Brain Stimulation 12 (2019) 1197–1204

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: http://www.journals.elsevier.com/brain-stimulation

Antidepressant effects of tDCS are associated with prefrontal gray matter volumes at baseline: Evidence from the ELECT-TDCS trial

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ARTICLE INFO

Article history:
Received 8 December 2018
Received in revised form
10 April 2019
Accepted 5 May 2019
Available online 8 May 2019

Keywords:
Antidepressant response
Magnetic resonance imaging
Major depressive disorder
Noninvasive brain stimulation
Structural neuroanatomy
Transcranial direct current stimulation

ABSTRACT

Background: Transcranial direct current stimulation (tDCS) is a promising intervention for major depression. However, its clinical effects are heterogeneous. We investigated, in a subsample of the randomized, clinical trial Escitalopram versus Electrical Direct Current Therapy for Depression Study (ELECT-TDCS), whether the volumes of left and right prefrontal cortex (PFC) and anterior cingulate cortex (ACC) were associated with prefrontal tDCS response.

Methods: Baseline structural T1 weighted MRI data were analyzed from 52 patients (15 males). Patients were randomized to the following conditions: escitalopram 20 mg/day, bifrontal tDCS (2 mA, 30min, 22 sessions), or placebo. Antidepressant outcomes were assessed over a treatment period of 10 weeks. Voxel-based gray matter volumes of PFC and ACC were determined using state-of-the-art parcellation approaches.

Results: According to our *a priori* hypothesis, in the left dorsal PFC, larger gray matter volumes were associated with depression improvement in the tDCS group ($n = 15$) compared to sham ($n = 21$) (Cohen's $d = 0.3$, 95% confidence interval [0.01; 0.6], $p = 0.04$). Neither right PFC nor ACC volumes were associated with depression improvement. Exploratory analyses of distinct PFC subregions were performed, but no area was associated with tDCS response after correction for multiple comparisons.

Conclusion: Left PFC baseline gray matter volume was associated with tDCS antidepressant effects. This brain region and its subdivisions should be investigated further as a potential neurobiological predictor for prefrontal tDCS treatment in depression and might be correlated with tDCS antidepressant mechanisms of action.

Abbreviations: ACC, anterior cingulate cortex; BA, Brodmann area; DLPFC, dorsolateral prefrontal cortex; ECT, electroconvulsive therapy; ELECT-TDCS, Escitalopram versus Electrical Direct-Current Therapy for Depression; HDRS-17, Hamilton Depression Rating Scale; MDD, major depression; NTBS, noninvasive transcranial brain stimulation; OLE, Omni-Lateral-Electrode; pACC, pregenual anterior cingulate cortex; PFC, prefrontal cortex; RCT, randomized controlled trial; ROI, region of interest; rTMS, repetitive transcranial magnetic stimulation; sgACC, subgenual anterior cingulate cortex; tDCS, transcranial direct current stimulation.

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https://doi.org/10.1016/j.brs.2019.05.006
1935-861X/

Introduction

Major depressive disorder (MDD) is a prevalent, morbid disease [1]. Pharmacological options are limited, as almost 30% of patients fail to achieve remission after four or more interventions [2] and some manifest only short-term benefits [3]. This highlights the need for novel treatment options, such as transcranial direct current stimulation (tDCS) [4]. The technique is based on the application of low, direct currents via electrodes placed over the scalp to change cortical activity according to the parameters of stimulation [5]. For MDD, tDCS electrodes are applied over prefrontal cortex (PFC) regions considering repetitive transcranial magnetic stimulation (rTMS) antidepressant efficacy over this region [6] and the PFC dysfunction observed in this disorder [7].

Although several randomized controlled clinical trials (RCT) on tDCS for MDD were performed, results have been heterogeneous. For instance, several studies including a large, multicentric RCT failed to show tDCS efficacy over placebo [8,9]. In our Escitalopram versus Electrical Current Therapy for Treating Depression Clinical Study (ELECT-TDCS) trial, a non-inferiority, sham-controlled study, we found that, although superior to placebo, tDCS was not non-inferior to escitalopram [10]. Moreover, meta-analyses were able to demonstrate a moderate antidepressant effect of prefrontal tDCS [11,12].

