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RESEARCH ARTICLE

One MRI-compatible tDCS session attenuates ventromedial cortical perfusion when exposed to verbal criticism: The role of perceived criticism

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Abstract

Transcranial direct current stimulation (tDCS) is a potential treatment strategy for mood and anxiety disorders, but how this application may influence emotional processes, and whether this is related to individual characteristics, is not well understood. It has been proposed that perceived criticism (PC) may represent a vulnerability factor for the development of such mental illnesses. To decipher whether neural mechanisms of action of tDCS potentially differ depending on PC status (low vs. high), we evaluated mood and brain perfusion before and after applying MRI-compatible tDCS, and after participants were exposed to verbal criticism in the scanner. Experimental design 30 healthy nondepressed females were included in a sham-controlled crossover MRI-compatible tDCS study. Brain perfusion was measured by means of arterial spin labeling (ASL) before and after tDCS applied to the left dorsolateral prefrontal cortex (DLPFC), and after hearing criticism. Before the experiment, all participants provided a rating of PC in their closest environment. Principal observations at the behavioral level, criticism made participants angrier. This was unrelated to the active or sham stimulation. After being criticized, females scoring high on PC had significantly decreased brain perfusion in the pregenual anterior cingulate cortex (pgACC) and medioprefrontal cortex (mPFC), after active tDCS but not sham. The decrease in pgACC/mPFC perfusion points to a significant impact of tDCS in brain areas related to stress responses and self-referential processes, especially in females scoring high on PC, which has been shown to be related to vulnerability for mood and anxiety disorders.

KEYWORDS

arterial spin labeling, medial prefrontal cortex, perceived criticism, transcranial direct current stimulation

1 | INTRODUCTION

Prefrontal transcranial direct current stimulation (tDCS) is used to treat a variety of neuropsychiatric disorders, with a focus on mood and psychotic illnesses (Lefaucheur et al., 2017). tDCS is a noninvasive, nonconvulsive neuromodulation technique (Baeken, Brunelin, Duprat, & Vanderhasselt, 2016; Sehm et al., 2012). It involves the application of a weak current (0.5–2 mA) between an anode and a cathode placed on specific locations over the human scalp. This way, tDCS induces polarization-shifts on the resting membrane potential, respectively enhancing or decreasing spontaneous neural activity in the underlying neuronal tissue (Nitsche et al., 2003; Brunoni et al., 2012; although, see Batsikadze, Moliadze, Paulus, Kuo, & Nitsche, 2013). Prefrontal anodal tDCS appears to not only result in focal effects in regions directly

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targeted by the electrodes but it can also affect regions anatomically and functionally connected to them (Keeser et al., 2011; Peña-Gómez et al., 2012; Stagg et al., 2013; review by Wörsching et al., 2016). Interestingly, tDCS has been used to temporarily modulate prefrontal neural activity and associated cognitive processes, both for nonemotional (Brunoni & Vanderhasselt, 2014; Dedoncker, Brunoni, Baeken, & Vanderhasselt, 2016a) and emotional information (Wolkenstein and Plewnia, 2013; Vanderhasselt, Brunoni, Loeys, Boggio, & De Raedt, 2013; Vanderhasselt et al., 2016).

As the dorsolateral prefrontal cortex (DLPFC) is implicated in regulating affective states, that is, emotion regulation, anodal tDCS applied over the left DLPFC has been used as a treatment to improve mood and cognitive functioning in depressed patients (Brunoni et al., 2016). The DLPFC provides cognitive control over stress and emotion responsiveness and may be hypoactive during depressive episodes (Disner et al., 2011), whereas hyperreactivity is observed in limbic areas as reflected in enhanced arousal and stress responses (Price and Drevets, 2012). It has been proposed that this dynamic interplay between DLPFC and limbic regions represents a neurobiological model underlying the relationship between stress and depressive episodes (De Raedt & Koster, 2010; De Raedt et al., 2015).

One source of psychosocial stress is criticism, which may be defined as negative evaluative feedback in social interactions (Lee, Siegle, Dahl, Hooley, & Silk, 2015). Importantly, higher perceived criticism (PC; a trait rating score of how critical people believe specific members of their family and/or friends to be of them) may be a risk factor for depressive relapse (Kwon, Lee, Lee, & Bifulco, 2006; review by Masland & Hooley, 2015), and may be a personal characteristic related to greater risk for developing mood, anxiety, and other disorders. Moreover, higher neural sensitivity to criticism has been shown to be a useful indicator of mood regulatory difficulties associated with a disrupted frontolimbic circuitry not only in depressed, remitted depressed but also in healthy individuals (Hooley, Siegle, & Gruber, 2012). Hooley et al. (2012) demonstrated that individuals scoring high on PC showed amygdala hyperactivation and prefrontal hypoactivation when criticized by their mothers, which is indicative of the implication of the above-mentioned neurocircuit underlying the relationship between stressors and depression (De Raedt & Koster, 2010).

