Association between tDCS computational modeling and clinical outcomes in depression: data from the ELECT-TDCS trial

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Abstract

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation intervention investigated for the treatment of depression. Clinical results have been heterogeneous, partly due to the variability of electric field (EF) strength in the brain owing to interindividual differences in head anatomy. Therefore, we investigated whether EF strength was correlated with behavioral changes in 16 depressed patients using simulated electric fields in real patient data from a

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controlled clinical trial. We hypothesized that EF strength in the dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC), brain regions implicated in depression pathophysiology, would be associated with changes in depression, mood and anxiety scores. SimNIBS were used to simulate individual electric fields based on the MRI structural T1-weighted brain scans of depressed subjects. Linear regression models showed, at the end of the acute treatment phase, that simulated EF strength was inversely associated with negative affect in the bilateral ACC (left: $\beta = -160.463$, CI $[-291.541, -29.385]$, $p = 0.021$; right: $\beta = -189.194$, CI $[-289.479, -88.910]$, $p = 0.001$) and DLPFC (left: $\beta = -93.210$, CI $[-154.960, -31.461]$, $p = 0.006$; right: $\beta = -82.564$, CI $[-142.867, -22.262]$, $p = 0.011$) and with depression scores in the left ACC ($\beta = -156.91$, CI $[-298.51, -15.30]$, $p = 0.033$). No association between positive affect or anxiety scores, and simulated EF strength in the investigated brain regions was found. To conclude, our findings show preliminary evidence that EF strength simulations might be associated with further behavioral changes in depressed patients, unveiling a potential mechanism of action for tDCS. Further studies should investigate whether individualization of EF strength in key brain regions impact clinical response.

Introduction

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation intervention that applies direct electric currents to modulate cortical excitability according to the parameters of stimulation [1]. The technique has been used in several neuropsychiatric conditions, most notably in major depressive disorder (MDD) [2, 3], in which electrodes are usually positioned over the dorsolateral prefrontal cortex (DLPFC), which tends to be hypoactive in depression [4, 5].

The clinical efficacy of tDCS for treatment of MDD has been investigated in several randomized clinical trials [6–8]. Although meta-analyses have shown active tDCS to be superior to sham for response, remission and depression improvement [3, 9], clinical results have been moderate and heterogeneous [3, 7, 10]. Recently, it has been hypothesized [11] that variations in the electrical current on the targeted brain region might account for such heterogeneity [12–15]. Although invasive estimation of such currents is not feasible in most cases, recent technical developments permit, using brain imaging, the simulation of the strength and spatial distribution of the electrical current injected into the brain, as well as to assess individual differences in strength and distribution of such currents owing to one's head and brain anatomy [16]. Neurophysiological studies have shown that tDCS-induced electric fields (EFs) in the brain of healthy volunteers correlate with changes in gamma-aminobutyric acid (GABA), measured by magnetic resonance spectroscopy [17], and with the resting motor threshold, measured by transcranial magnetic stimulation [18]. Nonetheless, individual EFs have not been systematically investigated as a predictor of tDCS clinical effects.

Given these initial results, we hypothesized that tDCS-induced EF strength (measured in Vm $^{-1}$ and representing the intensity of the electric field distributed over a given anatomical region) in brain regions of interest (ROIs) would be associated with behavioral changes in depressed patients within a controlled clinical trial previously performed by our group [7]. The selected ROIs were the DLPFC and the anterior cingulate cortex (ACC) bilaterally, since these regions are structurally implicated in MDD [19–21] and are targeted by brain stimulation interventions [22, 23]. For instance, a recent meta-analysis quantifying structural brain changes associated with MDD showed that gray matter reduction in the ACC to be one of the most robust findings between studies [19]. Additionally, clinical improvement has been associated with increase in gray matter volume of the DLPFC [24], and connectivity between these two regions predicted antidepressant response to rTMS [25]. Our primary outcome variable was changes in the Hamilton depression rating scale (HDRS-17) [26]. As secondary outcomes, we explored changes in affective scores (indexed by the Positive and Negative Affect Scale (PANAS) [27]) and in trait or state anxiety (measured by the State–Trait Anxiety Inventory (STAI) [28]), as previous studies have shown that prefrontal tDCS modulates affective and anxiety processing [29–31].

