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Prefrontal resting-state connectivity and antidepressant response: no associations in the ELECT-TDCS trial

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Abstract

Functional and structural MRI of prefrontal cortex (PFC) may provide putative biomarkers for predicting the treatment response to transcranial direct current stimulation (tDCS) in depression. A recent MRI study from ELECT-TDCS (Escitalopram versus Electrical Direct-Current Theror Depression Study) showed that depression improvement after tDCS was associated with gray matter volumes of PFC subregions. Based thereon, we investigated whether antidepressant effects of tDCS are similarly associated with baseline resting-state functional connectivity (rsFC). A subgroup of 51 patients underwent baseline rsFC-MRI. All patients of ELECT-TDCS were randomized to three treatment arms for 10 weeks (anodal-left, cathodal-right PFC tDCS plus placebo medication; escitalopram 10 mg/day for 3 weeks and 20 mg/day thereafter plus sham tDCS; and placebo medication plus sham tDCS). RsFC was calculated for various PFC regions and analyzed in relation to the individual antidepressant response. There was no significant association between baseline PFC connectivity of essential structural regions, nor any other PFC regions (after correction for multiple comparisons) and patients' individual antidepressant response. This study did not reveal an association between antidepressants effects of tDCS and baseline rsFC, unlike the gray matter volume findings. Thus, the antidepressant effects of tDCS may be differentially related to structural and functional MRI measurements.

Keywords Antidepressant response \cdot Resting state functional connectivity (rsFC-MRI) \cdot Major depressive disorder (MDD) \cdot Non-invasive transcranial brain stimulation (NTBS) \cdot Prefrontal cortex \cdot Transcranial direct current stimulation (tDCS)

Abbreviations

ACC	Anterior cingulate cortex
BA	Brodmann area
DMN	Default mode network
MPFC	Medial prefrontal cortex
DLPFC	Dorsal lateral prefrontal cortex
ELECT-TDCS	Escitalopram versus Electrical direct-
	current therapy for depression
HDRS-17	Hamilton depression rating scale

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NA	Negative affect
PANAS	Positive and negative affect scale
PA	Positive affect
PCC	Posterior cingulate cortex
PFC	Prefrontal cortex
ROI	Region of interest
rsFC	Resting state functional connectivity
TMS	Repetitive transcranial magnetic
	stimulation
tDCS	Transcranial direct current stimulation

Introduction

MRI derived resting-state functional connectivity (rsFC) is a promising approach for subtyping major depressive disorder (MDD) and the antidepressant response to several therapies [for reviews, consider 1–7]. A particular rsFC network associated with MDD is the default mode network (DMN), comprising the ventral and medial prefrontal (MPFC), the posterior cingulate (PCC) and lateral parietal cortices, [8–10]. Connectivity of regions of the DMN, such as the prefrontal cortex (PFC), the MPFC, and the dorsal lateral PFC (DLPFC), was associated with the depressive episode [2, 3, 11] and a marker of treatment response in depression, either to medication and/or psychotherapy [4, 12–15], electroconvulsive therapy [16–19], or transcranial magnetic stimulation (TMS) [20–24].

Transcranial direct current stimulation (tDCS) is a noninvasive neuromodulatory brain stimulation method that has been increasingly applied since the 2000s [25]. It is hypothesized to modify resting membrane potentials leading to excitatory and inhibitory effects on underlying brain regions [25, 26]. Clinical outcomes of prefrontal tDCS as add-on or monotherapy for depression are promising but heterogeneous [27–33]. This comes partially from heterogeneous treatment protocols in terms of numbers of sessions and treatment periods [33]; however, individual factors may also contribute to this variance.

One factor that may explain heterogeneous tDCS responses is the gray matter morphology of the tDCS target region, the left PFC, as was shown in our earlier complementary analysis of baseline MRI data from the Escitalopram versus Electrical Direct-Current Therapy for Depression (ELECT-TDCS) trial by revealing a positive correlation between gray matter volumes of PFC subregions and the antidepressant response to tDCS when compared to placebo [34]. Similar associations of cortical thickness in this region and tDCS effects on cognition were found in a study applying a decision-making paradigm [35]. This relationship between structural morphology and tDCS effects could be explained by the fact that the intensity of the electric current induced by tDCS at the cortical level depends on the individual brain structure and conductivity of the respective tissues including cerebrospinal fluid and skull [36, 37]. Thus, the variation of these factors could theoretically explain a variation of behavioral effects.