Although frontolimbic abnormalities in response to (psychosocial) stressors in depressed patients are commonly acknowledged, how noninvasive neurostimulation might impact these neurocircuitries in people at risk for mood and anxiety disorders is unclear. Furthermore, these frontolimbic neuronal patterns related to PC have never been examined in combination with neuromodulation techniques. Investigating how a manipulation of frontal functioning impacts neural processing elicited by being criticized, and whether this is different depending on PC status (low vs. high), may further elucidate the mechanisms underlying this risk factor.

Real-time neuroimaging methods could provide crucial information regarding the neural activity of specific brain areas and/or circuitries (Bergmann, Karabanov, Hartwigsen, Thielscher, & Siebner, 2016; Saiote, Turi, Paulus, & Antal, 2013). Arterial spin labeling (ASL), a noninvasive fMRI technique, uses arterial water as an endogenous tracer to measure cerebral blood flow (CBF). ASL therefore provides reliable absolute quantification of CBF (Borogovac & Asllani, 2012). It has already been reported that anodal tDCS applied to the left DLPFC affected perfusion in the stimulated areas and those functionally connected to them (Stagg et al., 2013). Furthermore, Antal et al. (2014) showed that in healthy participants prefrontal anodal tDCS was able to influence perfusion in brain areas related to stress responses and self-referential thought processing, such as the amygdala and the medial prefrontal cortex (mPFC). In this study, it is therefore hypothesized that prefrontal tDCS influences affective and self-referential processing, although it has not yet been demonstrated whether there are potentially different effects depending on individual vulnerability for psychiatric disorders.

Given the evidence of PC as a risk factor, indicative of vulnerability for depression, the aim of this study was to investigate whether this individual characteristic influences the neuromodulatory effects of tDCS after receiving criticism in a sham-controlled MRI-compatible tDCS crossover study. We expected that active but not sham tDCS would affect frontolimbic perfusion after criticism, with more vulnerable high PC individuals benefiting more from the neuromodulation. We thus also investigated whether the effect would be moderated by PC.

2 | METHODS AND MATERIALS

The Ethical Committee of the University Hospital of Ghent University approved the study and it was carried out according to the Declaration of Helsinki (2004). All participants gave written informed consent and were financially compensated. As inter-individual neurophysiological variability in response to the tDCS application may affect replicability (López-Alonso, Fernández-Del-Olmo, Costantini, Gonzalez-Henriquez, & Cheeran, 2015), we used a sham-controlled within-subjects crossover design.

2.1 | Participants

This study was part of a larger study examining the effects of MRI-compatible tDCS on brain functioning and cognition in real time. In that larger study, 46 participants were recruited through student forums of Ghent University as well as via social media. To avoid gender and age influences, we only included females within a narrow age range (20–30 years old; Mean age [*SD*] = 22.13 [2.16]). Complete ASL sets (i.e., 3 in the sham tDCS session and 3 in the active tDCS session) were only available for 30 participants. These complete datasets were included for the present analysis. All participants were screened before inclusion to confirm that they had: (a) no current/history of psychiatric disorders, using the MINI-International Neuropsychiatric Interview (M.I.N.I.; Sheehan et al., 1998) and were therefore never-depressed individuals, (b) a score below 14 on the BDI-II (Beck, Steer, & Brown, 1996) to avoid any confound with current mood problems, (c) no current/history of neurological problems or implanted metal objects in/over the head, (d) no current or past use of psychotropic medications, and that they were (e) right-handed.

2.2 | Study design

Before the start of the single-session crossover tDCS protocol, participants were randomly allocated (by flipping a coin) to an active-first