Methods

Study design

Our Escitalopram versus Electrical Current Therapy for Treating Depression Clinical Study (ELECT-TDCS) trial, a non-inferiority triple-arm study, randomized patients into three groups: sham-tDCS/placebo-pill (placebo group), sham-tDCS/escitalopram (escitalopram group) and active-tDCS/placebo-pill (tDCS group) [32]. The original study compared 22, 2-mA, 30-min tDCS sessions (1 × 1 tDCS-CT, SoterixMedical, New York, NY) applied in a 10-week period, with 15 sessions applied consecutively once a day (expect for weekends), and 7 more sessions applied once per week until the study endpoint at week 10, to a first-line antidepressant treatment (escitalopram 20 mg/day), and found it to be superior to placebo and not non-inferior to escitalopram [7]. Our study was registered in ClinicalTrials.gov (NCT01894815).

Participants

We recruited patients aged 18–75 years who were diagnosed with major depressive disorder during an acute depressive episode per DSM-5 criteria (Diagnostic and Statistical Manual of Mental Disorders, 5th edition). The main inclusion criteria were: (1) 17 points on HDRS-17; (2) baseline low risk of suicide; (3) at least 8 years of schooling; (4) and adherence to study protocol. Exclusion criteria were other neuropsychiatric disorders (except for anxiety disorders as a comorbidity), pregnancy, specific contraindications to tDCS (e.g., cranial plates), current or previous escitalopram use, and previous or concomitant participation in other tDCS trials. Patients under antidepressant drug therapy underwent drug washout. Benzodiazepines were allowed up to 20 mg/day diazepam-equivalent.

In this ancillary study, all participants received active tDCS according to the protocol described above. As they were part of a placebo-controlled study, these patients also received placebo pill, as they were not aware to which study group they were assigned to.

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 $1 \times 1 \times 1$ 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.

tDCS modeling

SimNIBS (v3.1, Danish Research Centre for Magnetic Resonance, Copenhagen, Denmark) [33] was used for tDCS modeling. It is a free and open-source software package for the simulation of tDCS-induced electric field in the individual brain. It allows for realistic calculations using the finite element method (FEM), and integrates free software for neuroimaging, computer graphics and FEM calculations into one coherent pipeline. TDCS modeling was done using T1-weighted anatomical images of each subject to reconstruct a high-resolution head model of that individual using the SimNIBS pipeline. We manually verified each segmentation to check for possible errors in the established boundaries between tissues, and no subjects were excluded in the process. The estimated EF distribution in one's brain is obtained by placing simulated electrodes on the head model and setting simulated electric current intensity according to the stimulation protocol used in the clinical trial.

Parameters of the tDCS modeling were set according to the ELECT-TDCS protocol [32]: current intensity was set to 2 mA and electrode sizes of 5×5 cm. For electrode positioning, we simulated the F5 and F6 areas, according to the EEG 10–20 system, for the anode and cathode, respectively, targeting the left and right DLPFC. The DLPFC has a complex cortical structure that is highly variable between individuals and, despite its widespread use as a target, there remains a lack of consensus for how this region should be best localised. Although in the original study we used the Omni-Lateral Electrode (OLE) system, the F5-F6 positioning was employed since it can be directly implemented in SimNIBS and considering that the simulated EF strength in the brain for both montages is similar [5].