As tDCS was shown to modulate rsFC of the DMN and frontal-parietal networks, involving regions in the PFC [38–40] and task activation of the left DLPFC, with the latter being suggested as a biomarker of antidepressant response following tDCS combined with psychotherapy [41], modulation of rsFC in the PFC and associated networks is being considered as a major mechanism behind tDCS effects. However, direct tDCS effects on rsFC show high interindividual variability [42], therefore there is a need to further investigate tDCS effects based on baseline rsFC among patients with MDD. Furthermore, no study has yet investigated the relationship of PFC's structural anatomy and rsFC with regards to the clinical outcome of depressed patients in the same sample, in particular one comparable to that from the ELECT-TDCS trial, which included a control group receiving sham tDCS and placebo medication. The results of our first ancillary study of MRI data from the ELECT-TDCS trial identified mainly the left PFC and in addition three subregions of the left and right PFC that were associated with tDCS response in terms of baseline gray matter volumes [34]. TDCS response was evaluated with changes in the Hamilton Depression Rating Scale (HDRS-17), which showed superior effects of tDCS over placebo in the main trial [43]. Here, we investigate whether baseline rsFC-MRI in these four a priori defined structural regions is associated with the antidepressant response to tDCS [34]. We then performed exploratory analyses of the full parcellation of the dorsal PFC to identify associations of rsFC and the antidepressant response to tDCS [44]. Additional analyses investigated whether rsFC could predict changes to negative and positive affect.

Methods and materials

Study design

This is an ancillary study of ELECT-TDCS, a randomized, double-blinded, sham-controlled, non-inferiority trial conducted between October 2013 and July 2016 at the University Hospital of the University of São Paulo. The full study design and results are described in detail elsewhere [27, 43]; in short, patients with MDD were treated over 10 weeks with (1) active tDCS and placebo medication, (2) sham tDCS and escitalopram, or (3) sham tDCS plus placebo medication. The primary outcome failed to showed non-inferiority of tDCS treatment compared to escitalopram treatment, but a superior effect of tDCS compared to placebo was observed in the secondary analyses [27]. Following our previous study on the relationship between improvement of depression after tDCS and MRI-based PFC gray matter volumes at baseline [35], we investigated in the current study whether MRI-based rsFC shows a similar association for PFC subregions.

Ethics approval

ELECT-TDCS was designed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its subsequent amendments or comparable ethical standards and approved by the Local and National Ethics Committee (CAAE:10173712.3.0000.0076). All participants signed an informed consent form prior to inclusion (clinicaltrials.gov NCT01894815).

Patients

MDD was diagnosed according to the Diagnostic Statistical Manual of Mental Disorder, fifth edition (DSM-5). Patients with \geq 17 points on the HDRS-17, a low risk of suicide, at least 8 years of school education (to ensure sufficient skills in reading and writing and the ability to give informed consent), and those who were able to follow the study protocol were included. Exclusion criteria were bipolar disorder, brain injury, pregnancy, specific contraindications to tDCS (e.g., cranial plates), current or previous use of escitalopram, and past or concomitant participation in other tDCS trials. Patients with anxiety disorders as comorbidity were not excluded. A drug washout was performed in patients who received antidepressants before study onset, and a drug-free period of at least 5 drug half-lives was kept. Benzodiazepines were allowed up to 20 mg/day diazepam-equivalent.

Interventions

After randomization, active or sham tDCS were conducted with 22 sessions (3 weeks daily tDCS Monday to Friday, 7 weeks tDCS once a week) as required by the respective condition. Active tDCS was applied at 2 mA for 30 min using a 1×1 tDCS-CT device (SoterixMedical, New York, NY) with the "Omni-Lateral-Electrode" (OLE) electrode montage (anode over left, cathode over right DLPFC) [45]. The same set up and duration was used for sham tDCS, except that the current was automatically turned off after 30 s.

The drug comparison was escitalopram, an effective antidepressant drug [46] (Reconter, Libbs Pharmaceutical Company, São Paulo, Brazil). The initial dose of 10 mg/day escitalopram was administered for 3 weeks to reduce possible adverse effects and blinding breaking. After 3 weeks, escitalopram was titrated up to 20 mg/day in all patients. Placebo medication was administered over full 10 weeks; the placebo pill looked and tasted exactly like the escitalopram pills and they were distributed in same bottles.

