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ORIGINAL RESEARCH

Prefrontal TDCS attenuates medial prefrontal connectivity upon being criticized in individuals scoring high on perceived criticism

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Abstract

The mechanisms by which transcranial direct current stimulation (tDCS) influences emotional processing - and whether this is related to individual vulnerability for psychopathology - are still poorly understood. The present study aimed to investigate if one prefrontal tDCS session modulates mood and neural functional connectivity after being exposed to negative information differently in individuals low or high in perceived criticism (PC), which has been related to vulnerability for psychiatric illness. In a randomized cross-over design, one session of MRI-compatible prefrontal tDCS (neuronavigated placement of the anodal electrode at the left dorsolateral prefrontal cortex and the cathodal electrode at the right supraorbital region; vs. sham) was administered to healthy females, prior to listening to self-referential criticism. PC-dependent (low vs. high PC) changes in mood and resting-state functional connectivity patterns following tDCS and after hearing criticism were explored. After being criticized all females (low and high PC) felt angrier and more depressed, both in the active tDCS or sham tDCS condition. However, in contrast to low PC females, in high PC females prefrontal tDCS reduced connectivity between the left dorsal anterior cingulate cortex and the right dorsomedial prefrontal cortex following criticism. Despite having no differential effects on self-reported mood, prefrontal tDCS reduces medial prefrontal neural connectivity after being criticized in high PC females compared to low PC females. Depending on individual vulnerability for psychopathology, a single tDCS session differentially affects neural processing of negative emotional information, especially in brain regions involved in monitoring, experiencing and appraising/evaluating emotional material.

Keywords Anterior cingulate cortex · Functional connectivity · Medial prefrontal cortex · Criticism · Transcranial direct current stimulation

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Abbreviations

EE	Expressed Emotion
PC	Perceived Criticism
tDCS	Transcranial Direct Current Stimulation
VAS	Visual Analogue Scale

Introduction

Transcranial direct current stimulation (tDCS) modulates cortical excitability by applying a weak direct electric current (usually 1-2 mA) through electrodes positioned over the scalp at the targeted neural region (Woods et al. 2016). Recent human electric field modeling studies suggest that – although at the skull surface the highest electric field strengths following tDCS are found beneath both the anodal electrode and the cathodal electrode – at the brain surface this distribution of field strengths tends to merge into one more central area with a peak electric field in between both electrodes (Opitz et al. 2015; Rampersad et al. 2014; De Witte et al. 2018). Given that the current flows from the anodal electrode to the cathodal electrode, on the other hand, the position of both electrodes and the associated orientation of the electric field co-determine the effects of tDCS on the targeted neural tissue (Wagner et al. 2014; Opitz et al. 2015; De De Berker et al. 2013).

Research over the past decade has demonstrated the effects of prefrontally-targeted tDCS on cognitive processing in healthy and clinical populations (meta-analyses by Brunoni and Vanderhasselt 2014; Dedoncker et al. 2016a). However, inter-individual differences in cognitive tDCS effects have been reported. Among other factors, this variation in cognitive efficacy has been related to differences in 'baseline' neurocognitive and psychological functioning of the participants (i.e., brain-state dependency; reviewed by Li et al. 2015). Prefrontal tDCS has also been used as a treatment for psychiatric illnesses (reviews by Kuo et al. 2014; Lefaucheur et al. 2017; Tortella et al. 2015). Nevertheless, the mechanisms by which tDCS influences emotional processing, and whether these mechanisms are related to 'baseline' individual characteristics, are less well understood (for a review, see Mondino et al. 2015). One behavioral study by Peña-Gómez et al. (2011), for instance, showed increased down-regulation of negative emotional processing after one prefrontal tDCS session, particularly in highly (subclinical) introverted individuals. This effect was suggested to be due to transient tDCS-induced increases in cognitive control and associated adaptive emotion regulation processes, with less vulnerable individuals being less malleable in this regard considering possible baseline neural activity differences (see also Joormann and Tanovic 2015). This study therefore suggests the existence of differential effects of tDCS on emotional processing that depend on individual characteristics known to be related to vulnerability for psychiatric disorders (e.g., mood or anxiety disorders).

Another approach is to evaluate whether prefrontal tDCS modulates self-reported affective states and neural connectivity under conditions of being challenged by negative emotional information in individuals who are more or less vulnerable to psychiatric illness. Relevant here is the Expressed Emotion (EE) construct. EE is a measure of the amount of criticism, hostility, and/or emotional over-involvement expressed by the relative of a psychiatric patient during an interview with a researcher. High EE has long been established as a risk factor for patient relapse across a range of psychiatric disorders (Hooley and Teasdale 1989; Hooley 2007; see meta-analysis by Butzlaff and Hooley 1998). However, being able to reliably measure EE through a semi-structured clinical interview – the Camberwell Family Interview (CFI; Vaughn and Leff 1976) – requires adequate training. It is also very time-consuming (approximately 1.5 h of administration time with an additional 2–4 h needed for coding). The Perceived Criticism (PC) measure, developed by Hooley and Teasdale (1989), provides a much quicker alternative transdiagnostic vulnerability marker (Hooley and Parker 2006).