Electric field values

According to our hypotheses, a ROI-based approach was used to define the DLPFC and ACC, brain areas in which simulated EF strength was evaluated. To define the DLPFC, we used the Sallet et al. atlas [34], which provides a parcellation of the dorsal frontal cortex based on functional and tractography data in a cross-species comparison of both humans and primates, and divides it into 10 subregions (clusters) also identified by their corresponding Brodmann areas (BAs). This approach was used in a previous study by our group correlating structural DLPFC changes with tDCS antidepressant response [15]. This atlas was chosen as it allows to identify ROIs in the proximity of the DLPFC area, while incorporating anatomical and functional data. The Sallet et al. atlas also incorporates motor and premotor areas, but they were not included in our analysis as they were not part of our hypotheses. We defined the DLPFC by Sallet et al. clusters 3, 4, 5, 6, 7, 8 and 10, which correspond to Brodmann Areas (BAs) 8, 9, 10 and 46. For the ACC ROI, we used the parcellation of the

Brainnetome atlas [35], a whole-brain, multimodal parcellation atlas based on structural magnetic resonance imaging (MRI), diffusion tensor imaging and resting-state fMRI connectivity.

As significant effects in these hypothesis-driven regions were observed for HDRS-17 and PANAS, and as performed in our previous study [15], we analyzed subregions of the DLPFC and the ACC in an exploratory manner so as to identify subregions driving these effects. In the DLPFC, we investigated 7 clusters according to Sallet et al.: cluster 3 (corresponds to BA 9), cluster 4 (BA 10), cluster 5 (BA 9/46D), cluster 6 (BA 9/46V), cluster 7 (BA 46), cluster 8 (BA 8A) and cluster 10 (BA 8B). In the ACC, we further explored the subgenual ACC (sgACC) and pregenual ACC (pgACC) using the "A32sg" and "A32p" ROIs from the Brainnetome atlas, because of their particular roles in predicting antidepressant response specifically in the rTMS literature [36–38].

Statistical analysis

We used Python 3.7.0 [39], Spyder 3.3.6 and the StatsModels library [40] to perform a regression analysis to explore in which brain regions simulated EF strength was associated with depression improvement. Statistical results were considered significant under a p threshold of 0.05.

EF strength was obtained as the average EF strength within the ROI (Emean), calculated by summing the simulated EF in each voxel and dividing it by the number of voxels. We used linear regression models, adjusted for gender and age, with changes in the HDRS-17, STAI, and PANAS scales as dependent variables and Emean at the ROIs as independent variables. We evaluated whether simulated EF would be correlated with changes immediately after the end of the acute treatment phase (i.e., 15 sessions) and at study endpoint (i.e., week 10). These two time frames were also used in main and ancillary analyses of ELECT-TDCS [7, 15, 41, 42] and reflect timepoints in which acute and long-lasting tDCS effects are usually observed [3]. These analyses were not corrected for multiple comparisons since they were hypothesis driven. Also, five patients did not complete the study, and models for study endpoint include only trial completers.

Additionally, we investigated the subregions of the DLPFC and ACC in an exploratory manner using the same models, which produced another 9 models for each hemisphere per outcome. For this exploratory analysis, the correction for multiple comparisons was done using the Bonferroni correction for each outcome individually, in both hemispheres. For each outcome variable, a total number of 18 tests were performed (9 subregions—7 in the DLPFC and 2 in the ACC—in two hemispheres); therefore, the correction was performed using a threshold $\alpha = 0.05/18$.

Results

Out of the original sample, only 68 patients received MRI at baseline. The most important reasons for the absence collection of MRI were (1) the delayed start of the MRI collection that initiated only after 30% of the sample had already been recruited, (2) patient refusal, and (3) lack of MRI slots available. Other reasons included MRI contraindications and

technical reasons. Moreover, MRI scans of 15 patients were excluded after an initial quality check (absence of T1 anatomical sequences, abnormal anatomical findings, and poor quality due to head motion). The remaining 53 scans were divided into three groups: active tDCS (16 patients), escitalopram (16 patients) and placebo (21 patients). Here, we performed simulations in the 16 patients who had undergone tDCS. Their characteristics are shown in Table 1, and the individual simulated EF strength distribution in Fig. 1. It can be visually depicted that such distribution is notably different between participants (Table 2).