MR acquisition and analysis

A 3 T MR system (Achieva, Philips Healthcare, Netherlands) was used. Structural images were acquired with a T1-weighted, 3D FFE pulse sequence (FOV $240 \times 240 \times 180$ mm³, spatial resolution $1 \times 1 \times 1$ mm³, TR 7 ms, TE 3.2 ms, FA 8°, 180 sagittal slices). Functional connectivity was acquired in resting state using an EPI single shot (FOV $240 \times 240 \times 144$ mm³, spatial resolution $3 \times 3x4$ mm³, TR 2000 ms, TE 30 ms, imaging matrix 80×79 , FA 80°, 32 slices, 200 volumes). MRI scans

performed at the Institute of Radiology (Hospital das Clínicas da Universidade de São Paulo, São Paulo) up to 8 days before the start of the trial.

We adhered to our automated pipelines for pre-processing and analysis of functional data sets, for details, see (https ://doi.org/10.5281/zenodo.3530897) [38, 42, 47-49]. Some of the crucial steps consisted of the automated conversion of DICOM format files into NIFTI under anonymization of the header information, relying on a patient-specific codes, and quality check using the XNAT app (https://doc.brain -stimulation.de/xnat-app-upload/). Low- and high-bandpass filtered (0.1-0.009 Hz), slice timed, and motion-corrected time series were transformed to subject-space using the linear and non-linear transformation from the FSL software package (FSL 5.0.10 (https://www.fmrib.ox.ac.uk/fsl/index .html). Motion and mean signal intensity of the white matter and cerebrospinal fluid were used as nuisance regressors before the residuals were exported using AFNI ((https ://afni.nimh.nih.gov/afni). These residuals were demeaned, averaged, and smoothed before averaged time series were extracted and correlated to the whole-brain residual masks. The regions of interest (ROIs) from which averaged time series were extracted (four in the primary analysis, ten in exploratory analysis) are described in the next paragraph. These correlation maps were then transformed into z-values using Fisher's R-to-Z transformation and thresholded into positive and negative correlations using thresholds of z > 0.3and z < -0.3, which equals a conservative significance level of $p \le 0.0027$ [49]. The z masks were transformed into MNI standard space and averaged z values as well as numbers of voxels over threshold of z = 0.3 were extracted from the respective ROIs (i.e. correlations within these ROIs, "regional rsFC"), as well as the whole brain mask (i.e. correlations of ROI to the whole brain, "global rsFC"). While z values give averaged and transformed correlation intensity, the numbers of activated voxels give the spatial extent of correlations, i.e. how many of those voxels in the regional mask show these suprathreshold correlations [49]. As we have shown the spatial extent of connectivity to be a reliable outcome interest [42, 49], this is what we used as the primary outcome of interest (for scatter plots showing numbers of activated voxels and z-values, see Suppl. Figure 3).

Regions in the prefrontal cortex

Our primary hypothesis was to investigate the rsFC in four left and right PFC regions, for which we have shown an association of gray matter volumes and reduction of HDRS-17 scores after 10 weeks of tDCS treatment in a previous ancillary study of the ELECT-TDCS trial [34]. We have chosen the ROI-based approach and the restriction to predefined hypotheses due to our limited sample size; more refined approaches, such as individual component analysis, would be even more vulnerable to this limitation of our study. The prefrontal cortex regions were defined according to a previously published parcellation of the dorsal frontal cortex based on functional and tractography data from a crossspecies approach in humans and primates by Sallet et al. [50]. It divides the dorsal frontal cortex into ten subregions (clusters), which are attributed to Brodmann areas (BAs) and their later adaptations [51, 52]. This atlas was chosen as it allows to identify regions in proximity of the dorsolateral PFC area, taking anatomical and functional data equally into account. The specific ROIs from the primary hypothesis were: the whole left dorsal prefrontal cortex region ("Left PFC") and its subregions-left BA9, BA10, and BA9/46D (anterior subregion), left BA10 (single anterior subregion), and right BA9 (medial single subregion, see supplemental information). In a second exploratory analysis, all 10 PFC regions from our previous analysis were analyzed [34] (see Suppl. Figure 1).