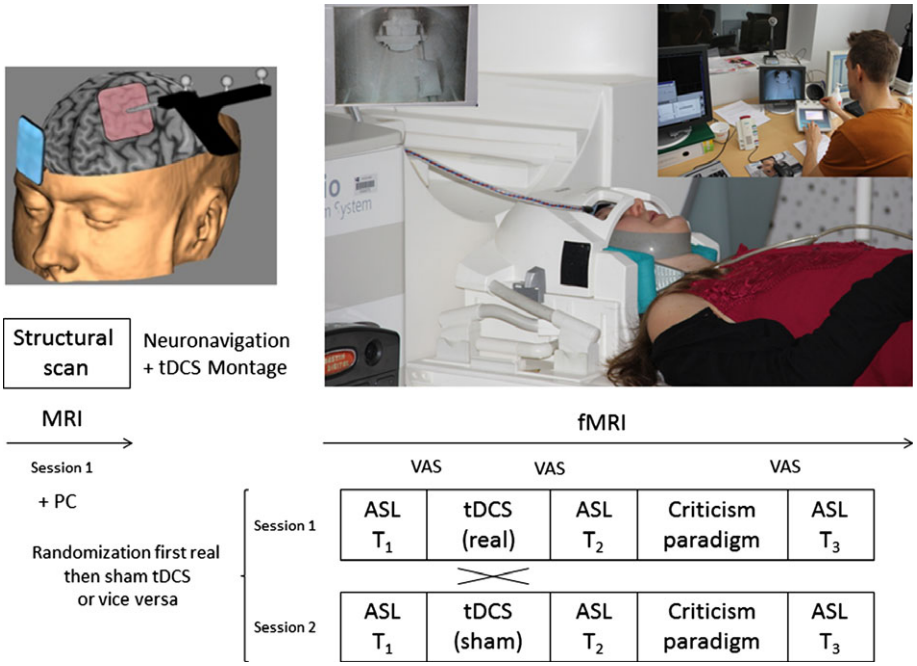

FIGURE 1 Experimental setup. Before entering the experimental tDCS/ASL protocol, at the first session all participants underwent a T1-weighted MRI scan of the brain used to locate and to accurately target the left dorsolateral prefrontal cortex (anode in red) with the Brainsight neuronavigation system (Brainsight™, Rogue Research, Inc.). Cathode in blue placed on the right supraorbital region. Participants were randomized to first receive active or sham tDCS, with reversing the order at session two. All were verbally assessed in the scanner with the VAS scales after ASL T_1 and before stimulation; before ASL T_2 and after stimulation; and after the audio recordings, before ASL T_3. Therefore, for each participant, in total, six ASL measurements were collected. Rating possibilities were clearly visibly projected on a screen in the scanner. VAS = visual analog scales; ASL = arterial spin labeling; PC = perceived criticism [Color figure can be viewed at wileyonlinelibrary.com]

(n = 14) or a sham-first (n = 16) stimulation condition. All participants were stimulated and criticized in the MRI scanner in real-time. Furthermore, all behavioral measurements, including PC and mood assessment, were performed in the MRI scanner. In each tDCS session, ASL scans were performed three times: before (T_1) and after tDCS (T_2), and also after the completion of the entire criticism paradigm (T_3). Thus, for each participant, in total, six ASL measurements were collected. For an overview of the study design (Figure 1).

2.2.1 | tDCS

For neuronavigation purposes, all subjects underwent a T1-weighted structural MRI brain scan at the start of the session (3D-TFE, TR/TE = 2,530/2.58; flip angle = 7°; FOV = 220 × 220 mm^2; resolution = 1 × 1 × 1 mm^3; number of slices = 176), using a Siemens 3 T TrioTim MRI scanner (Siemens, Erlangen, Germany; 32-channel SENSE head coil). Subjects were removed from the scanner, after which the tDCS surface electrodes (25 cm^2) were covered in electrode gel and positioned on the scalp based on each participant's structural scan using the Brainsight neuronavigation system (Brainsight™, Rogue Research, Inc., Montreal, Quebec, Canada). The anodal electrode was placed over the left DLPFC, which was visually located on the three-dimensional (3D) surface rendering of the brain based on the known gyral morphology (i.e., center part of the middle prefrontal gyrus, Brodmann area 9/46) De witte (2018). The cathodal electrode was placed on the right supraorbital area (1 cm above the eyebrows; Figure 1). During tDCS administration in the MRI scanner, a constant direct current of 1.5 mA was delivered for 20 min with a 30 s ramp-up by a MRI-compatible battery-driven stimulator (NeuroConn, DC-STIMULATOR MR). For sham stimulation, the electrodes were placed in the same positions as in the active tDCS condition; however, the current was ramped down after 30 s. This procedure has been shown to be a reliable sham condition (Nitsche et al., 2008). To avoid carry-over tDCS effects, based on our recent meta-analysis (Dedoncker, Brunoni, Baeken, & Vanderhasselt, 2016b), the time interval between the two stimulation sessions (active/sham tDCS) was at least 2 days.

2.2.2 | Self-referential auditory stimuli

While in the scanner participants listened to prerecorded auditory stimuli through nonferrous, gradient damping headphones (For a full overview see Supporting Information). The 30-s recordings were standardized and featured the same adult female voice. These recordings were developed by one of the authors based on past research (Hooley et al., 2009, 2012) and were designed to trigger self-referential processes in healthy participants. Across the two tDCS sessions, participants never heard the same comment twice (i.e., counterbalanced). The order of the type of comments was always the same: participants first heard 2 neutral, followed by 2 praising, then another 2 neutral, and finally 2 criticism comments.[1] According to the well-established effective contrast theory (Manstead, Wagner, & MacDonald, 1983), the impact of an emotional state depends on the contrast with the preceding state. When the emotional status of an individual contrasts

[1]The praising and neutral comments were used to compare the effects of personal comments with different valence on brain activity. These results will be published elsewhere.