Changes in depression scores

For the acute treatment phase, HDRS-17 change was significantly correlated with Emean in the left ACC ($\beta = -156.91$, CI [-298.51, -15.30], $p = 0.033$) (Table 3). No other significant correlation was found for this time frame or at study endpoint (Tables 2 and 3).

Changes in positive and negative affect

For the acute treatment phase, negative affect reduction was associated to Emean in the left DLPFC ($\beta = -93.21$, CI [-154.96, -31.46], $p = 0.006$) (Table 2), right DLPFC ($\beta = -82.56$, CI [-142.87, -22.62], $p = 0.011$) (Table 2), left ACC ($\beta = -160.46$, CI [-291.54, -29.38], $p = 0.021$) (Table 3), right ACC ($\beta = -189.19$, CI [-289.48, -88.91], $p = 0.001$) (Table 3) (Fig. 2). No significant correlation was found for the 10-week period (Tables 2 and 3).

No significant correlations were found between change in positive affect and EF strength (Table 2 and 3).

STAI improvement

No significant correlations were found between trait and state anxiety changes and simulated EF strength for any of the explored clusters in any time frame (Table 2 and 3).

Exploratory analysis in subregions of DLPFC and ACC

Post-acute treatment phase changes in negative affect were significantly associated with Emean after Bonferroni correction in right BA 9/46D ($\beta = -83.87$, CI [-130.02, -37.71], $p = 0.002$, $p_{corr} = 0.034$), right pgACC ($\beta = -159.92$, CI [-245.51, -74.32], $p = 0.002$, $p_{corr} = 0.028$), and left BA 9 ($\beta = -49.38$, CI [-74.22, -24.53], $p = 0.001$, $p_{corr} = 0.018$). No other significant associations were observed for other outcomes, regions, or timeframes (data not shown).

Discussion

In this study, we investigated the association between individual tDCS-induced simulated EF strength, using state-of-the-art computational simulation modeling approaches, and behavioral outcomes in depressed patients, based on our ELECT-TDCS trial. To the best of our knowledge, this is the first study correlating simulated EF strength with clinical outcomes in a depressed sample submitted to tDCS treatment.

Our findings showed that simulated EF strength in the left ACC was correlated with changes in HDRS-17. This is relevant since ACC acts as a bridge between attentional and emotional processing. In fact, alterations in its structure and function have been implicated in the pathophysiology of MDD. Depressed patients show decreased gray matter volume in the ACC [43], and, although our previous study did not find a significant correlation between baseline gray matter volume in the ACC and tDCS treatment response [15], it has been suggested that increases in ACC volume after repetitive transcranial magnetic stimulation (rTMS) and electroconvulsive therapy (ECT), other brain stimulation techniques, are correlated with its antidepressant effect [44, 45]. Additionally, connectivity between the DLPFC and ACC is altered in MDD [46], and changes in DLPFC-ACC connectivity are associated with rTMS efficacy [36, 47]. Therefore, our finding suggests that the ACC is implicated in prefrontal tDCS antidepressant effects. Future studies should investigate whether tDCS induces volumetric or connectivity changes in the ACC of depressed patients, and whether such changes are correlated with the EF strength in this brain region.

We also found that simulated EF strength in the bilateral ACC and DLPFC was inversely associated with negative affect, i.e., greater score reductions were associated with larger EF strengths in these regions. Since both brain regions are involved in implementing emotion regulation strategies and modulating activity in other emotion-encoding brain regions [48–52], it is possible that the applied EF contributed to increasing the functional coupling within this neural circuitry, facilitating emotional regulation of affect. In fact, this finding might be associated with the direct effects of tDCS over the PFC that regulates negative affect [53]. In previous studies using ELECT-TDCS data, we found that negative affect was the most important predictor associated with tDCS antidepressant response [54] and that the DLPFC volume predicted antidepressant response [15]. Moreover, several studies showed that prefrontal tDCS can enhance affective processing of emotionally loaded tasks [55–57]. Thus, our study confirms and expands previous evidence suggesting that changes in negative affect are implicated in tDCS antidepressant mechanisms of action. Further studies are necessary to explore this hypothesis and determine the specific mechanisms by which this is accomplished.