The most important component of the EE measure is criticism (Butzlaff and Hooley 1998; Hooley 2007). Reflecting this, the PC measure asks individuals to respond to a single question: "How critical do you think your relative (or significant other) is of you?" using a 1–10 scale. PC can therefore be considered a simple and subjective measure of the degree of criticism one perceives in their most significant relationship(s) (i.e., how much criticism gets through to an individual, Masland and Hooley 2015). Research has shown that PC is a temporally stable and valid construct (Hooley and Teasdale 1989). PC ratings also appear to be unrelated to demographic (e.g., sex, education level, race) and personality characteristics (Renshaw 2008) as well as to current mood state (Gerlsma et al. 2014) and current symptom severity (Hooley et al. 2012; Renshaw et al. 2003), demonstrating strong discriminative validity. Importantly, a review by Renshaw (2008) has supported the use of this single-item rating scale in research and clinical settings given the observation that this construct was a stronger predictor of relapse than an adapted 5-item format (Kwon et al. 2006), and the medium-to-large effect sizes obtained using its single-item format. The use of this inexpensive and easy measure is further supported by evidence of good convergent and predictive validity (reviews by Chambless and Blake 2009; Renshaw 2008).

Indicating a role as a reliable and importantly, transdiagnostic vulnerability marker, the PC measure has been shown to predict worse clinical outcomes in depression (Hooley and Teasdale 1989; Kwon et al. 2006), anxiety (Chambless et al. 2017; Renshaw et al. 2003) and substance use disorders (Fals-Stewart et al. 2001) as well as suicidal ideation/attempts (Hagan and Joiner 2017; see also reviews by Masland and Hooley 2015; Renshaw 2008; and some trans-diagnostically inconsistent findings by Miklowitz et al. 2005; Steketee et al. 2007; Taylor and Meeks 1996). Using a non-clinical community sample, Masland et al. (2015) were also able to demonstrate that, when exposed to negative emotional information, people who scored high on the PC measure showed impaired attentional control on a socially relevant flanker task. They also interpreted emotionally ambiguous auditory information (i.e., word morphs) more negatively. These findings linking PC with attentional and interpretation biases upon confrontation with negative emotional stimuli are in line with Hooley et al.' (2012) findings of aberrant corticolimbic processing in high PC individuals who listened to maternal criticism. More specifically, upon being criticized by their mothers, high PC individuals showed amygdala hyperactivation and prefrontal hypoactivation, a pattern indicative of the implication of a neurocircuit known to be related to dysfunctional emotion regulation, depression vulnerability (De De Raedt and Koster 2010; Kovacs et al. 2008; Zhong et al. 2011) and pathophysiology (Price and Drevets 2012).

Given these interindividual differences in neural response to receiving negative emotional information in high PC and low PC individuals, we expected that temporarily increasing this prefrontal activity by administering tDCS would affect functional connectivity and mood. More specifically, we anticipated that this would occur after being emotionally challenged and depend on individual vulnerability for psychopathology as assessed through PC-status. Furthermore, we expected tDCS to particularly modulate functional connectivity in regions known to be involved in emotion processing and regulation (e.g., medial and/or lateral prefrontal areas). To the extent that more vulnerable high PC individuals might benefit more from this treatment, this would suggest that tDCS influences emotional processing differently depending on 'baseline' individual vulnerability characteristics.

To test this hypothesis, in the present study we administered one session of MRI-compatible prefrontal tDCS (vs. sham) prior to hearing self-referential criticism (as modified from Hooley et al. 2005, 2009) in young healthy females. Conforming to a standard tDCS approach for improvement of emotion regulation in depressed patients, we placed the anodal electrode at the left DLPFC and the cathodal electrode at the right supraorbital region (rSO; Lefaucheur et al. 2017). This electrode montage was preferred over a bifrontal left DLPFC – right DLPFC setup of which the efficacy is currently not sufficiently proven (Lefaucheur et al. 2017). Furthermore, MRI-based finite element modeling studies have suggested a slightly more focal electric field strength following unilateral tDCS than after a bifrontal setup (Wagner et al. 2007; Rampersad et al. 2014). Changes in self-reported mood and whole-brain functional connectivity patterns differing between low and high PC individuals were explored directly following tDCS (T2) and after hearing criticism (T3), compared to baseline (T1). The aim of this study was to further examine the trans-diagnostic construct of PC by investigating if PC moderates tDCS effects on emotional processing following an affective challenge.

Materials and methods

Participants

The study was approved by the Ethical Committee of the University Hospital of Ghent University (UZ Gent) and was carried out following the guidelines of the Declaration of World Medical Association (2004). At the end of the experiment, all participants were financially compensated.