Analysis methods and outcome variables

Linear mixed-effects models (LMM) were calculated to identify the associations of baseline MRI-based rsFC ("regional" connectivity within the respective ROIs and "global" connectivity from ROI to the whole brain) and improvement of depression with treatment group and time point as fixed effects, and individual intercepts as random effects (R 3.6.0 [53, https://www.R-project.org/], RStudio 1.1.463 [54, https ://www.rstudio.com/], and packages ggplot2 3.2.1 [55], lme4 1.1-21 [56], and ImerTest 3.1-1 [57]) MRIcron was used for visualization [58]. The primary outcome, i.e. "improvement of depression" was defined as the change in HDRS-17 score; the secondary analyses were performed using the positive (PA) and negative affect (NA) symptom subscale from the Positive and Negative Affect Scale (PANAS) as dependent variables. There were five timepoints (week 0, 3, 6, 8, 10) for the HDRS-17 score and four timepoints (week 0, 3, 6, 10) for the PANAS. If for a specific time point, the outcome measure was missing, a linear model based on the baseline, age, and gender was generated to predict the missing value, following the procedures used in the original manuscript [27]. In terms of HDRS, up to 25% of the sample were missing values (13 cases per week 6 and 8, 10 cases per week 10), for PA and NA, these were 12 missing points at week 6 and 10 at week 10.

The association of rsFC and antidepressant response was considered significant if p < 0.05 for the comparison of tDCS vs. placebo group of the triple-interaction of treatment group, baseline rsFC, and time point, a model used in our previous work [34]. The group differences in rsFC–outcome interactions were then evaluated using the slope, Cohen's *d* (estimated from the model residual standard deviation) [59], their 95% confidence intervals, and significance levels. Correction for multiple comparisons was performed using Bonferroni corrections. Cohen's d values of 0.2, 0.5, and 0.8 indicate small, medium, and large effect sizes, respectively. A power analysis was not performed a-priori due to the ancillary nature of our investigation, yet we calculated post-hoc estimates of achievable effect sizes and sample sizes based on out model parameters (see supplementary information, Figs. 6 and 7).

Results

Patient characteristics and description of clinical outcomes in this subsample

Of the 245 patients included in the original ELECT-TDCS trial, patients were not included in the current analysis due to missing MRI baseline data a) due to the delayed start of the MRI collection after 30% of the sample had already been recruited, b) due to patient refusal, as MRI collection was not mandatory, c) patient exclusion due to MRI contraindications, d) or scheduling issues (such as lack of slots available for performing MRI up to 8 days before baseline, during holidays, or non-availability of the MRI scanner due to maintenance; n = 177). Furthermore, datasets were excluded due to low quality (high head motion, abnormal anatomy; n = 16). One dataset included in the previous structural analysis [34] did not include an EPI sequence, resulting in 51 datasets available for this rsFC analysis. Significant differences between treatment groups were seen for benzodiazepine use and anxiety levels, as well as the smoking status (Table 1). Reduction of depression scores were largest for the escitalopram group (n = 16), followed by the tDCS (n = 15) and placebo (n = 20) groups. For PA and NA, reductions were largest for tDCS group, followed by escitalopram and placebo groups (Table 1). Differences were not statistically significant.

Functional connectivity of essential structural regions and clinical improvement

In the four a-priori defined regions (left PFC; combined left BA9, BA10, BA9/46D; left BA10; and right BA9) the improvement of patients' HDRS-17 scores after 10 weeks of tDCS treatment was not associated with baseline rsFC (p > 0.05, global nor regional rsFC, Fig. 1, Table 2).

Further analysis showed that there was no association between baseline rsFC in these regions and changes in specific symptom domains such as PA and NA (Suppl. Figure 2, Table 3).