We found no correlation between trait or state anxiety and EF strength over the DLPFC and ACC. Although some studies suggested that tDCS can downregulate anxiety [31, 58], negative findings have been also reported. For instance, recent trials showed modest or null effects of prefrontal tDCS in ameliorating anxiety symptoms [59, 60]. In this context, other tDCS protocols that could be more effective in improving anxiety symptoms should be investigated [61]. In addition, tDCS effects on anxiety might be more effective when down-regulating stress-induced tasks [62, 63].

All the observed effects occurred immediately after the acute treatment phase (3 weeks of trial onset), but not at study endpoint (week 10). Interestingly, most studies have observed that tDCS effects are delayed, i.e., only differentiate from placebo after the acute treatment phase [7, 64, 65]. It is possible that other, non-specific factors (e.g., placebo effects, natural history of disease, regression to the mean) occurring between weeks 3 and 10 mitigated a possible association between simulated EF strength and our behavioral outcomes.

Conversely, another possible explanation is that missing data from patients who did not complete the trial decreased the power of our analyses.

Our study has several limitations worth notice. First, our sample size is small as only a subsample of patients from the original study had MRI data collected. Therefore, some analyses might have been underpowered and our results should be primarily interpreted as hypothesis driven for future studies. Our limited sample size highlights the urgent need for larger tDCS depression studies performing baseline MRI measurements for replication of our findings. In addition, as 40 models were performed, at least 2 false positive findings might have emerged just by chance. Second, we are using simulated electric fields in reconstructed models of patient's heads. Although validated and considered state of the art [66, 67], they nonetheless represent an approximation of the "real" current distribution in the brain, which cannot be measured in a non-invasive manner. Third, the electrode positioning for the simulations on the models does not follow the exact correct location of the electrodes on the montage of the clinical trial (OLE system, which uses a 10 cm distance between electrodes), because of technical difficulties positioning virtual electrodes over simulated models' scalps using a 10 cm distance on irregular surfaces with distinct curvatures. Instead, the F5-F6 montage used in this study's simulations favors uniformity in the electrode positioning between subjects. Finally, the model is static, i.e., it does not incorporate fluctuations in blood flow and changes in tissue conductivity that likely occur when tDCS is applied [68].

Whether further studies confirm that EF strength of certain brain regions correlates with clinical response, it would be possible to tailor individual tDCS montages and parameters to increase EF strength in such areas, theoretically improving clinical outcomes. This would represent an advancement towards individualizing tDCS parameters [69] whose parameters have been hitherto mostly fixed, not considering one's brain and skull anatomy.

Conclusion

We have investigated the association between simulated EF strength in brain regions implicated in depression pathophysiology and changes in behavioral outcomes in 16 depressed patients. We found that simulated EF strength presented a large variation in individual brains, even under the same parameters of stimulation. According to our hypotheses, associations were observed between simulated EF strength in the DLPFC and ACC and negative affect and depression scores. Nonetheless, the sample size was small and multiple tests were performed. Therefore, our findings should be regarded as exploratory. Notwithstanding, they show that EF strength might be associated with behavioral changes in clinical samples, suggesting a potential mechanism of action of tDCS antidepressant effects and fomenting further studies exploring whether tDCS interventions could be tailored to maximize EF strength in key brain regions to enhance clinical outcomes.