Forty-six right-handed healthy young females were invited to participate in this study after giving written informed consent. However, results will only be reported for those 41 participants [age mean (SD) = 22.9 (2.61), age range 20–29 years old] for whom all resting-state fMRI scans were available (i.e., 3 scans in the active tDCS condition, 3 scans in the sham tDCS condition). For 5 out of the 46 participants we were not able to run all 6 scans due to scanner problems. These five participants were therefore excluded from further analyses. Participants were included in the study if they had no current or history of psychiatric disorders (M.I.N.I., edition 5.0.0 based on DSM-IV; Sheehan et al. 1998; Dutch translation by Overbeek et al. 1999), a score below 14 on the BDI-II (Beck et al. 1996; Dutch version by Van der Does 2002), no current/history of neurological problems or implanted metal objects in/over the head, and no current use of psychotropic medications. In addition to the BDI-II, participants completed the following trait questionnaires: Rosenberg Self-Esteem Scale (RSES; Rosenberg 1965; Franck et al. 2008); Rumination Response Scale (RRS; Treynor et al. 2003; Dutch translation by Raes et al. 2009).

Transcranial direct current stimulation (tDCS)

For this single session crossover design (see Fig. 1), participants were randomized to an active-first ($n = 20$) or sham-first ($n = 21$) stimulation condition. Based on a recent meta-analysis by Dedoncker et al. (2016b), an interval-between-sessions of at least 2 days was chosen. tDCS sponge-electrodes (25cm^2) were positioned on the scalp under neuronavigation guidance (BrainsightTM, Rogue Research, Inc.) based on an individual T1-weighted MRI (3D-TFE, TR/TE = 2250/4.18; flip angle = 9°; FOV = 256 × 256mm^2; resolution = 1.0 × 1.0 × 1.0mm^3; Siemens 3 T TrioTim, Siemens, Erlangen, Germany). The anodal electrode was placed over the left DLPFC, while the cathodal electrode covered the contralateral supra-orbital region. tDCS was administered in the MRI scanner, at an intensity of 1.5 mA for 20 min (30s ramp-up) by an MRI-compatible battery-driven stimulator (NeuroConn, DC-STIMULATOR MR). For the sham stimulation, direct current was ramped down after 30s (Nitsche et al. 2008).

Self-referential auditory comments

After receiving tDCS (vs. sham), and while being instructed to focus on a fixation cross projected on a mirror in the scanner, participants were exposed to a series of standardized self-referential auditory comments through non-ferrous gradient-damping headphones (Fig. 1). All participants heard exactly the same comments. Each comment lasted 30s and was preceded and followed by 30s of silence in a blocked design (i.e., 8 min 30s in total). The comments were critical, praising, or neutral in nature (see Hooley et al. 2005, 2009). They were designed to be broadly applicable and personally relevant for a

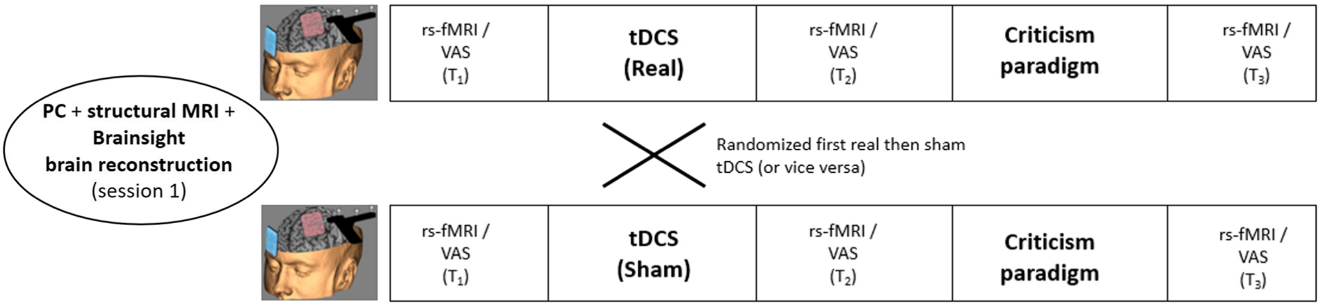

Fig. 1 Study design. In a sham-controlled cross-over setup, all subjects participated in two sessions separated for at least 2 days, and were randomized in either the active tDCS-first order, or the sham-first order. At the start of the first session, PC was assessed. For subsequent neuronavigation purposes, at the first session all participants underwent a T1-weighted MRI scan of the brain used to locate and to accurately target the left dorsolateral prefrontal cortex. The cathode was placed at the contralateral supraorbital region. After electrode placement, participants (re-)entered the MRI scanner for the remainder of the session. Prior to receiving tDCS (vs. sham) stimulation, rs-fMRI and mood ratings (VAS) were assessed (T1), followed by a re-assessment after stimulation (T2) and following the criticism paradigm (T3). Abbreviations: PC, Perceived Criticism; rs-fMRI, resting-state fMRI; VAS, visual analogue scales

wide range of participants. In each session, participants heard two neutral comments, followed by two praising comments, followed by two neutral comments and then two criticism comments. No comment was repeated across sessions. This specific order was chosen in accordance with the affective contrast theory (Manstead et al. 1983), which states that the impact of an emotional experience (e.g., being criticized) is contingent on the level of contrast with a preceding emotional state (e.g., being praised).[1] Importantly, participants were instructed to listen carefully to the auditory comments, and asked to imagine they were overhearing someone talking to them.