Table 1 Patient characteristics

	Escitalopram	tDCS	Placebo	р
n	16	15	20	
Age	42.31 (13.23)	43.33 (11.06)	36.90 (10.98)	.220
Males (%)	3 (18.8)	7 (46.7)	5 (25.0)	.200
Study years	14.20 (3.88)	14.64 (3.69)	15.42 (4.32)	.669
Smoking (%)	3 (18.8)	7 (46.7)	1 (5.3)	.014
Benzos (%)	0 (0.0)	5 (33.3)	6 (30.0)	.039
BMI	27.95 (7.12)	26.75 (3.36)	25.96 (5.16)	.556
Recurrent MD (%)	14 (87.5)	10 (66.7)	12 (60.0)	.183
Nr. of episodes	10.03 (12.48)	4.91 (2.23)	7.48 (13.67)	.448
Chronic (%)	7 (43.8)	6 (40.0)	10 (50.0)	.834
Melancholic (%)	24.81 (11.82)	27.33 (13.23)	24.90 (8.97)	.775
Anxiety (%)	8 (50.0)	9 (60.0)	4 (20.0)	.041
Response	4 (25.0)	9 (60.0)	7 (35.0)	.121
HDRS change	10.07 (5.63)	7.16 (11.26)	5.63 (8.64)	.322
PA change	3.94 (9.62)	6.53 (8.45)	3.65 (8.55)	.602
NA change	6.61 (9.18)	7.99 (8.66)	4.77 (7.73)	.535

Clinical characteristics of the treatment groups; if not specified, mean and standard deviation are shown, otherwise number and percentage (%). Differences between groups were tested using ANOVA or chisquare test

Recurrence was defined as >3 previous episodes; chronicity as \geq 12-month duration, response was defined as a >50% reduction from the baseline 17-item Hamilton Depression Rating Scale (HDRS-17) score; HDRS=scores on the HDRS-17 (scores range from 0 to 52); PA=positive affect scores and NA=negative affect scores on the Positive and Negative Affect Schedule (PANAS; scores range from 10 to 50). Change in depression/affect scores refers to the difference from week 10 to baseline, which is calculated so that a larger change corresponds to a larger improvement of depressive symptoms

Exploratory analyses

In the exploratory analyses, baseline regional (within ROI) rsFC of the right-sided BA9/46 V,46 and the right-sided BA46 regions was associated with improvement of depression on the HDRS-17, when compared to the placebo group, showing a positive association of baseline regional rsFC and depression improvement (right BA9/46 V,46: slope = -4.92, std.error = 2.13, p = 0.02, Cohen d = -0.32 CI [-0.60; -0.05]; right BA46: slope = -12.38, std.error = 5.29, p = 0.02, Cohen d = -0.33 CI [-0.60; -0.05]; Fig. 2). Global rsFC of a right-sided BA9/46D region was associated with larger improvement of NA when compared to the placebo group, showing a negative association of baseline rsFC and NA improvement (slope = 0.26, std.error = 0.10, p = 0.01, Cohen d = 0.35 CI [0.07; 0.62]; Fig. 2), although it should be stated that this effect might be driven by the placebo group. Yet none of these effects sustained after Bonferroni corrections for multiple comparisons (p > 0.50). In general, the baseline rsFC and gray matter volume showed no associations (p > 0.05, Suppl. Figure 4; their distributions are shown in Suppl. Figure 5).

Discussion

In this ancillary investigation of rsFC-MRI data from the ELECT-TDCS trial, we did not identify any association between prefrontal regional and global functional connectivity and improvement of depressive symptoms after tDCS treatment. This study adds to our first ancillary investigation of structural MRI data from the ELECT-TDCS trial [34].

Lack of an association of baseline rsFC and antidepressant effects in the ELECT-TDCS trial

In our first ancillary study of structural MRI data from the ELECT-TDCS study, we showed that gray matter volumes of a larger, left-sided PFC region were associated with clinical improvement of MDD after 10 weeks of tDCS treatment [34]. This effect was carried by bilateral MPFC regions, that showed higher electric field intensities based on computational models from MRI data [34]. Thus, we followed this finding using rsFC-MRI data for the same PFC subregions according to the Sallet et al. atlas [50], however, we were not able to detect a similar association between antidepressant effects and functional connectivity in these regions.

There are several possible explanations for obtaining significant results for structural, but not for rsFC-MRI data.

While there is some evidence that, at least in unimodal regions, such as primary sensory and motor regions the functional connectivity is constrained by the structural connectivity [60], in other regions, however, this relationship is not that clear [60, 61]. Several reviews and one metaanalysis on structural and functional imaging concluded on their property to show region-specific and modality-specific predictions of antidepressant response [1, 4-6]. For some regions, such as the hippocampus, they provided data in support of a link between structural or rsFC characteristics and the antidepressant response (following rTMS treatment in the case of hippocampus), yet for most regions, there were no such associations [5], Whether this is due to a true absence of a structure-function relationship, or rather due to the limited number of studies comparing structure and function within the same regions, or a publication bias towards significant findings is less clear. A recent review explained this apparent "uncoupling" of structure and function on the level of their respective connectivities; they hypothesized that current models are not sufficient to predict FC from structural connectivity due to the lack of biological data and suggested to enrich structural network reconstructions with cellular and molecular metadata to improve the models of structure–function relationships [61].