Taken together, these findings suggest that tDCS may be effective for MDD but shall be optimized further – for instance by investigating putative neurobiological markers of response to prefrontal tDCS. Of potential biomarkers worth examining, MRI-based biomarkers are particularly promising for neuromodulation techniques as brain areas implicated in the pathophysiology of the disorder are stimulated – in other words, they are potential target candidates. In MDD, MRI-based meta-analyses found reductions in prefrontal gray matter volumes such as the bilateral anterior cingulate cortices (ACC), the limbic cortex, and the dorsolateral prefrontal cortex (DLPFC) [13–17]. In MDD patients who received pharmacotherapy, pre-treatment gray matter volumes of the ACC [18–21] and subregions of the PFC [19] predicted antidepressant response. Moreover, clinical improvement was associated with the increase of gray matter volumes in these regions [22,23]. For rTMS, for example, decreased global metabolism of left DLPFC and left ACC [24], or functional coupling between the DLPFC and ACC [25], predicted the antidepressant response.

However, associations of baseline MRI-based biomarkers and tDCS antidepressant effects have not been investigated to date [26]. This was investigated in a subsample of ELECT-TDCS. According to the available literature at study design [27], we hypothesized that the gray matter volumes of the left and right DLPFC and the ACC would be directly related to depression improvement in the tDCS vs. placebo groups. The study hypotheses were specified *a priori* in a study design publication [27] and in our study protocol [10]. We also explored other group comparisons and whether specific subregions of ACC and DLPFC, based on novel neuroanatomical parcellations published after ELECT-TDCS was initiated, were associated with tDCS antidepressant response.

Methods and materials

Overview

ELECT-TDCS is a single-center, randomized, double-controlled, and double-blinded non-inferiority trial; the full study design and results are described in detail elsewhere [10,27]. In this ancillary study of ELECT-TDCS, a subsample who received MRI scans at baseline was investigated [10]. Patients with MDD were recruited from the University Hospital (University of São Paulo, São Paulo) and computer-based randomized to three groups: active tDCS plus placebo medication (tDCS group), sham tDCS plus escitalopram (escitalopram group), and sham tDCS plus placebo medication (placebo group). Randomization was performed in a 3:3:2 ratio, corresponding to the groups tDCS, escitalopram, and placebo, respectively, using randomly permuted blocks with random block sizes. The randomization scheme was generated using the Web site www.randomization.com that employs the Wichmann-Hill random number generator.

The study is in accordance with the Declaration of Helsinki and was approved by the Local and National Ethics Committee (CAAE:10173712.3.0000.0076); it is registered in clinicaltrials.gov (NCT01894815: https://clinicaltrials.gov/ct2/show/NCT01894815?term=NCT01894815&rank=1). Written, informed content was obtained from all patients before inclusion. Patients were enrolled between October 2013 and July 2016.

Patients

We included patients with MDD according to the Diagnostic Statistical Manual of Mental Disorder, fifth edition (DSM-5) according to the following inclusion criteria: $\geq$ 17 points on the Hamilton Depression Rating Scale (HDRS-17), a low risk of suicide, at least 8 years of schooling (to ensure sufficient skills in reading and writing and the ability to give informed consent), and adherence to study protocol. Exclusion criteria were bipolar disorder, brain injury, pregnancy, specific contraindications to tDCS (e.g., cranial plates), current or previous escitalopram use, and previous or concomitant participation in other tDCS trials. Patients with anxiety disorders as comorbidity were not excluded. Trained psychiatrists and psychologists, blinded to the assigned treatment, performed the clinical assessments.

Patients under antidepressant therapy underwent drug washout and remained antidepressant free for at least 5 drug half-lives. Benzodiazepines were allowed up to 20 mg/day diazepam-equivalent.

Interventions

The patients underwent 10 weeks of prefrontal tDCS (1×1 tDCS-CT, SoterixMedical, New York, NY) – 3 weeks of daily tDCS, except the weekends, and 7 weeks of weekly tDCS – resulting in a total of 22 sessions. Anode and cathode electrodes were placed over the left and right DLPFC, respectively, using the "Omni-Lateral-Electrode" (OLE) system [28]. During active sessions, 2 mA direct current was administered for 30 min. During sham treatment, the current was turned off automatically after 30 s according to the randomization code.

Patients in the drug group received 10 mg/day of escitalopram (Reconter, Libbs Pharmaceutical Company, São Paulo, Brazil) during the first 3 weeks, and 20 mg/day thereafter. The placebo medication was visually indistinguishable, tasted exactly like the escitalopram pills and both were administered in the same bottles.

Magnetic resonance imaging

All images were acquired in 3 T MR system (Achieva, Philips Healthcare, Netherlands). Volumetric images were based on T1-weighted sequences using a 3D FFE pulse sequence with the following parameters: FOV $240 \times 240 \times 180$ mm^3, spatial resolution 1×1x1 mm^3, TR 7 ms, TE 3.2 ms, FA 8°, 180 sagittal slices. MR acquisitions were performed up to 8 days before baseline and were performed at the Department of Radiology (Hospital das Clínicas da Universidade de São Paulo, São Paulo) during the weekends.