TABLE 1 Mean ratings and standard deviations for the different visual analog subscales (VAS) before (T_1), immediately (T_2) after tDCS (active or sham condition), and postcriticism (T_3)

	Active tDCS			Sham tDCS		
	T1	T2	T3	T1	T2	T3
VAS fatigued	3.50 (1.43)	4.36 (1.97)	4.46 (1.99)	3.71 (2.07)	4.46 (2.27)	4.00 (2.34)
VAS vigorous	4.64 (2.13)	4.07 (2.21)	4.11 (2.04)	4.18 (2.09)	3.75 (2.08)	3.79 (2.01)
VAS angry	0.21 (0.57)	0.29 (0.66)	0.68 (1.09)	0.43 (1.07)	0.29 (0.66)	0.50 (0.84)
VAS tensed	2.18 (1.81)	2.82 (2.02)	2.79 (2.25)	2.79 (1.85)	3.00 (2.16)	2.89 (1.79)
VAS depressed	0.39 (0.79)	0.46 (0.96)	0.61 (1.20)	0.39 (0.78)	0.29 (0.60)	0.39 (0.88)
VAS cheerful	4.82 (2.18)	4.61 (2.27)	4.43 (2.04)	4.68 (2.37)	4.36 (2.31)	4.18 (1.89)

with the previous one, its salience is enhanced, leading to an increased impact. Each recording was preceded and followed by a silence of 30 s in a blocked design, making the paradigm 8 min and 30 s long in total. During the blocks, participants were instructed to keep their eyes open while focusing on a fixation cross, which was projected on a mirror inside the scanner.

2.3 | Behavioral and neuroimaging assessments

Questionnaires were projected onto the screen during the scanning session. Furthermore, the questions were read aloud to the participants through the headphones. Participants responded verbally through a built-in microphone.

2.3.1 | Perceived criticism

Perceived criticism (PC; Hooley et al., 2012) was measured at the start of the first scan session (ASL T_1; Figure 1) with a single question: "How critical do you think people in your nearest environment—such as family, friends …—are of you?" (adapted from Hooley & 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. Ratings were made using a scale from 0 (i.e., not at all critical) to 10 (i.e., very critical; in accordance with VAS ratings, see infra). Participants' scores ranging from 0 to 5 were considered low in PC, while scores ranging from 6 to 10 were considered high in PC (Hooley & Teasdale, 1989). In our sample, the mean PC score was 5.55 (*SD* = 1.62).

2.3.2 | Momentary mood assessment

Momentary mood states were assessed using six visual analog scales (VAS) measuring how fatigued, "vigorous" angry, tense, depressed, and "cheerful" participants were feeling "at this moment". The VAS is a 10 cm line, with endpoints from "not at all" to "very much", which was visually depicted as a ruler in the scan. Visual analog scales were verbally registered in the scanner at the start of the session (ASL T_1), following the tDCS administration (ASL T_2), and after the auditory fragments were presented to the participant (ASL T_3; Figure 1 and Table 1). The "vigorous" and "cheerful" VAS were reverse-scored, with higher scores indicating less vigorousness/cheerfulness.

2.3.3 | Arterial spin labeling

Multi-delay pulsed arterial spin labeled (pASL) images with a 3D GRASE readout were obtained with the following parameters: TR = 3.4 s, TE = 14.46 ms, labeling duration = 1,400 ms, postlabeling delay changing from 300 to 3,000 ms in steps of 300 ms, resulting in 12 pairs of NS and SS images, scan duration = 5.26 min. For each of the two sessions (active and sham tDCS) this scanning procedure was repeated three times: before tDCS (ASL T_1), after tDCS (ASL T_2), and after the criticism paradigm (ASL T_3; Figure 1). During the ASL measurements, participants were asked to stay awake with their eyes closed.

2.4 | Data analysis

2.4.1 | Behavioral

Behavioral data were analyzed with SPSS 24 (Statistical Package for the Social Sciences; IBM SPSS Statistics for Windows, Version 24.0, IBM Corp., Armonk, NY). Greenhouse–Geisser correction was applied when necessary to ensure the assumption of sphericity. For all analyses, the significance level was set at $p < .05$ (two-tailed). For the momentary mood assessment, a $3 \times 2 \times 2$ MANOVA was conducted with *Time* (VAS T_1 = after ASL T_1 and before stimulation; VAS T_2 = after stimulation, before ASL T_2; and VAS T_3 after audio fragments, before ASL T_3) and *Stimulation* (active vs. sham tDCS) as the within-subject factors, and *PC* (high vs. low) as the between-subjects factor. The six VAS mood scales were the multiple dependent variables. Significant main and interaction effects were followed-up univariate tests followed by *t* tests.