Funding

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Fig. 1.
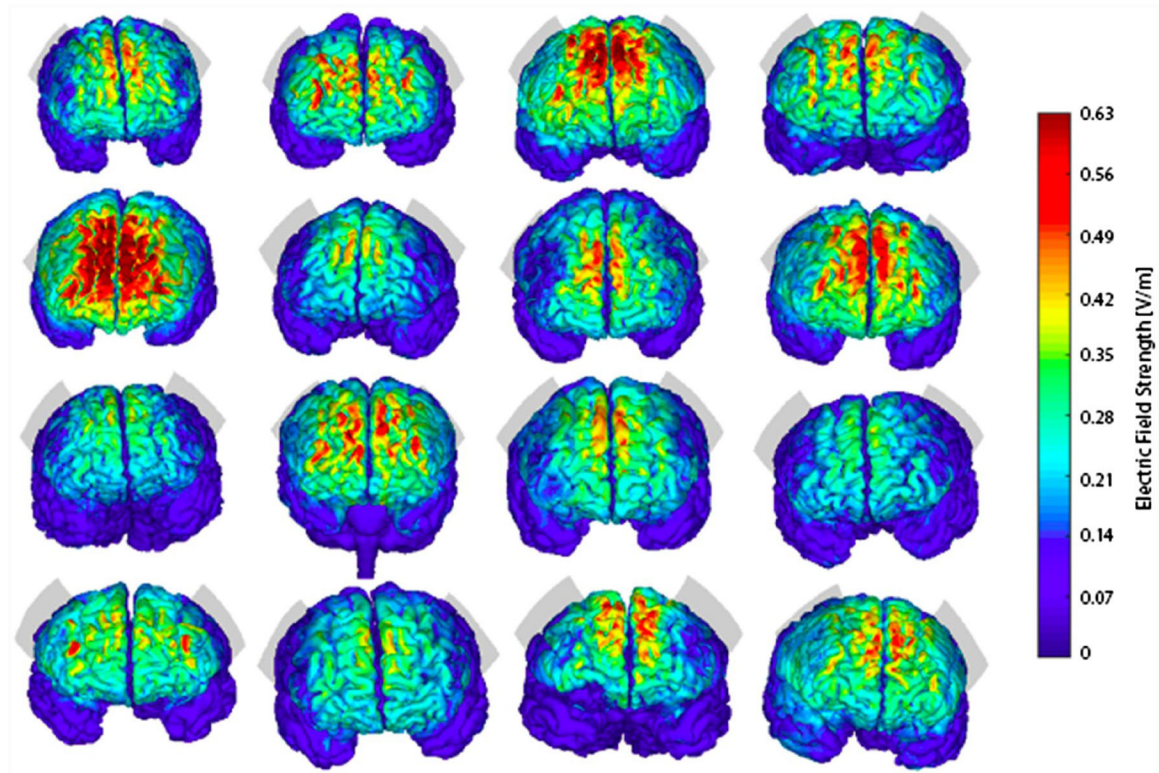Individual tDCS-induced simulated brain electrical field strength distribution. Illustrates the location of the stimulation electrodes (EEG-based F5-F6 location) and the distribution of the electric field on all 16 subjects of the study. Peak electric field strength (measured in V/m) occurs in intermediate regions between stimulation electrodes and is notably different between participants
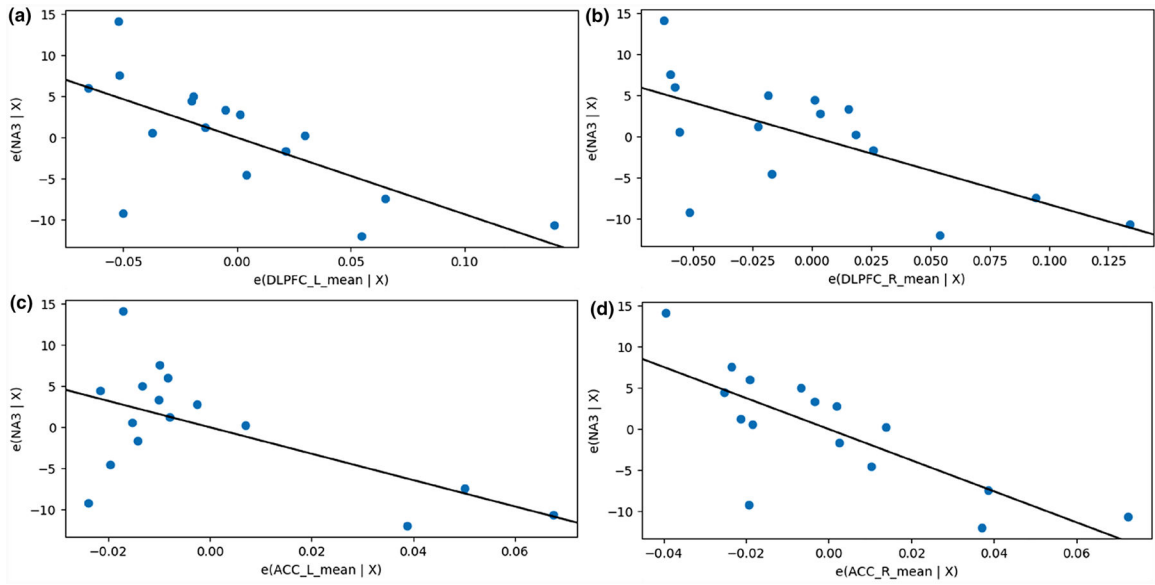
Fig. 2.
Association between negative affect and EF strength for brain regions of interest. Partial regression plots of the mean electric field strength (measured in V/m) in hypothesis-defined regions of interest in relation to change in negative affect after acute treatment phase. A higher mean field value corresponds to a more pronounced decrease of negative affect as measured by the Positive and Negative Affect Scale (PANAS). **a**, **b**, **c** and **d** show the partial regression plots of the left dorsolateral prefrontal cortex, right dorsolateral prefrontal cortex, left anterior cingulate cortex and right anterior cingulate cortex, respectively. *DLPFC* dorsolateral prefrontal cortex, *ACC* anterior cingulate cortex, *NA* negative affect