Fig. 1 No associations of resting-state functional connectivity in essential structural prefrontal cortex regions and improvement of depression after tDCS. This figure shows no significant associations of baseline regional (within ROI) and global (ROI to the whole brain) resting-state functional connectivity (rsFC) and improvement of depression on the 17-item Hamilton Depression Rating Scale (HDRS-17) in the treatment arm that received transcranial direct current stimulation (tDCS), as compared to the two control arms,

in essential structural regions (shown in the top row). For visualization purposes, the regression lines show associations with change in HDRS scores; statistics were calculated using mixed linear effects models with HDRS as the outcome variable, group, rsFC, and timepoint as fixed, and individual intercepts and slopes as random effects. *RSFC* represents numbers of activated voxels × 10³. *BA* Brodmann area, *PFC* prefrontal cortex

Region	Slope	Std.error	p.value	Cohen.d	95% CI
Global rsFC					
Left PFC	0.04	0.10	0.68	0.06	[-0.22; 0.33]
Left BA9, BA10, and BA9/46D	0.05	0.10	0.64	0.07	[-0.21; 0.34]
Left BA10	0.05	0.10	0.65	0.06	[-0.21; 0.34]
Right BA9	0.06	0.10	0.55	0.08	[-0.19; 0.36]
Region	Slope	Std.error	<i>p</i> .value	Cohen.d	[min; max]
Regional rsFC					
Left PFC	- 0.34	0.96	0.72	- 0.05	[-0.32; 0.22]
Left BA9, BA10, and BA9/46D	0.05	1.77	0.98	0.00	[- 0.27; 0.28]
Left BA10	2.91	4.14	0.48	0.10	[-0.18; 0.37]
Right BA9	9.16	10.83	0.40	0.12	[-0.16; 0.39]

Table 2 Associations between baseline resting-state functional connectivity in prefrontal regions and the antidepressant response to tDCS

Contrast tDCS vs. placebo is shown here, derived from linear mixed-effects models showing the effects of group interaction, resting-state functional connectivity (rsFC; global, i.e. from region to the whole brain, or regional, i.e. within the region), and timepoint on change of the 17-item Hamilton Depression Rating Scale (HDRS-17) score. The group differences in rsFC–outcome interactions were evaluated using the slope, standard error, significance levels, and Cohen's d (estimated from the model residual standard deviation; d of 0.3 represents moderate effect size) and its 95% confidence intervals (95% CI [lower bound; upper bound])

Table 3 Associations of baseline resting-state functional connectivity in prefrontal regions and positive/negative affect change after tDCS

Region	Estimate	Std.error	p.value	Cohen.d	95% CI
A) Positive affect					
Global rsFC					
Left PFC	- 0.10	0.13	0.44	- 0.11	[-0.38;0.17]
Left BA9, BA10, and BA9/46D	- 0.14	0.14	0.35	- 0.13	[-0.41;0.14]
Left BA10	- 0.22	0.14	0.13	- 0.21	[- 0.49;0.06]
Right BA9	- 0.18	0.14	0.21	- 0.18	[-0.45;0.10]
Regional rsFC					
Left PFC	0.27	1.34	0.84	0.03	[-0.25;0.30]
Left BA9, BA10, and BA9/46D	0.63	2.47	0.80	0.04	[-0.24;0.31]
Left BA10	- 7.15	5.70	0.21	- 0.18	[-0.45;0.10]
Right BA9	- 10.93	15.01	0.47	- 0.10	[- 0.38;0.17]
B) Negative affect					
Global rsFC					
Left PFC	0.10	0.13	0.46	0.10	[- 0.17;0.38]
Left BA9, BA10, and BA9/46D	0.17	0.14	0.22	0.17	[- 0.10;0.45]
Left BA10	0.25	0.14	0.08	0.25	[-0.03;0.52]
Right BA9	0.13	0.14	0.36	0.13	[-0.14;0.40]
Regional rsFC					
Left PFC	- 0.63	1.31	0.63	- 0.07	[-0.34; 0.21]
Left BA9, BA10, and BA9/46D	- 1.07	2.38	0.65	- 0.06	[-0.34;0.21]
Left BA10	1.44	5.42	0.79	0.04	[-0.24; 0.31]
Right BA9	3.02	14 89	0.84	0.03	$[-0.25 \cdot 0.30]$