Perceived criticism

Perceived criticism (PC) was assessed at the start of the first scan session with a single question: "How critical do you think people in your nearest environment – such as family, friends … - are of you?" (adapted from Hooley and Teasdale 1989). Although PC ratings typically are made with reference to a particular person, we modified the procedure to include more than one reference person in an effort to provide a broader (and potentially more reliable) perspective. Participants gave a rating on a scale from 0 (i.e., not at all critical) to 10 (i.e., very critical; in accordance with VAS ratings, cf. infra). Given a mean PC score in our sample of 5.66, and in line with the original cut-off scores proposed by Hooley and Teasdale, scores ranging from 0 to 5 were categorized as low PC, and scores ranging from 6 to 10 were categorized as high PC.

Momentary mood assessment

Momentary mood states were assessed in the scanner using six visual analogue scales (VAS) measuring how fatigued, vigorous, angry, tensed, depressed and cheerful participants were feeling "at this moment". To this end, the VAS were represented as a 10 cm line with endpoints from "not at all / 0" to "very much / 10", and were projected on a mirror in the scanner. Participants were asked to give a rating on a scale from 0 to 10 on three separate occasions: at the start of the session (T1), following the tDCS administration (T2), and after the auditory comments were presented to the participant (T3; Fig. 1).[2]

Resting-state fMRI

Resting-state fMRI (rs-fMRI) scans were obtained with the following parameters: EPI sequence, TR/TE = 2500/35 ms; flip angle = 80°; FOV = 224 × 224mm^2; resolution = 3.5 × 3.5 × 3.0mm^3; slice thickness = 3.00 mm; number of slices = 170. For each of the 2 sessions (active tDCS, sham tDCS) the scanning procedure was repeated 3 times: rs-fMRI before tDCS (T1), rs-fMRI after tDCS (T2), rs-fMRI after the criticism paradigm (T3; Fig. 1). During the rs-fMRI measurements, participants were asked to stay awake with their eyes closed.

Data analysis

All collected behavioral data ($n = 40$; one dataset did not contain VAS ratings) were analyzed with SPSS 24 (Statistical Package for the Social Sciences; IBM SPSS Statistics for Windows, version 24.0, IBM Corp., Armonk, NY). Where necessary, we applied the Greenhouse-Geisser (GG) correction to ensure the assumption of sphericity. The significance level was set at $p < 0.05$ for all analyses (two-tailed). For the clinical characteristics analyses we used independent t-tests with *Perceived Criticism* as the grouping factor [low ($n = 17$)

[1] A detailed comparison of tDCS effects on functional connectivity during either neutral feedback, praise or self-referent criticism will be published elsewhere.

[2] The effects of the procedure on ruminative thinking (Momentary Ruminative Self-Focus Inventory, MRSI; Mor et al. 2015) and implicit and explicit self-esteem (Implicit Relational Assessment Procedure, IRAP, and explicit ratings of the words used in the IRAP) are published elsewhere (De De Raedt et al. 2017).

vs. high ($n = 23$)] and continuous PC scores, BDI depression scores, RRS rumination scores, and Rosenberg self-esteem scores as the test variables. For the VAS mood analysis we used a 3 × 2 × 2 MANCOVA with *Time* (VAS_1 = after rs-$fMRI_1$ and before stimulation; VAS_2 = after stimulation, before rs-$fMRI_2$; and VAS_3 after the self-referential audio scripts, before rs-$fMRI_3$) and *Stimulation* (active vs. sham tDCS) as the within–subject factors, and *Perceived Criticism* [low ($n = 17$) vs. high ($n = 23$)] as the between-subjects factor, controlling for age effects (to be in line with the FC analyses, see below). Of note: adding *Order* (first active then sham, $n = 19$ vs. first sham then active, $n = 21$) as a factor did not influence the outcome (*F*-tests, $p > 0.05$), and was therefore not considered further. The six VAS mood scales were the multiple dependent variables. Importantly, the 'vigorous' and 'cheerful' VAS were reversed-scored for interpretation purposes (i.e., higher scores on all VAS scales indicate more negative affect). To follow up significant multivariate effects, we checked the univariate effects. Significant main and interaction effects were followed-up with *t*-tests.