Table 1

Patient group characteristics

	tDCS
Gender (male/female)	7/9
Age (mean ± SD), years	42.8 ± 10.9
HDRS[a]	
Baseline	21.6 ± 3.9
Week 3	14.3 ± 6.1
Week 10	13.8 ± 10.1
PA	
Baseline	17.1 ± 6.3
Week 3	21.5 ± 9.1
Week 10	25.0 ± 11.4
NA	
Baseline	29.6 ± 9.3
Week 3	26.4 ± 11.4
Week 10	21.8 ± 10.1
STAI—state	
Baseline	54.6 ± 10.1
Week 3	51.6 ± 13.4
Week 10	48.3 ± 16.4
STAI—trait	
Baseline	65.6 ± 6.3
Week 3	60.6 ± 11.5
Week 10	54.3 ± 17.7
Emean (V/m)	
DFLP—left	0.317 ± 0.055
DLFPC—right	0.332 ± 0.059
ACC—left	0.153 ± 0.030
ACC—right	0.145 ± 0.030

Distribution of characteristics, clinical outcomes, and mean electric field strength of the four main analyzed regions. Values are displayed as mean ± standard deviation

HDRS Hamilton depression rating scale, *PA* positive affect, *NA* negative affect, *STAI* state–trait anxiety inventory, *Emean* Mean electric field strength inside ROI, *DLPFC* dorsolateral prefrontal cortex, *ACC* anterior cingulate cortex

[a]Scores on the 17-item Hamilton depression rating scale (0–52, the higher the more severely depressed)