Contrast tDCS vs. placebo is shown here, derived from linear mixed-effects models showing the effects of the group interaction, resting-state functional MRI connectivity (rsFC; global, i.e. from region to the whole brain, or regional, i.e. within the region), and timepoint of change of the positive and negative affect scores derived from the Positive and Negative Affect Schedule (PANAS). The group differences in rsFCoutcome interactions were evaluated using the slope, standard error, the significance levels, and Cohen's d (estimated from the model residual standard deviation; d of 0.3 represents moderate effect size) and its 95% confidence intervals (95% CI [lower bound; upper bound])

Second, methodological aspects could provide an explanation for our inability to identify the association of structure and function with the antidepressant response in the ELECT-TDCS trial. Studies apply different measures to assess structure and function. "Structure" is commonly assessed on the cortical level by voxel-based morphometry, surface-based measurement of cortical thickness, calculation of gray matter volumes in volumetric space, or in terms of structural connectivity by investigating the integrity of white matter tracts. Likewise, "function" may be expressed as functional connectivity measured in the resting state or functional activation of regions during a task, intended at activating regions responsible for specific functions (e.g. working memory). Theoretical constructs of rsFC measures themselves differ among studies; often they are defined as functional connectivity in resting-state networks as a whole or depict regions with increased or decreased connectivity within these networks. This variation of methods and underlying constructs makes it difficult to compare results between studies, and the type of measure may bias findings towards decoupling (or coupling?) of structure and function. For example, the non-linear relationship of structure and function mentioned in the previous paragraph is based on measures of structural and functional connectivity [60, 61], while the meta-analysis referred to task-based functional activation and voxel-based morphometry [4].

Though such theoretical considerations are tempting, a simple explanation for the lack of significant rsFC findings in spite of our previous findings for PFC grey matter volumes are type II errors. A major limitation in this study was the sample size which was the reason for staying with our a priori hypotheses and not advancing to independent component analyses or other more refined approaches. As our analyses are largely vulnerable to type II errors, the negative findings in our study do not prove the absence of an association between antidepressant effects and functional connectivity data. This is particularly relevant as both samples were practically identical (i.e. 51 and 52 patients from the ELECT-TDCS trial; one patient with missing EPI data, thus explaining the difference). The effects sizes of the tDCS vs. placebo model were rather small to moderate, tending



Fig.2 Effects of resting-state functional connectivity on depression improvement and positive/negative affect change after tDCS, exploratory analysis of prefrontal cortex regions. **a** describes the extent to which each region of the PFC contributes to tDCS effects on depression (change in 17-item Hamilton Depression Rating Scale [HDRS-17] score, left) or negative (NA, middle) and positive affect (PA, right) symptom change, as assessed by the Positive and Negative Affect Schedule (PANAS). Effect sizes (Cohen *d* and 95% confidence intervals [CI]) refer to the output of interest, the triple-interaction of the tDCS versus placebo treatment group, baseline rsFC, and

towards smaller effect sizes for functional connectivity analyses [34].

Effects of non-invasive transcranial brain stimulation (NTBS) may depend on resting state functional connectivity

For tDCS, data on rsFC MRI predicting tDCS effects on a cognitive, behavioral or even clinical level are very limited, though tDCS can modulate brain activity while showing behavioral effects; e.g. bifrontal tDCS was shown to improve performance in a working memory task and reduce left MPFC and ACC delta activity [62]. While no tDCS studies directly investigated baseline rsFC as a putative predictor for its effects, a recent study by Nord et al. suggested that higher

time point, extracted from linear mixed effect models. Effect size of 0.3 represents small to medium-sized effects; regions which larger effect sizes are extracted in the bottom row and show associations of baseline rsFC with the change in respective symptom score among the treatment groups (**b**). Note that HDRS-17 and NA are positively, while PA is negatively associated with sereneness of depression, which explains the different patterns observed for these scores. *RSFC* represents numbers of activated voxels × 10³. *BA* Brodmann area, *PFC* prefrontal cortex

baseline task activation in the left DLPFC during a working memory task might be a predictor of tDCS response [41].