The anatomical and fMRI images ($n = 41$) were preprocessed and analyzed using the Matlab-based Functional Connectivity (CONN) toolbox (version 17.f; https://www.nitrc.org/projects/conn; Whitfield-Gabrieli and Nieto-Castanon 2012) of SPM12 (Wellcome Trust Centre for Neuroimaging, London, UK). Preprocessing included functional realignment and unwarping, slice-timing correction (Siemens Interleaved), outlier detection (ART-based identification of outlier scans for scrubbing), and functional and structural segmentation and normalization (i.e., simultaneous gray matter, white matter, and cerebrospinal fluid segmentation and normalization to the standard brain template from the Montreal Neurological Institute, MNI). No subject was excluded from further analyses based on preprocessing. ROI-to-ROI functional connectivity analyses were performed on unsmoothed volumes (see infra). To reduce noise, preprocessed images were subsequently band-pass filtered (0.01–0.1 Hz) and motion regression was performed (motion realignment parameters + first derivatives). Outliers were 'scrubbed' out (i.e. regressing out outliers detected by the ART toolbox). White matter and CSF signal were regressed out by the implemented aCompCor strategy (Behzadi et al. 2007).

ROI-to-ROI functional connectivity analyses were performed by first extracting the average BOLD time series across all voxels in a predefined ROI. 277 ROIs (of 4 mm sphere radius) were defined, partly based on the functional network parcellation by Power et al. (2011; 264 nodes categorized into distinct functional neural networks), added with 13 extra ROIs of relevance (i.e., bilateral nucleus accumbens, caudate nucleus, amygdala, ventral hippocampus, locus coeruleus, sgACC, VTA and Raphe nucleus; 4 mm spheres). Next, for the first-level analysis, a weighted general linear model (GLM; HRF weighing) was used to determine resting state connectivity at the individual level.

Based upon 1st level results, bivariate correlation coefficients were computed separately for the average BOLD signals in each pair of seed-and-target ROIs, and converted to Fisher transformed Z scores to ensure normal distribution. Finally, a mixed within-between ANCOVA test was used with a threshold set at $p < 0.01$ false discovery rate (FDR) corrected. We aimed to explore whether there was a differential effect of our conditions (within-subjects factors Stimulation - active vs. sham tDCS - and Time - before stimulation, after stimulation, after the self-referential audio scripts) between low ($n = 17$) vs. high PC ($n = 24$) females (between-subjects factor Perceived Criticism), controlling for age effects. Of note, adding Order (first active then sham vs. first sham then active) as a factor did not influence the outcome (*F*-tests, $p > 0.05$; SPSS), and was therefore excluded from further analyses. Due to significant baseline differences between active vs. sham tDCS (cf., online resource 1), interaction effects were followed-up by post-hoc univariate ANCOVAs in SPSS. Direct effects for active and sham tDCS were separately examined by determining the dependent variable (i.e., connectivity values after stimulation), the fixed factor (i.e., *Perceived Criticism*: low vs. high), and the covariate (i.e., connectivity values before stimulation). Effects of being criticized following either active or sham tDCS were examined with the dependent variable (i.e., connectivity values after the self-referential audio scripts), the fixed factor (i.e., *Perceived Criticism*: low vs. high), and the covariate (i.e., connectivity values after stimulation).

Results

Clinical characteristics

Results of an independent t-test showed that the PC scores in the PC low group were by design significantly lower than the PC scores in the PC high group [$t(39) = -11.43$, $p < 0.001$]. Further independent t-tests showed no significant differences between the PC low and the PC high group for BDI depression scores [$t(39) = -0.58$, $p > 0.05$], RRS rumination scores [$t(39) = 1.52$, $p > 0.05$], and the Rosenberg self-esteem scores [$t(39) = 1.23$, $p > 0.05$; Table 1].

Mood

Results of a 3 × 2 × 2 (*Time* x *Stimulation* x *Perceived Criticism; controlling for age effects*) MANCOVA showed a significant main effect of *Time* ($F(12,140) = 6.33$, $p < 0.01$, $\eta_p^2 = 0.35$). Other main and interaction effects were non-significant (all *F*'s < 2.19, *p*'s > 0.05). Univariate tests further showed a significant main effect of *Time* for fatigue ($F(2,74) = 8.24$, $p < 0.01$, $\eta_p^2 = 0.18$), anger ($F(1.34,49.49) = 7.99$, $p < 0.01$, $\eta_p^2 = 0.18$, GG-corrected), vigor

Table 1 Clinical characteristics of the sample. Mean (+/-SD) participant scores at the PC measure, and the BDI, RRS, and Rosenberg scales for both the PC low group and the PC high group are presented. Statistically significant differences are marked in bold

	PC Low ($N = 17$) M (SD)	PC High ($N = 23$) M (SD)	p-value
PC	3.94 (0.90)	6.88 (0.74)	**<0.001**
BDI	3.24 (3.27)	4.04 (5.03)	0.57
RRS	37.12 (7.69)	32.83 (9.67)	0.14
Rosenberg	22.18 (4.16)	20.50 (4.38)	0.23