Table 2

Linear models for the DLPFC

Linear models for DLPFC	Left hemisphere			Right hemisphere		
	Beta	**95% CI**	**p**	**Beta**	**95% CI**	**p**
HDRS (week 3)	−48.25	[− 131.74, 35.25]	0.232	− 45.34	[− 123.32, 32.64]	0.229
HDRS (week 10)	24.23	[− 174.97, 223.42]	0.782	19.40	[− 169.51, 208.31]	0.815
PA (week 3)	42.50	[− 33.92, 118.91]	0.249	41.22	[− 29.86, 112.30]	0.230
PA (week 10)	−43.92	[− 185.99, 98.15]	0.489	− 45.02	[− 178.65, 88.60]	0.452
NA (week 3)	**− 93.21**	**[− 154.96, − 31.46]**	**0.006**	**− 82.56**	**[− 142.87, − 22.62]**	**0.011**
NA (week 10)	17.51	[− 133.60, 168.63]	0.792	23.52	[− 118.78, 165.82]	0.708
STAI—state (week 3)	− 12.21	[− 112.61, 88.19]	0.795	2.73	[− 91.36, 96.83]	0.951
STAI—state (week 10)	43.78	[− 177.29, 264.86]	0.654	73.82	[− 128.24, 275.88]	0.416
STAI—trait (week 3)	− 3.72	[− 117.92, 110.48]	0.945	− 6.73	[− 113.40, 99.94]	0.893
STAI—trait (week 10)	30.84	[− 208.47, 270.14]	0.769	49.3	[− 174.47, 273.07]	0.618

Results of the linear models obtained for the dorsolateral prefrontal cortex in both brain hemispheres. Table values marked in bold indicate regions in which the correlation was found to be significant. Beta is the linear coefficient of the relation between mean electric field strength and negative affect change. 95% CI is the confidence interval for the linear coefficient with a 95% confidence level. *p* is the *p*-value of the linear model and was not corrected for multiple comparisons since these analyses were hypothesis driven

HDRS Hamilton depression rating scale, *PA* positive affect, *NA* negative affect, *STAI* state–trait anxiety inventory, *DLPFC* dorsolateral prefrontal cortex

Table 3

Linear models for the ACC

Linear models for ACC	Left			Right		
	Beta	**95% CI**	*p*	**Beta**	**95% CI**	*p*
HDRS (week 3)	**− 156.91**	**[− 298.51, − 15.30]**	**0.033**	− 110.46	[− 257.21, 36.29]	0.127
HDRS (week 10)	− 55.89	[− 398.49, 286.72]	0.711	14.24	[− 338.41, 366.89]	0.927
PA (week 3)	101.91	[− 41.73, 245.54]	0.148	86.84	[− 50.67, 224.34]	0.194
PA (week 10)	− 1.61	[− 256.31, 253.08]	0.988	− 57.70	[− 312.12, 196.71]	0.608
NA (week 3)	**− 160.46**	**[− 291.54, − 29.38]**	**0.021**	**− 189.19**	**[− 289.48, − 88.91]**	**0.001**
NA (week 10)	− 1.18	[263.70, 261.35]	0.992	30.73	[− 235.43, 296.88]	0.792
STAI—state (week 3)	− 30.98	[− 225.64, 163.69]	0.735	− 74.34	[− 252.33, 103.66]	0.381
STAI—state (week 10)	10.11	[− 377.74, 397.95]	0.953	41.68	[− 351.86, 435.33]	0.809
STAI—trait (week 3)	− 54.18	[− 273.47, 165.11]	0.600	− 34.63	[− 242.26, 172.99]	0.723
STAI—trait (week 10)	− 63.78	[− 476.09, 348.55]	0.725	− 4.53	[− 428.75, 419.69]	0.980

Results of the linear models obtained for the anterior cingulate cortex in both brain hemispheres. Table values marked in bold indicate regions in which the correlation was found to be significant. Beta is the linear coefficient of the relation between mean electric field strength and negative affect change. 95% CI is the confidence interval for the linear coefficient with a 95% confidence level. *p* is the *p*-value of the linear model and was not corrected for multiple comparisons since these analyses were hypothesis driven

HDRS Hamilton depression rating scale, *PA* positive affect, *NA* negative affect, *STAI* state–trait anxiety inventory, *ACC* anterior cingulate cortex