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Preventing Prefrontal Dysfunction by tDCS Modulates Stress-Induced Creativity Impairment in Women: An fNIRS Study

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Abstract: Stress is a major external factor threatening creative activity. The study explored whether left-lateralized activation in the dorsolateral prefrontal cortex (dlPFC) manipulated through transcranial direct current stimulation (tDCS) could alleviate stress-induced impairment in creativity. Functional near-infrared spectroscopy (fNIRS) was used to explore the underlying neural mechanisms. Ninety female participants were randomly assigned to three groups that received stress induction with sham stimulation, stress induction with true stimulation (anode over the left dlPFC and cathode over the right dlPFC), and control manipulation with sham stimulation, respectively. Participants underwent the stress or control task after the tDCS manipulation, and then completed the alternative uses task to measure creativity. Behavioral results showed that tDCS reduced stress responses in heart rate and anxiety. The fNIRS results revealed that tDCS alleviated dysfunction of the prefrontal cortex (PFC) under stress, as evidenced by higher activation of the dlPFC and frontopolar cortex, as well as stronger inter-hemispheric and intra-hemispheric functional connectivity within the PFC. Further analysis demonstrated that the cortical regulatory effect prevented creativity deficiencies induced by stress. The findings validated the hemispheric asymmetry hypothesis regarding stress and highlighted the potential of brain stimulation for intervention in stress-related mental disorders and enhancement of creativity.

Keywords: Stress; Creativity; Brain stimulation; Prefrontal cortex; Functional near-infrared spectroscopy

1 Introduction

The World Health Organization (WHO) has declared stress as the health epidemic of the twenty-first century. Stress causes the homeostasis of the human organism to be out of balance, which limits the normal processing of various cognitive functions regulating thoughts and behaviors, such as attention, memory extraction, and decision-making (Shansky and Lipps, 2013; Arnsten, 2015; Goldfarb et al., 2017; Gabrys et al., 2019; Zhao et al., 2022). Creativity is a complicated thinking process closely related to these cognitive functions (Müller et al., 2016; Zabelina et al., 2019), and as such it is particularly vulnerable to stressors and the human stress response (Beversdorf, 2019; Duan et al., 2022). However, people are often required to deliver creative outputs to a high standard even while under some severe stress conditions (e.g., a major examination under time pressure or a critical interview). Such difficulties challenge individual and organizational performance and achievement while raising the risk of physical and mental diseases in vulnerable individuals (O'Connor et al., 2010; Gulley et al., 2016). Therefore, it is of far-reaching significance in relation to potential practical and clinical interventions to identify the most efficient means of stress alleviation to improve creative performance and illuminate underlying neural mechanisms.

Stress depleted cognitive resources can cause a diminished ability to perceive, process, and evaluate information, which makes individuals more inclined to respond stereotypically rather than creatively (Arnsten and Goldman-Rakic, 1998; Arnsten, 2009). A growing body of studies has demonstrated the damaging influence of stress on creativity (Akinola et al., 2019; Duan et al., 2019; Wang et al., 2019; Wang et al., 2022). As an example, Duan et al. (2020) explored the direct relationship between stress and creative thinking using a classical stress-induction paradigm and showed that stress hinders divergent and convergent thinking in creative problem-solving by inhibiting cognitive flexibility. Using Event-Related Potential (ERPs) techniques, Wang et al. (2019) further found that high-frequency alpha waves were diminished during the earlier idea generation phase of the creative cognitive process when individuals were in a stressful state. This resulted from a lack of cognitive resources to extract and combine relevant information from memory, which led to difficulties in making distant associations and forming semantic maps, ultimately resulting in a decline in creative performance.

Stress is accompanied by the body’s physiological responses, mainly the co-activation of the

sympathetic nervous system (SNS) and the hypothalamic pituitary adrenal (HPA) axis, releasing catecholamines and glucocorticoid respectively (Chrousos, 2009; Hernaus et al., 2018). Restricted prefrontal cortex (PFC) activity resulting from stress-related neurotransmitters and hormones is an important neurophysiological basis for impaired creative task performance. The PFC is a crucial brain region controlling emotion regulation and cognitive processing that requires complicated and flexible thinking. It is widely distributed with receptors for dopamine and norepinephrine, regulating its catecholamine inputs (De Kloet et al., 2005). Overactivation of the SNS under stress can lead to receptor obstruction and catecholamine depletion, which in turn reduces the signal-to-noise ratio and suppresses related functions in the PFC (Arnsten, 2009). Meanwhile, glucocorticoids can block extraneuronal catecholamine transporters on glial cells, thereby exaggerating the role of catecholamines in the PFC (Gründemann et al., 1998). These effects may reduce the activation of PFC and disrupt its functional network connectivity with other regions and within subregions. Recent neuroimaging studies in humans have revealed reduced activation in the PFC under stressful tasks (Qin et al., 2009; Al-Shargie et al., 2017). A stronger stress level was also demonstrated to be associated with lower activation and weaker functional connectivity within the PFC (Alyan, Saad, and Kamel, 2021; Alyan, Saad, Kamel, et al., 2021).