We used FSL 5.0.10 (http://www.fmrib.ox.ac.uk/fsl/index.html), AFNI (Analyses of Functional Images, http://afni.nimh.nih.gov/afni)

and in-house scripts [29] for pre-processing steps [30]. Following quality check and after brain extraction, the T1-weighted images were segmented into gray matter, white matter, and cerebrospinal fluid using FAST [31]. After FLIRT and FNIRT, a linear and non-linear registration method [32], the images were warped into the MNI standard space. All data sets were deidentified by using patient-specific codes in the DICOM header information and the face was removed with the help of *pydeface* to guarantee the privacy of the patients. In-house scripts [33] and volumetric data are available under request.

Gray matter volume

According to our *a priori* hypothesis, a region-of-interest (ROI) based approach was applied to calculate the volumes of DLPFC and ACC. As the DLPFC cannot be located within the classical anatomical boundaries, we used the Sallet et al. atlas [34]. This atlas provides a parcellation of the dorsal frontal cortex based on functional and tractography data from a cross-species approach in humans and primates, and divides the dorsal frontal cortex into 10 subregions (clusters), which are attributed to Brodmann areas (BAs) and their later adaptations [35,36]. This atlas was chosen as it allows to identify ROIs in proximity of the dorsolateral PFC area, while incorporating anatomical and functional data equally. Although the Sallet et al. atlas also maps premotor areas, they were not included in our analyses as these areas were not previously specified in our hypothesis. Therefore, we calculated the volume of a dorsal PFC ROI, which includes only the anterior PFC regions and corresponds to BAs 8, 9, 10, and 46 (Fig. S1).

For the definition of the ACC ROI, we used the parcellation of the Brainnetome atlas (http://atlas.brainnetome.org/bnatlas.html), a whole-brain multimodal parcellation atlas based on anatomical, diffusion tensor imaging, resting state functional MRI connectivity, and behavioral datasets [37] (Fig. S2).

As significant effects in these hypotheses-driven regions were observed, we analyzed subregions of the PFC and ACC in an exploratory way to identify regions possibly driving these effects. In the PFC, we investigated 7 clusters according to Sallet et al. (2013): cluster 3 (corresponding to BA9), cluster 4 (BA10), cluster 5 (BA9/46D), cluster 6 (BA9/46 V), cluster 7 (BA46), cluster 8 (BA8A), and cluster 10 (BA8B). Moreover, two further group ROIs not initially proposed by Sallet et al. that include clusters 3, 4 and 5 (corresponding to BAs 9, 10 and 9/46D, i.e. "BA9,10,9/46D″) and clusters 6 and 7 (BAs 9/46 V and 46, i.e. "BA9/46 V,46") were analyzed to account for the non-focality of prefrontal tDCS (Fig. S1).

Considering the different roles of the subgenual (sgACC) and pregenual ACC (pACC) in predicting antidepressant response, particularly in rTMS literature [26,38–41], we further explored the volumes of these subregions, also using the sgACC ("A32sg") and pACC ("A32p") ROIs from the Brainnetome atlas (Fig. S2).

All gray matter volume calculations were corrected for the intracranial volumes between subjects.

Statistical analysis

We used R 3.4.3 [[42], https://www.R-project.org/], RStudio 1.1.383 [[43], http://www.rstudio.com/], and the package ggplot2 2.2.1 [44] to create line charts. We used the packages lme4 1.1–14 [45] and lmerTest 3.0–1 [46] to perform linear mixed effects analyses to explore which brain regions were associated with depression improvement. MRIcron was used to visualize ROIs as an overlay on the ch2better standard template [47].

The primary outcome was the HDRS-17 score evaluated at each time point as stated in the original study (baseline, 3, 6, 8, and 10 weeks, respectively). The primary investigated regions were the bilateral dorsal PFC and the bilateral ACC ROIs. To assess group differences, four separate linear mixed effects models were calculated for each one of these regions with the primary outcome (HDRS-17) as dependent variable; group, gray matter volume of ROI, time point, and their interaction were used as fixed variables, and individual intercepts and slopes as random effects (see supplemental material). Significant findings were only observed in the interaction of the three fixed variables. Hence, we further report values only based on this interaction. The group differences in ROI volume–outcome interactions were evaluated using the slope, Cohen's *d* (estimated from the model residual standard deviation) [48], their 95% confidence intervals, and significance levels. Cohen's *d* values of 0.2, 0.5, and 0.8 indicate small, medium, and large effect sizes, respectively. In addition, we report results from the same mixed effects model focused solely on the tDCS group. As these regions were hypotheses-driven, we did not apply a correction for multiple testings.