BDI, Beck Depression Inventory; *M*, Mean; *PC*, Perceived Criticism; *RRS*, Ruminative Responses Scale; *SD*, Standard Deviation

($F(1.69,62.65) = 10.31$, $p < 0.01$, $\eta_p^2 = 0.22$, GG-corrected) and cheerfulness ($F(2,74) = 8.42$, $p < 0.01$, $\eta_p^2 = 0.19$), and a trend for depressive feelings ($F(1.65,60.94) = 3.18$, $p = 0.058$, $\eta_p^2 = 0.08$, GG-corrected). The main effect of *Time* was not significant for tenseness ($p > 0.05$). Finally, pairwise comparisons indicated that participants felt more fatigued (M_{T1} (SE) = 3.61 (0.20), M_{T2} (SE) = 4.45 (0.25), $p < 0.01$), less vigorous (M_{T1} (SE) = 6.58 (0.30), M_{T2} (SE) = 7.01 (0.29), $p < 0.01$), and less cheerful (M_{T1} (SE) = 6.16 (0.31), M_{T2} (SE) = 6.62 (0.28), $p < 0.01$) directly following the tDCS stimulation regardless of whether that stimulation was active or sham. Importantly, all felt more angry (M_{T2} (SE) = 0.34 (0.11), M_{T3} (SE) = 0.69 (0.15), $p < 0.01$) and more depressed (M_{T2} (SE) = 0.41 (0.12), M_{T3} (SE) = 0.55 (0.15), $p < 0.05$), after being criticized than they felt directly after the tDCS stimulation. In summary, our tDCS procedure did not influence negative affect differently between individuals low and high in PC. However, independent from having had active or sham tDCS, all individuals felt more fatigued, less cheerful and less vigorous directly following stimulation, and more angry and depressed after hearing criticism.

Functional connectivity

Whole-brain seed-based ROI-to-ROI functional connectivity analyses revealed significant modulation of latero- and medial prefrontal neural connectivity. More specifically, the between-group [*Perceived Criticism*; low ($n = 17$) vs. high ($n = 24$)] 2 × 3 ANCOVA (*Stimulation*, *Time*; covariate *Age*) revealed significant modulation of two functional connections during rest (seed-level corrected at p-FDR < 0.01): (1) left dorsolateral prefrontal cortex (DLPFC; MNI: x = −42, y = 25, z = 30) connectivity to left posterior insula (MNI: x = −30, y = −27, z = 12; $F(2,37) = 17.33$, p-FDR < 0.01), and (2) left dorsal anterior cingulate cortex (dACC; MNI: x = −11, y = 26, z = 25) connectivity to right dorsomedial prefrontal cortex (DMPFC; MNI: x = 6, y = 54, z = 16; $F(2,37) = 13.73$, p-FDR < 0.01; Fig. 2a).

For the left DLPFC – left posterior insula connection, post-hoc univariate ANCOVAs revealed a significant between-group effect of tDCS (Fig. 2b). More specifically, having adjusted for baseline connectivity values (i.e., covariate; T1), connectivity post tDCS (i.e., dependent variable; T2) was significantly different in low vs. high PC individuals in the active stimulation condition [$F(1,38) = 6.601$, $p < 0.05$, $R^2_{sp} = 14.16\%$; Low PC M(SD): 0.07 (0.04); High PC M(SD): -0.07 (0.03)] as well as the sham stimulation condition [$F(1,38) = 4.750$, $p < 0.05$, $R^2_{sp} = 10.34\%$; Low PC M(SD): -0.04 (0.03); High PC M(SD): 0.05 (0.02)]. However, functional connectivity following hearing criticism (i.e., T3) was not significantly different in low vs. high PC individuals for either the active or the sham stimulation condition after having corrected for connectivity values post-tDCS (i.e., T2; respectively active and sham; p-values for both Fs > 0.05). In summary, directly following active tDCS, left DLPFC – left posterior insula functional connectivity was lower in high PC females compared to low PC females. In contrast, high PC females show increased connectivity after sham tDCS compared to low PC females. No changes in left DLPFC – left posterior insula functional connectivity were observed in response to hearing criticism after active and sham stimulation.

For the left dACC – right DMPFC connection, post-hoc univariate ANCOVAs revealed that functional connectivity after active as well as sham tDCS (i.e., T2) was not significantly different in low vs. high PC individuals after correcting for connectivity at baseline (i.e., T1; respectively active and sham; p-values for both Fs > 0.05). However, having adjusted for connectivity post-tDCS (i.e., T2), functional connectivity after hearing criticism (i.e., T3) was significantly different in low vs. high PC individuals following active stimulation [$F(1,38) = 6.607$, $p < 0.05$, $R^2_{sp} = 14.62\%$; Low PC M(SD): 0.08 (0.04); High PC M(SD): -0.07 (0.04); Fig. 2c], but not sham stimulation ($p > 0.05$). Thus, left dorsal ACC – right DMPFC functional connectivity was only modulated differently in low and high PC individuals in response to hearing criticism after active (but not sham) stimulation, with high PC females showing decreased functional connectivity compared to low PC females.