2.4.2 | Neuroimaging

The anatomical and pASL images were preprocessed and analyzed using SPM12 (Wellcome Trust Centre for Neuroimaging, London, UK) and FSL (FMRIB, Oxford, UK). Using the standard segmentation option in SPM12, all high-resolution structural images were segmented into gray matter, white matter, and cerebrospinal fluid. The SPM realign function was used to correct for motion (realignment of slice-selective [SS] and nonselective [NS] image pairs to the mean image). Then, the SPM co-register function was used to affine-register the mean image across all realigned images to the anatomical image, and the resulting warps were applied to all the realigned images. Then, 12 perfusion-weighted images were generated by surround subtraction, that is, the differences between the paired SS and NS images. The perfusion-weighted images were submitted for CBF estimation using *"oxford_asl"* in FSL. The PETPVE12 toolbox (Gonzalez-Escamilla, Lange, Teipel, Buchert, Grothe, 2017; https://github.com/GGonEsc/petpve12) performed regression algorithm correction for partial volume effects in generated CBF maps. Finally, the SPM normalize and

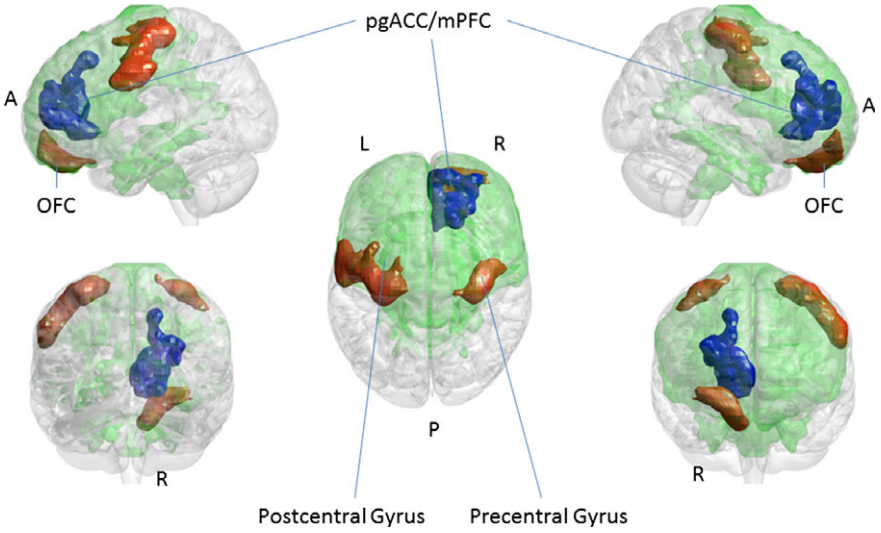

FIGURE 2 Brain imaging results sagittal, coronal, and axial views of glass brains, where the green depicts the frontolimbic mask. The four significant interaction clusters are depicted in red (right orbitofrontal cortex [OFC], left postcentral gyrus, and right precentral gyrus), or blue the pregenual anterior cingulate cortex (pgACC) and mediopreffrontal cortex (mPFC). Follow-up *t* tests revealed that being criticized perfusion significantly decreased in the right pgACC/mPFC (in blue), but only after active tDCS [Color figure can be viewed at wileyonlinelibrary.com]

smooth function was used to spatially normalize these CBF maps into MNI space and perform smoothing with an 8 mm full-width half-maximum Gaussian kernel. Because we were particularly interested in the effects of tDCS stimulation in the frontolimbic areas we used the WFU PickAtlas Tool Version, 3.0.4 (Maldjian, Laurienti, Kraft, & Burdette, 2003) to define the mask comprising the frontal and limbic lobes, including the brainstem (Figure 2).

For the whole brain imaging analysis, the ASL maps were used in a 3 × 2 × 2 mixed ANOVA using GLMFlex (http://mrtools.mgh.harvard.edu/index.php/GLM_Flex), with *Time* (ASL T_1: pre tDCS/ASL T_2: post tDCS/ASL T_3: postcriticism) and *Stimulation* (active vs. sham tDCS) as the within-subjects factors, and *PC* (high vs. low) as the between-subjects factor, while correcting for *age*. These analyses used a cluster significance level of $p < .05$, FWE corrected at the cluster level. Significant interaction effects were followed-up with *t* tests using a cluster significance level of $p < .05$, uncorrected, with a chosen cluster size ≥100 voxels. The anatomical labels and Montreal Neurological Institute (MNI) coordinates for all analyses were obtained from the xjView MATLAB toolbox (http://www.alivelearn.net/ xjview).