Finally, we exploratively investigated the volumes of subdivisions of the DLPFC and ACC applying the same models. This approach resulted in 11 additional models that were carried out for each hemisphere. We provide results of this exploratory analysis in the form of *uncorrected* results, as well as Bonferroni *corrected* p-values.

Results

Out of the original sample, 68 patients received MRI at baseline. The most important reasons for the omitted use of MRI were (1) the delayed start of the MRI collection, which only started after 30% of the sample had already been recruited, (2) patient refusal, as MRI collection was not obligatory for trial participation and occurred only at the weekends, and (3) lack of slots available for performing MRI up to 8 days before baseline. Other minor reasons included contraindications for MRI, the impossibility of performing MRIs during holidays, and technical reasons (for instance, MRI not available due to MRI maintenance).

Moreover, MRI scans of 16 patients were excluded after an initial quality check (absence of T1 anatomical sequences, abnormal anatomical findings, and poor quality due to head motion). Finally, MRI data of 52 patients were included, with 15, 16, and 21 patients in tDCS, escitalopram, and placebo groups, respectively.

Demographic and clinical characteristics of the 52 patients were distributed equally among the three treatment groups, with the exception for benzodiazepine use (Table 1). Volumes of MRI ROIs at baseline did not significantly differ between the three groups (Table 1). Mirroring the results of the main trial, our subgroup did not differ from the original sample, neither in most of the characteristics, nor in the outcomes (Table S1).

Hypotheses-driven regions

Prefrontal cortex

In the left PFC, larger gray matter volumes were associated with depression improvement in the tDCS compared to sham group (Cohen's $d = 0.3$, 95% confidence interval [0.01; 0.6], $p = 0.04$; Table S3, Fig. 1). Within the tDCS group, there was a trend for a direct association between PFC volume at baseline and further reduction of HDRS scores (factor $= 0.8 \pm 0.4$, $d = 0.5$, [-0.009; 1.0], $p = 0.055$).

In the right PFC, no significant difference between placebo vs tDCS ($d = 0.1$ [-0.1,0.4], $p = 0.4$; tDCS only: $d = 0.2$ [-0.3,0.7], $p = 0.4$) was observed.

Anterior cingulate cortex

In the left ACC, no significant differences between placebo vs tDCS group on depression improvement were found ($d = -0.01$

Table 1
Patient group characteristics.

n	tDCS	Escitalopram	Placebo	p
	15	16	21	
Males (%)	7 (46.7)	3 (18.8)	5 (23.8)	0.2
Age	43.8 ± 11.2	42.0 ± 13.4	36.4 ± 10.9	0.1
HDRS[a] at baseline	21.8 ± 4.1	21.2 ± 3.4	21.7 ± 3.8	0.9
HDRS[a] at week 3	14.6 ± 6.2	10.9 ± 3.9	12.7 ± 5.8	0.2
HDRS[a] at week 6	13.8 ± 6.8	11.5 ± 3.5	11.9 ± 5.1	0.4
HDRS[a] at week 8	10.2 ± 7.7	9.6 ± 3.5	14.4 ± 8.2	0.08
HDRS[a] at week 10	14.6 ± 9.9	11.1 ± 4.7	15.8 ± 8.3	0.2
Total HDRS[a] improvement	7.2 ± 11.3	10.1 ± 5.6	5.8 ± 8.5	0.3
Characteristics of current depressive episode[b]				
- Chronic (%)	6 (40.0)	7 (43.8)	11 (52.4)	0.7
- Severe (%)	3 (20.0)	3 (18.8)	5 (23.8)	0.9
- Recurrent (%)	10 (66.7)	14 (87.5)	12 (57.1)	0.1
- Resistant (%)	4 (26.7)	3 (18.8)	5 (23.8)	0.9
Years of schooling	13.8 ± 4.8	13.3 ± 5.2	15.2 ± 4.2	0.4
Benzodiazepine use (%)	5 (33.3)	0 (0.0)	6 (28.6)	0.04
Low income (%)	10 (66.7)	13 (81.2)	14 (66.7)	0.6
BMI	26.8 ± 3.4	28.0 ± 7.1	25.9 ± 5.0	0.5
Gray matter volumes (cm^3) at baseline				
Left PFC	24.3 ± 1.5	23.2 ± 2.4	23.8 ± 2.3	0.38
Right PFC	24.4 ± 1.4	23.5 ± 2.4	23.9 ± 2.1	0.53
Left ACC	7.2 ± 0.7	6.9 ± 0.9	7.3 ± 0.8	0.36
Right ACC	6.1 ± 0.5	5.7 ± 0.7	6.0 ± 0.7	0.15