Discussion

The present MRI-compatible tDCS study aimed to examine whether in response to hearing self-referential criticism, a single prefrontal tDCS session (vs. sham) causes differential mood and neural connectivity changes in young healthy females differing in PC status. In line with recent meta-analyses showing no single session tDCS effects on self-reported affective states (Mondino et al. 2015; Remue et al. 2016), no differential effects on mood were found. Regardless of whether they received active or sham tDCS, all female participants (low and high PC) felt more tired, less cheerful and less

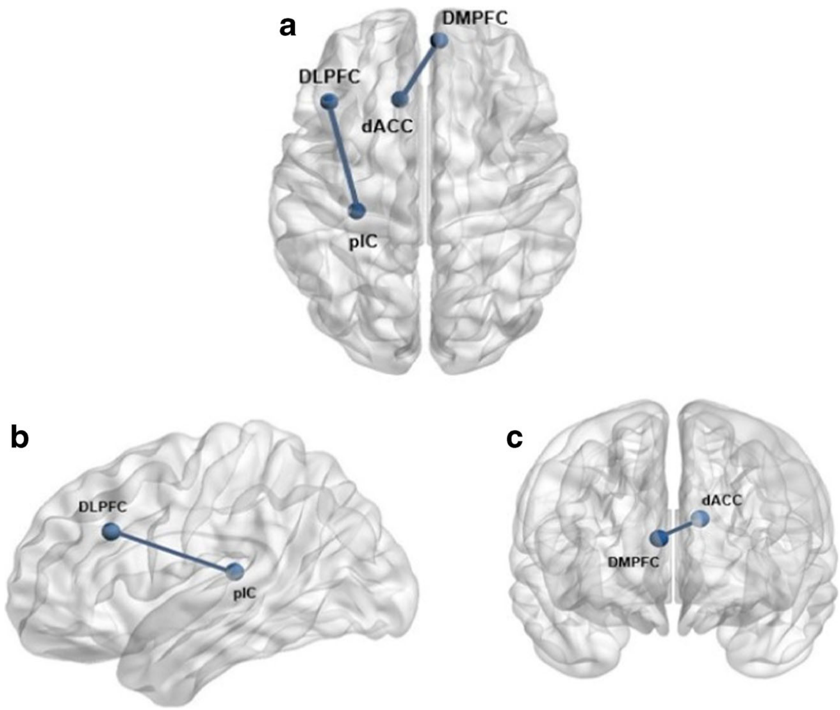

Fig. 2 Resting-state functional connectivity. **a** Results of the ROI-based correlation analyses showing the functional connectivity differences between low PC and high PC females following tDCS (vs. sham) and after listening to criticism (dorsal view). **b** Active tDCS reduced connectivity between the left dorsolateral prefrontal cortex (DLPFC) and left posterior insular cortex (pIC) in high PC females compared to low PC females or sham stimulation (left hemisphere, lateral view). **c** Listening to criticism after active tDCS reduced connectivity between the left dorsal anterior cingulate cortex (dACC) and right dorsomedial prefrontal cortex (DMPFC) in high PC females compared to low PC females (coronal view). ROIs are represented by spheres, and the blue edges represent a reduced connectivity between the ROI nodes (BrainNet viewer; Xia et al. 2013)

vigorous following stimulation. Participants also felt angrier and more depressed after being criticized. However, our tDCS protocol influenced functional connectivity patterns differently depending on PC status.

First, in contrast to the sham stimulation or the active stimulation in low PC scoring females, one session of left DLPFC-targeted tDCS triggered a local reduction in functional connectivity between the left DLPFC and the left posterior insula in individuals who scored high on PC (i.e., PC-dependent tDCS effect, prior to hearing criticism). The DLPFC has been associated with directing attention to internal representation of sensory stimuli (Curtis and D'Esposito 2003) and monitoring/manipulating information in working memory (i.e., cognitive control; MacDonald et al. 2000; Ridderinkhof et al. 2004; reviewed by Curtis and D'Esposito 2003). The posterior insula, on the other hand, is suggested to be involved in the interoceptive – and objective – representation of the physiological bodily conditions (e.g., upon confrontation with negative/painful stimuli; Craig 2002; Segerdahl et al. 2015; Singer et al. 2004; review by Menon and Uddin 2010). Our findings therefore suggest brain-state dependent effects of prefrontal tDCS, with distinct modulations in neural processing following tDCS depending on prior vulnerability level (i.e., high vs. low PC).