3 | RESULTS

The fMRI compatible tDCS application was well tolerated and no major side effects were reported.

3.1 | Behavioral results

VAS data for one participant and the PC score for another participant were missing. Therefore, we analyzed VAS mood changes on the remaining 28 participants (low PC: $n = 13$; high PC: $n = 15$). In the present sample, 2 out of 30 participants had a score of 11 on the BDI-II. All other participants scored between 0 and 8, with a mean BDI-II score of 3.38 (*SE* 0.60) and a median score of 2. BDI-II scores and PC scores were not correlated ($n = 29$, $r = -.04$, $p = .86$). Furthermore, an independent *t* test showed that the PC scores in the PC low group [*M* (*SD*) = 4.08 (0.96)] were significantly lower than the PC scores in the PC high group [*M* (*SD*) = 6.75 (0.86); $t(27) = 7.95$, $p < .001$]. Further independent *t* tests showed no significant differences between the PC low and the PC high group on age [$t(27) = -1.09$, $p > .05$], or BDI-II depression scores [$t(27) = 0.62$, $p > .05$].

Although the 3 × 2 × 2 repeated measures MANOVA showed no main effect of *Stimulation* ($p > .05$, $\eta_p^2 = 0.32$) or *PC* ($p > .05$, $\eta_p^2 = 0.17$) on VAS, the main effect of *Time* was significant [$F(12,96) = 4.41$, $p < .01$, $\eta_p^2 = 0.36$]. No two-way interactions reached significance (*p*'s > .05; Stimulation × PC, $\eta_p^2 = 0.18$; Time × PC, $\eta_p^2 = 0.14$; Stimulation × Time, $\eta_p^2 = 0.10$), and also the three-way interaction between *Time*, *Stimulation*, and *PC* was not significant ($p > .05$, $\eta_p^2 = 0.08$). To follow up on the significant main effect of *Time*, univariate tests showed a significant effect of *Time*, particularly on tiredness [$F(2,52) = 4.96$, $p < .05$, $\eta_p^2 = 0.16$], angriness [$F(1.37,35.61) = 3.78$, $p < .05$, $\eta_p^2 = 0.13$; Greenhouse–Geisser corrected], vigorousness [$F(1.58,41.03) = 7.72$, $p < .01$, $\eta_p^2 = 0.23$; Greenhouse–Geisser corrected], and cheerfulness [$F(2,52) = 4.23$, $p < .05$, $\eta_p^2 = 0.14$]. Pairwise comparisons for these four VAS subscales revealed that after the tDCS procedure at T_2 (mean = 4.37, *SE* = 0.31) participants felt more tired than they did before (mean = 3.58, *SE* = 0.23, $p < .01$), less vigorous (mean = 7.05, *SE* = 0.36) than before (mean = 6.56, *SE* = 0.36, $p < .001$), and less cheerful (mean = 6.48, *SE* = 0.41) than before (mean = 6.21, *SE* = 0.40, $p < .05$). After being criticized at T_3 participants felt angrier (mean = 0.58, *SE* = 0.16) than they did at T_2 before being criticized (mean = 0.27, *SE* = 0.11, $p < .05$). All other mood effects were not significant ($p > .05$).

3.2 | Brain imaging results

The PC score was missing for one participant, hence ASL analyses were performed on 29 subjects (high PC: $n = 16$; low PC: $n = 13$). A 3 × 2 × 2

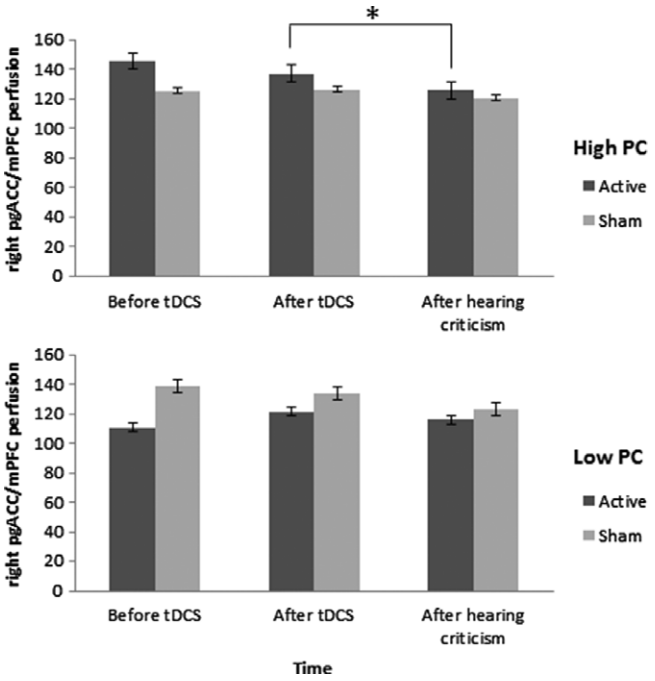

FIGURE 3 Bar graphs of the right pgACC/mPFC cluster perfusion patterns (means and SE) for the groups respectively scoring high and low on perceived criticism (PC) before (ASL T_1) and after (ASL T_2) tDCS and after hearing criticism (ASL T_3), and this for the active and sham tDCS condition. *significance set at $p < .05$, two-tailed