Distribution of characteristics, clinical outcomes, and baseline gray matter volumes of the four main regions among intervention groups. Values are displayed as count and percentage for categorical variables, visible by (%), or mean ± standard deviation. Differences between groups were tested using ANOVA or chi-square test.
PFC = prefrontal cortex, ACC = anterior cingulate cortex.
[a] Scores on the 17-item Hamilton Depression Rating Scale (HDRS-17; 0 to 52, the higher the more severe depressed).
[b] These variables include characteristics of current episode: chronicity (≥12-month duration), severity (a score of 24 or more on HDRS-17), recurrence (>3 previous episodes), and treatment resistance (≥1 treatment failure in the current episode or >4 treatment failures over the lifetime).

[-0.3,0.3], p = 0.9; tDCS only: $d = 0.02$ [-0.5,0.5], p = 0.9). Accordingly, there were also no differences observed in the right ACC (d = 0.2 [-0.07,0.5], p = 0.1; tDCS only: $d = 0.4$ [-0.09,0.9], p = 0.1; Table S3).

Exploratory outcomes

Prefrontal cortex

For placebo vs tDCS, left BA9,10,9/46D ($d = 0.3$ [0.04; 0.6], $p_{uncorr} = 0.03$, $p_{corr} = 0.6$), left BA10 ($d = 0.3$ [0.04; 0.6], $p_{uncorr} = 0.02$, $p_{corr} = 0.5$), and right BA9 ($d = 0.3$ [0.03; 0.6], $p_{uncorr} = 0.03$, $p_{corr} = 0.7$, Fig. 1) were associated with depression improvement. A trend was observed for left BA46 ($d = 0.2$ [-0.04; 0.5], p = 0.09) (Table S3, Fig. S3). Small effect sizes were found for these regions (Fig. 2). For other regions, including the right hemisphere, placebo vs tDCS was not significant.

The comparisons of escitalopram vs tDCS showed trends only for the left BA9,10,9/46D ($d = 0.2$ [-0.03; 0.5], p = 0.08), left BA10 ($d = 0.2$ [-0.03; 0.5], p = 0.08), and right BA9 ($d = 0.2$ [-0.03; 0.5], p = 0.08) (Table S3, Fig. S3). No significant effects were detected for placebo vs escitalopram (Table S4).

In addition, we found no differences between the other groups (placebo vs escitalopram) in the left ($d = 0.09$ [-0.2; 0.4], p = 0.5) nor the right PFC ($d = 0.05$ [-0.2; 0.3], p = 0.7; Table S4).

Anterior cingulate cortex

No significant differences were observed for the left or right sgACC and pACC for any pairwise comparisons (Table S3&S4, Fig. S4).

Discussion

In this ancillary MRI study from the ELECT-TDCS trial [10], we investigated whether the baseline volumes of DLPFC and ACC, prefrontal brain regions that are associated with MDD pathophysiology and putatively involved in the mechanisms of action of tDCS [27], were associated with antidepressant improvement in 52 depressed subjects receiving tDCS, escitalopram, or placebo. As predicted *a priori*, our findings and visual evaluations strongly suggest a direct association between left PFC gray matter volume and tDCS antidepressant effects.

The left PFC has been associated with MDD pathophysiology in the past [19,20,22,49,50] and is general target region for NTBS (rTMS and tDCS) in MDD [6,11,51]. Some studies suggested that left PFC is relatively hypoactive compared to the right PFC, explaining why this region is targeted [7,52], but this was not confirmed by others [53].

Moreover, as "conventional" tDCS provides non-focal stimulation, large prefrontal areas are stimulated, and it is unclear whether the antidepressant effect is carried by the whole PFC region, its subregions, or more complex network interactions. For rTMS in MDD, the quality of DLPFC targeting, e.g. by applying neuronavigation [54], or more lateral and anterior targeting [55] predicted the antidepressant response to rTMS. In particular the functional connectivity between DLPFC target regions and the ACC has been discussed as mediator of this predictive effects [25,41], supporting the role of the DLPFC specifically. For prefrontal tDCS, very recent studies show that its effects on neurocognitive performance in healthy subjects and on symptoms in MDD patients may depend on structural (i.e. cortical thickness) or functional characteristics of DLPFC regions [70,71].

