS + CCT
Active tDCS + CCT