mixed ANOVA (controlled for age) showed a significant *Time* (ASL T_1, ASL T_2, and ASL T_3), *Stimulation* (active tDCS and sham tDCS), *PC* (low PC and high PC) three-way interaction effect in four clusters in the prefrontal cortex: two large clusters were bilaterally located in the somatomotor cortex (k = 1,100; peak MNI coordinates of the left cluster: x = −63, y = −15, z = 33, somatosensory cortex; k = 383; right cluster: x = 27, y = −30, z = 63, sensorimotor cortex) and the other two clusters were located in the right medial prefrontal cortex (k = 597; peak MNI coordinates of right ventromedial orbitofrontal cluster: x = 15, y = 45, z = −30; right pregenual anterior cingulate cortex (pgACC) and medioprefrontal cortex (mPFC): k = 506; x = 3, y = 54, z = 6; see also Supporting Information Table S1 and Figure 2).

Follow-up t tests showed distinct perfusion changes in low versus high PC individuals (see for a complete overview Supporting Information Table S1 for peak coordinates). To answer our main question, being criticized resulted in decreased perfusion in the right pgACC/mPFC (k = 147; peak MNI coordinates x = 9, y = 36, z = −9), however this was only the case for females scoring high on PC, and only after active tDCS (Figures 2 and 3).

To check whether right pgACC/mPFC perfusion differed at baseline between high and low PC scorers, we extracted in MarsBaR (Brett, Anton, Valabregue, & Poline, 2002) the baseline individual time series out of this significant pgACC/mPFC interaction cluster at their first session. Independent t tests (log-transformation) confirmed that high PC scorers showed higher right pgACC/mPFC perfusion compared to low PC scorers [$t(27) = 2.23$, $p = .03$, Cohen's $d = .83$]. Pearson correlation analysis further showed a positive correlation between the individual PC scores and pgACC/mPFC perfusion [$r = .42$, $n = 29$, $p = .03$].

3.3 | Blinding

After the entire experimental procedure, participants were asked participants to make a forced choice which of the two stimulation sessions was the active or the sham procedure. Only when seriously in doubt they could opt for "I do not know". Sixteen out of 30 opted for the latter because they were not sure. Ten participants felt confident about their answers and answered correctly. Four others were also confident but answered incorrectly meaning they thought the active tDCS session was sham (or vice versa). Pearson chi-square ($\chi^2[1, 30] = 1.07$, $p = .31$) did not show significant differences between order and the provided answer (correct vs. pooling the wrong answers and "I don't know").

4 | DISCUSSION

Using ASL, we investigated how tDCS may influence frontolimbic perfusion after hearing criticism in healthy female individuals who scored high or low on PC.

As measured by the six VAS mood scales, a single tDCS session did neither affect mood after being criticized in our healthy female participants, nor were there different effects depending on PC status. The lack of effect on mood after active versus sham stimulation agrees with the general finding that one tDCS session does not significantly influence mood in the healthy state (for a review, see Remue, Baeken & De Raedt, 2016). However, criticism was effective at generating feelings of anger, unrelated to the type of stimulation. These observations corroborate with earlier findings in healthy individuals as well as in recovered depressed patients of a negative mood induction followed by criticism (Hooley et al., 2009, 2012).

After being criticized, we observed a significant decrease in (right) pregenual and medioprefrontal cortical perfusion, but only for those females scoring high on PC and only after active tDCS. The three other significant interaction clusters (bilateral somatomotor cortices and OFC)—although also related to emotional processing and implicated in self-criticism (Doerig et al., 2014)—were not affected by the criticism paradigm as the follow-up t tests before and after being criticized were not significant. Indeed, the bilateral frontal clusters have been shown to discriminate among emotion categories—including vocal expressions—in those who perceive them and provide somatosensory representations linking perception and sensory experience (Kragel & LaBar, 2016). Of interest, Weber, Messing, Rao, Detre, and Thompson-Schill (2014) investigated the prefrontal tDCS fMRI/ASL neural effects while performing the Balloon analog risk task (BART), which assesses losses, wins, and risk. Although this "visual emotional" task did not result in behavioral differences related to the type of stimulation (active/sham), prefrontal, orbitofrontal, and ACC areas were influenced by tDCS.