The left dors*omedial* PFC, a region that provides hub connections to several functional networks, is impaired in MDD [56] and should be discussed as target engagement candidate mediating antidepressant effects of tDCS as well. Indeed, recent rTMS trials in MDD have stimulated the left dorsomedial cortex, with positive results [57]. In fact, a recent electric field modeling study that simulated the electrode positioning used in ELECT-TDCS showed peak current densities in lateral and medial PFC areas [58].

Furthermore, in past modeling studies [64] and intracranial recordings [65,66], administration of 2 mA currents, as used in our study, led to different individual electric field intensities. Inter-individual differences in gray matter structural anatomy [67,68] could have contributed to different responses between individuals after prefrontal tDCS. Thus, it is possible that brain volume and tDCS-induced currents in the brain are correlated and that continuous treatment over weeks with higher electrical charge contributes to larger clinical responses. In future studies, individual dose-response relationships at targets for therapeutic effects should be further elaborated. The standard use of 1 mA or 2 mA should be overcome, favoring individual intensity tailoring based on neuroanatomical and functional findings. Possibly, intensities higher than 2 mA might produce greater clinical effects in MDD that shows a reduced gray matter volume in the PFC [18–21].

Our exploratory investigations suggest a direct association between antidepressant effects of tDCS and the volume of several subregions of the PFC, particularly a smaller area corresponding to BAs 9, 10 and 46 in the left hemisphere, a region corresponding to left BA 10 and another region in the right hemisphere that corresponds to BA9. These regions were located medially to the "classic" DLPFC location and potentially underline the role of medial regions for tDCS antidepressant effects, as stated in the previous paragraph. On the other hand, our results suggest also an involvement of the right PFC where, in the present study, cathodal tDCS was applied. Nonetheless, these exploratory investigations were no longer