Second, we showed that being criticized following active (but not sham) prefrontal tDCS resulted in a reduction in functional connectivity between the left dACC and right DMPFC in high versus low PC females (i.e., PC-dependent criticism effect, controlling for pure tDCS effects). Irrespective of clinical status (i.e., depression, remission, healthy), being exposed to criticism has previously been shown to disturb corticolimbic processing - a pattern implicated in depressive illness - particularly in individuals scoring high on PC (Hooley et al. 2012). Hooley et al. (2009) have also shown that being criticized decreased activity in the left dACC, right DMPFC and right DLPFC in formerly depressed individuals as compared to healthy individuals. These findings by Hooley et al. (2009; 2012) suggest that individuals with vulnerability to depression - such as formerly depressed patients - might less adequately monitor (dACC-mediated; Spunt et al. 2012) and evaluate emotionally-salient stimuli (DMPFC-mediated; Etkin et al. 2011; Kalisch et al. 2006; Kober et al. 2008) and – particularly when highly sensitive to perceived criticism – may be less able to adequately regulate resulting stress and negative affect (DLPFC-mediated; De De Raedt and Koster 2010). Our observations of decreased dACC-DMPFC functional connectivity indicates that prefrontal tDCS – administered in females scoring high on PC – is able to reduce responsiveness to being criticized. More specifically, as the dACC is involved in monitoring emotionally-salient stimuli (Spunt et al. 2012), and the DMPFC moderates experiencing and evaluating the significance of an emotional context (Etkin et al. 2011; Kalisch et al. 2006; Kober et al. 2008; Lamm et al. 2011; Ochsner and Gross 2005) and making self-referential mental-state attributions (Fossati et al. 2003; Northoff et al. 2006; Ochsner et al. 2005), our findings suggest that prefrontal tDCS is followed by a decreased emotional responsiveness towards criticism, particularly in high PC females thought to have increased neuropsychiatric vulnerability. Interestingly, Di Di Simplicio et al. (2012) reported a similar down-regulation of negative self-referential processing in the medial prefrontal cortex in individuals at risk for depression following 7 days of administering the selective serotonin reuptake inhibitor Citalopram (vs. placebo). They also did not report any effects of the SSRI on self-reported mood. The similar result we observed by applying only one 20 min-lasting session of prefrontal tDCS may be indicative of similar working mechanisms.

Despite apparent advantages, such as the online MRI-compatible tDCS administration which diminishes potential sources of noise by not requiring participants to go in and out of the scanner, several limitations of this study warrant mention. First, although previous research has shown that the PC construct is a temporally stable and valid vulnerability marker (Hooley and Teasdale 1989; Masland and Hooley 2015) categorization of participants into the low or the high PC group was based on a single question. In accordance with previous PC research (Hooley et al. 2012) however, we have also categorized individuals scoring 0–5 as low PC, and 6–10 as high PC (consistent with a mean PC score of 5.66). Another methodological choice that could be regarded as a potential limitation is that, instead of rating PC in a particular relationship (e.g., relative, significant other), we asked participants for a more general PC rating of their social environment including family and friends to obtain a more general measure of how individuals perceive themselves as being criticized. However, recent research suggests that when people are asked to provide PC ratings for different social relationships, these ratings are significantly inter-correlated (Felix and Hooley 2018). In other words, people reporting high PC in one relationship tend to perceive high levels of criticism in other relationships, suggesting that PC may provide insights into some of the more global aspects of the social environment. We were also able to demonstrate that our adapted PC measure was not confounded by differences in current depressive symptoms, rumination, or self-esteem in the high and low PC groups, reflecting earlier research indicating a lack of association between PC and both symptom severity (Hooley et al. 2012; Renshaw et al. 2003) and personality characteristics (Renshaw 2008). However, further research is needed to examine the effect of our modification of the PC question more thoroughly.

Baseline differences in connectivity strength were found in the active and the sham tDCS condition in low PC as well as high PC individuals. We accounted for these baseline differences by performing univariate ANCOVAs controlling for baseline connectivity strengths. Nonetheless, interpretation of our results should be limited to young healthy females. Further research, exploring whole-brain functional connectivity when being criticized after tDCS in other high and low PC samples involving males (as well as children or adolescents) is therefore warranted. Lastly, we would encourage further research aiming to replicate and expand on our findings by administering tDCS either during or after exposure to criticism. This way, one would expect criticism-induced emotional dysregulation in high PC individuals, respectively coupled with or followed by applying neuromodulation in an attempt to normalize brain activity.

In conclusion, our results indicate that one session of active prefrontal tDCS - but not sham - reduces dACC-DMPFC functional connectivity following hearing criticism in females scoring high on PC. This finding suggests that a single-session of prefrontal tDCS might have differential effects on the neural processing of negative emotional information depending on PC, which has been shown to be related to vulnerability for psychopathology, thereby expanding upon the trans-diagnostically relevant features of the perceived criticism construct. More specifically, our results may provide a more biologically-oriented framework of how prefrontal tDCS could be especially efficient for individuals more susceptible to develop mood and/or anxiety disorders (i.e. scoring high on PC). Future tDCS research focusing on emotional processing may do well to consider individual trait variability characteristics when evaluating tDCS effects on functional connectivity.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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