Our most compelling finding, the perfusion decreases in the pgACC/mPFC after being criticized suggests that one session of active stimulation may result in a downregulation of negative information processing in healthy females scoring high on PC, possibly through attenuating attention and arousal to the critical comments. In support of this, we note that these ventromedial cortical regions have

been shown to have a regulatory role in generating emotional responses related to consciousness and emotional awareness (Amting, Greening, & Mitchell, 2010; Etkin, Egner, & Kalisch, 2011; Ochsner & Gross, 2005). Indeed, when subjects evaluate their subjective emotional responses, robust neural activity is elicited in pregenual ACC as well as in the medial parts of the PFC (BA 10/32) (for an overview see Smith & Lane, 2015). Increased activity of the pgACC is often observed in response to emotional relative to neutral cues (Smith, Fass, & Lane, 2014), for both negative and positive emotional valence (Lindgren et al., 2012; Miedl et al., 2016), and particularly in self-referential contexts (Herbert, Herbert, & Pauli, 2011). Moreover, our observations align with the findings of Antal et al. (2014) who showed that prefrontal anodal tDCS resulted in increased perfusion in the right ventromedial parts of the prefrontal cortex, with perfusion decreases after having completed the Trier social stress test (TSST). These perfusion decreases were accompanied by an attenuation of the stress hormone cortisol, indicative of a diminution of the stress response. Third, the pgACC (and sgACC) plays an important role in the visceromotor responding that accompanies self-conscious emotion (Sturm et al., 2013); and in modulating affect such as sadness and ruminative thought patterns (Disner et al., 2011). Successful pharmacotherapy, invasive and noninvasive neurostimulation techniques have been documented to attenuate metabolic sgACC hyperactivity in depressed patients (Mayberg, 2009; Baeken et al., 2015).

Finally, it is of interest that the ventromedial parts of the prefrontal cortex are affected with our specific left DLPFC anodal and right supra-orbitofrontal cathodal tDCS setup. Although the highest electric field values at the skin level occur beneath the electrodes, it is in line with the assumption that the maximum field strength shifts away placing the peak almost in the middle between the anode and cathode (Rampersad et al., 2014). This might explain the observations in other studies with a similar tDCS setup where Keeser et al. (2011) demonstrated that active as compared to sham tDCS modulated regional brain connectivity related to the default mode network (DMN). With a comparable tDCS setup, Peña-Gómez et al. (2012) also reported that active and not sham tDCS reduced synchrony in the DMN components, concluding that deactivations of the DMN may prompt or facilitate reallocation of cerebral resources to support task performance facilitated by tDCS. In light of the known decreases in anterior DMN connectivity by successful antidepressant interventions (Brakowski et al., 2017), our perfusion decreases in the pgACC/mPFC (part of the DMN) after criticism and after active tDCS alone, may be indicative of how tDCS influences neuronal processes especially in participants more at risk for developing mood and anxiety disorders. We also observed that high PC scorers showed higher right pgACC/mPFC perfusion compared to low PC scorers at baseline, which indicates that to decrease neural responsivity to interpersonal stressors tDCS may be particularly indicated for individuals scoring high on PC.

Notwithstanding that our experimental design has certain advantages, such as the use of neuronavigated anodal localization of the left DLPFC, and that measurements were not contaminated by any disruptions due to participant replacement in and out the scanner, all tDCS related conclusions on perfusion findings and PC should be limited to relatively young healthy females. Moreover, we chose to categorize participants into either a low PC or a high PC group based on a single question. The PC construct has however been shown to be a temporally stable and valid marker of vulnerability (Hooley & Teasdale, 1989; Masland & Hooley, 2015). Consistent with this previous PC research we have also dichotomized individuals scoring 0–5 as low PC and 6–10 as high PC (given a mean score of 5.5; Hooley et al., 2012). Given the methodological differences between both studies, we were not able to replicate the Hooley et al. (2012) findings hearing criticism in the sham condition. Finally, a more specific assessment of complex social emotions, such as embarrassment, guilt, envy, and schadenfreude would have been also appropriate (Bastin, Harrison, Davey, Moll, & Whittle, 2016; Jankowski & Takahashi, 2014).

In conclusion, one active anodal left DLPFC/right cathodal orbitofrontal tDCS session was able to attenuate ventromedial perfusion after being criticized, explaining to some extent how tDCS might operate on the brain level, especially in (female) individuals scoring high on PC. Given the potential of neurostimulation methods to reset dysregulated frontolimbic connections in mood disorders (De Raedt et al., 2015), our current observations may guide future tDCS treatment protocols, not only in individuals at risk but also in patients suffering from mood and anxiety disorders.

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DISCLAIMERS

The authors state that the views in the submitted article are his or her own and not an official position of the institution or funder.

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CONFLICT OF INTEREST

All authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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