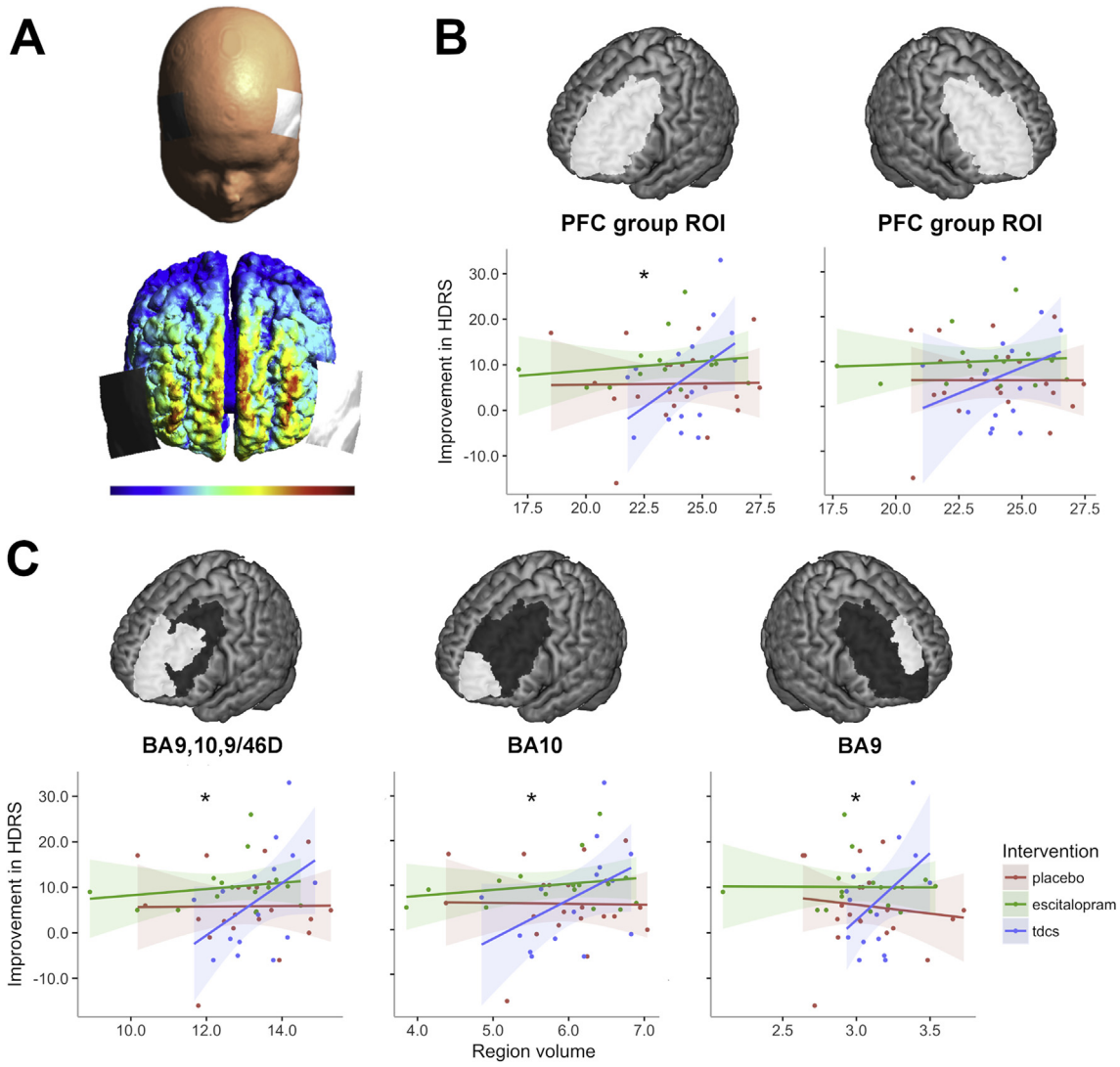

Fig. 1. Effect of prefrontal cortex volume on depression improvement

Figure 1 A illustrates the location of the stimulation electrodes and the distribution of the electric field on a study-specific group template (EEG-based F5–F6 location was used as approximation of the originally used Omni-Lateral-Electrode [OLE] position, as they show good accordance [28] and can be directly implemented in the electric field modeling software SIMNIBS [69]).

B&C show the outcomes according to the *a priori* hypothesis and the significant findings from the exploratory analyses, respectively. Shown are locations of the prefrontal cortex (PFC) regions when investigating the interactions of region-of-interest (ROI) volumes (cm^3) with depression improvement from baseline to week 10 on the Hamilton Depression Rating Scale (HDRS). A direct correlation was observed in the active tDCS group (blue) in opposition to the two control groups (placebo shown in red, escitalopram in green). Lines show regression graphs with 95% confidence intervals. The star (*) indicates statistical significance for comparison of tDCS vs placebo group. BA = Brodmann area. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

significant after Bonferroni corrections and hence, should be understood as exploratory for further hypothesis generation in future studies.

Contrary to our initial hypothesis, ACC volumes were not associated with the antidepressant response, whereas a recent meta-analysis showed that ACC volume was a robust predictor of the clinical response to antidepressant medication [18–20,26,59]. A possible explanation is that tDCS electrodes are directly placed over the scalp, hence rather modulating cortex regions at the convexity such as the DLPFC than inner cortical structures such as the ACC, which can be more properly targeted via invasive methods such as deep brain stimulation [60]. In addition, previous studies have shown that antidepressant effects may be related to functional or metabolic states of the ACC, rather than its structure [25,38–40,59,61] and future studies should better investigate the state effects rather than accept it as a trait.

Our findings cannot be presently compared with other tDCS studies in MDD as, to the best of our knowledge, this is the first controlled clinical trial investigating MRI parameters associated with antidepressant response to prefrontal tDCS. In fact, our results are relatively novel also considering other antidepressant therapies, as placebo-controlled trials investigating structural predictors of antidepressant response are insufficient and results from studies investigating different therapeutics are heterogeneous [26]. Short and long-term response to fluoxetine, for example, was associated with larger hippocampus volumes [62,63] and faster response was associated with larger volumes in several areas, such as the ACC, insula, or the left PFC [20]. In