In contrast, a larger body of evidence is available for TMS suggesting an impact of rsFC MRI data on TMS responses, e.g. rsFC between regions such as the ACC, MPFC, lateral parietal cortex, and the DLPFC were predictive of TMS response [21, 23]. In particular, anticorrelations of two regions, the left DLPFC and subgenual ACC predicted the clinical efficacy of left DLPFC TMS [20, 24] while for left MPFC TMS, functional connectivity for left dorsal MPFC left DLPFC, left amygdala and several other regions was associated with clinical response [63].

Being aware of the risk of overanalyzing the data, we further investigated additional PFC subregions. Interestingly, these exploratory analyses suggested an association of rsFC in *lateral* portions of the PFC with tDCS response, although these effects did not survive the corrections for multiple comparisons. This is particularly notable as structurally relevant regions were located rather *medially* in the PFC [50]. The above-mentioned evidence from tDCS and TMS studies supports indeed the involvement of the DLPFC in stimulation effects [20, 24, 38, 41], yet is not restricted to this region. In fact, it seems unusual that the association of rsFC and antidepressant response was observed under the right-sided, cathodal stimulation electrode, as stronger antidepressants effects are attributed to excitatory stimulation, hence high-frequency TMS or anodal tDCS [26, 64].

Of note, an additional incidental visual finding in our data is the side-dependence of the regional rsFC and improvement of symptoms, with lower baseline rsFC in left-sided regions, located below the anode, and higher baseline rsFC in right-sided regions, located below the cathode, being associated with greater improvement (Fig. 2). A possible interpretation in favor of our findings might be that anodal tDCS induces excitatory, and cathodal tDCS induces inhibitory effects [25, 26], thus "normalizing" a possibly pathological rsFC in these regions. Generally speaking, a deviation in both directions of baseline rsFC might facilitate the polarity-dependent tDCS effects.

Strengths and limitations

To the best of our knowledge, this is the first study investigating whether the antidepressant response to tDCS may be associated with distinct baseline rsFC MRI patterns in PFC regions. The original trial, where the current ancillary analysis has been conducted in a subsample of subjects with MRI data, is a milestone study in the field with an elaborate three-arm design, comparing tDCS plus placebo medication, pharmacotherapy plus sham tDCS and a double-placebo condition (i.e. sham tDCS and placebo medication). While the pharmacotherapy and placebo groups are advantageous in terms of the presence of control conditions, a major limitation is the relatively small sample size in the group of interest, the tDCS group. Although the analyses might be underpowered, we formulate clear hypotheses based on previous findings from structural features, which we can investigate in further trials including larger samples. Methodologically, comparison of our results to other studies is limited due to several factors, such as differences in stimulation parameters of tDCS (1 mA vs. 2 mA, placement of electrodes), differences between different mechanisms of stimulation modalities (tDCS vs. TMS) and differences in measures of MRI parameters (derived from, for example task fMRI or metabolic PET investigations) or connectivity (looking at positive or negative correlations, ICA-based rsFC networks versus seed-based rsFC analysis). In future studies, our findings should be replicated with regards to structural features to identify multimodal mediators of tDCS

response. Clinical characteristics [44] and depression subgroups [63] should also be considered.

A strength of our study is that it is based on a prior investigation of a subgroup from the same trial and it allows us to address a problem from different points of view; the influence of specific regions on the same outcome from the perspective of structural, hence long-term, or functional, hence state-dependent, parameters. In fact, although the structure of the human brain has a marked imprint on its function, this interaction is complex and rules out simple one-to-one correspondence/transmission [61].

Conclusion

While rsFC of several regions and networks centered around the DLPFC and MPFC is being discussed as a putative biomarker of TMS response in depression [7, 21, 23, 24], we did not identify a similar association of rsFC in PFC regions and tDCS response. This is of particular interest as, the tDCS response was associated with baseline gray matter volumes, indicating that tDCS may be differentially related to structural and functional biomarkers. The whole array of individual structural and functional MRI information offers a unique potential for identifying sensitive and specific MRIbased predictors of the antidepressant response. A deeper understanding of the stimulation brain interaction, however, is needed for the selection of predictive factors.

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Compliance with ethical standards

Conflict of interest EM, PS, PVB, FD, GB, EAJ, IMB, PAL, WG, SG, and DK reported no biomedical financial interests or potential conflicts of interest.

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