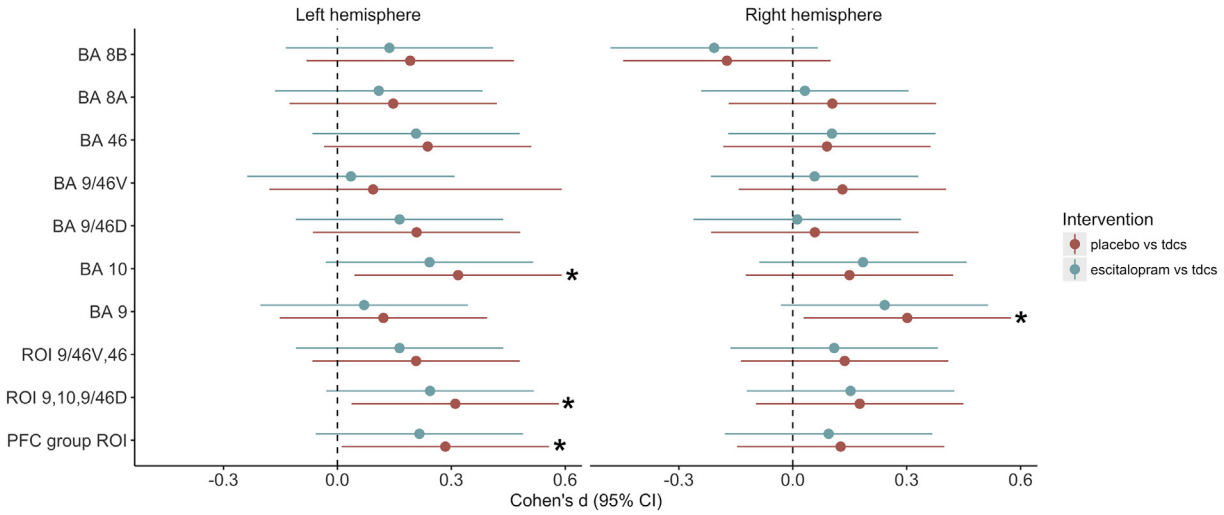

Fig. 2. Effect size of group differences. This figure shows the Cohen's *d* and the 95% confidence intervals of the difference of interactions of prefrontal cortex (PFC) volumes with depression improvement between the tDCS group and placebo group, and escitalopram group, respectively. Cohen's *d* values of 0.2, 0.5, and 0.8 indicate small, medium, and large effects, respectively. The star indicates statistical significance. BA = Brodmann area, ROI = region of interest.

our sub-sample, no association between volumes and response to escitalopram were observed. Nonetheless, as a direct association between PFC volume and tDCS response was observed, relatively small PFC volumes could be indicative of preferring escitalopram over tDCS. However, we did not identify PFC volume as a predictor of differential response between tDCS and escitalopram.

Limitations and strengths

Some study limitations should be underscored. First, for several reasons, MRI scans could only be obtained in a subsample of the original trial. Therefore, some non-statistically significant findings might be false-negative results owing to low statistical power. Nonetheless, our results should be regarded as exploratory and hypothesis-driven for future trials. Second, other neuroimaging approaches, such as resting-state functional MRI connectivity, or individual distributions of electric fields, were not explored in the present study. Although resting-state fMRI was collected at baseline, these data have not yet been analyzed and will be explored further.

Study strengths include: first, our hypotheses were defined *a priori*, enhancing the validity of our findings; second, the study employed a parallel, three-arm design, allowing comparisons of tDCS with both placebo and escitalopram; third, patients were not using any treatment at the beginning of the study, which could have been a potential source of confounding, and; fourth, we used novel approaches for defining PFC and ACC subregions, as the ROIs were based on the Sallet et al. [34] and Brainnetome atlases [37], which delimit brain regions based on anatomical and functional aspects, in contrast to standard atlases included in neuroimaging software packages.

Conclusion

Our findings provide a neurobiological underpinning for antidepressant effects of prefrontal tDCS in patients with MDD, as we showed that the response was associated with the volume of a left-sided PFC region at baseline for tDCS, but not escitalopram and placebo. Nonetheless, our results should be regarded as exploratory and hypothesis-generating for further study trials. In addition, our findings provided first evidence that baseline MRI measurements may be used for identifying patient groups that benefit from tDCS, which can be useful in future studies investigating multimodal predictors of tDCS response.

Funding

ELECT-TDCS funding: São Paulo Research State Foundation (FAPESP) and others. Registration: ClinicalTrials.gov NCT01894815.

Acknowledgments & DISCLOSURES

This study was primarily supported by a São Paulo Research State Foundation (FAPESP) grant (2012/20911-5). ARB is a recipient of a CAPES/Alexander von Humboldt fellowship award for experienced researchers and receives speakers' fee from Neurocademy GmBH (Munich, Germany). The Laboratory of Neuroscience receives financial support from the Beneficent Association Alzira Denise Hertzog da Silva and the CAPES / INCT program "National Institute of Biomarkers in Psychiatry" (INBioN). FP is a member of the European Scientific Advisory Board of Brainsway Inc., Jerusalem, Israel, and has received speaker's honoraria from Mag&More GmbH and the neuroCare Group. His lab has received support with equipment from neuroConn GmbH, Ilmenau, Germany, and Mag&More GmbH and Brainsway Inc., Jerusalem, Israel. This work was also supported by the German Center for Brain Stimulation (GCBS) research consortium (Work Package 5) [grant number 01EE1403E], funded by the Federal Ministry of Education and Research (BMBF). The work of LB is part of a PhD/residency program of the Ludwig-Maximilians University (LMU) and the International Max Planck Research School for Translational Psychiatry (IMPRS-TP) financially supported by the Else Kröner Fresenius Foundation. PVB, FD, GB, EAJ, IMB, PAL, WG, SG, and DK reported no biomedical financial interests or potential conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2019.05.006.

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