Subregions of the PFC, such as the dorsolateral prefrontal area (dlPFC), frontopolar cortex (FPC), inferior prefrontal gyrus (IFG), and orbitofrontal cortex (OFC), play critical roles in the two creative cognitive processing stages of idea generation and idea evaluation (Dietrich, 2004; Gonen-Yaacovi et al., 2013; Li et al., 2015; Kleinmintz et al., 2019). PFC dysfunction has been shown to restrict individuals in exploring and discovering novel connections and generating creative ideas in a wide range of problem spaces (De Souza et al., 2010; Chrysikou, 2019). At the same time, impaired prefrontal control can also impact the evaluation of the novelty and appropriateness of ideas (Chrysikou, 2019). Therefore, the present study attempted to explore effective intervention methods to recover deactivation and network connectivity disruptions of the PFC, so as ultimately to prevent the occurrence of impaired creativity induced by stress.

Transcranial Direct Current Stimulation (tDCS) is a noninvasive technology for transcranial neural intervention. It supplies a constant direct current flow to the cerebral cortex. Inward current from the anode electrode and outward current from the cathode electrode form a direct current electric field that regulates membrane depolarization and hyperpolarization (Radman et al., 2009).

The cortex under the anode forms a surface positive that increases excitability, while the cortex under the cathode forms a surface negative that decreases excitability (Jacobson, et al., 2012; Jackson et al., 2016). tDCS is a promising tool for the intervention of stress and creativity (Schulreich and Schwabe, 2021; Gao et al., 2023; Huang et al., 2023), that could alter brain functional connectivity and enhance neural activity in regions involved in the dopamine system (Fonteneau et al., 2018; Meyer et al., 2019; Ren et al., 2022). A few studies have revealed the restorative effect of post-stress tDCS on cognitive impairment (Antal et al., 2014; Wang et al., 2022). Some studies have also verified the reduction of stress responses through tDCS intervention in specific brain regions before stress or during stress (Bogdanov and Schwabe, 2016; Carnevali et al., 2020). However, limited understanding is available regarding the underlying mechanisms by which cerebral activity pre-induced by tDCS can affect neural responses during stress, and whether this influence can further prevent cognitive impairment under stress.

As one of the major subregions of the PFC, the dlPFC is extensively implicated in the regulation of the neuroendocrine system on stress responses and is crucial in the top-down modulation of negative mood and cognitive control (Cerqueira et al., 2008; Luettgau et al., 2018). Convergent lines of evidence have indicated that the PFC has hemispheric asymmetry during stressful conditions. The right PFC dominates the activation of stress physiological signals, while the left PFC counteracts this activation through interhemispheric inhibition (Sullivan, 2004; Cerqueira et al., 2008; Ishikawa et al., 2014). This stress-related right hemisphere dominance is also observed in the dlPFC. For example, the dynamic causal interactions of the right dlPFC with the right amygdala have been demonstrated to be associated with greater anxiety symptoms and stress responses (Warren et al., 2020). Overactivation of the right dlPFC has been observed in patients with stress-related mental disorders (Strigo et al., 2010; Lopez-Duran et al., 2012), which contributes to more profound traumatic memory and reflects a stronger compensatory reaction to threatening cues (Yin et al., 2011; Berretz et al., 2022).

In contrast, when coping with emotionally challenging situations, the left dlPFC appears to be significantly activated to suppress negative distractors (Bryant et al., 2021). Compared to anxious individuals, healthy individuals exhibit higher left dlPFC activation during stress in stressful tasks to increase cognitive regulation of emotions (Koric et al., 2012). Such research indicates that the left dlPFC plays a part in responding to stress stimuli and emotional regulation. Noninvasive brain

therapies have generally exploited the left dlPFC as the main stimulation target. On the behavioral level, activating this target has been shown to drastically reduce the heart rate response in stressful situations and to alleviate clinical symptoms of stress-related psychiatric disorders (Ironside et al., 2016; Ahmadizadeh et al., 2019; Carnevali et al., 2020). Using the left PFC as the target area, brain stimulation has also been found to be effective in alleviating pathological symptoms of stress-related mental disorders and enhancing brain functional connectivity (Fox et al., 2012; Snyder, 2013). Thus, dlPFC activation with a left-sided preponderance may be a feasible pathway to enhance stress modulation, thereby alleviating PFC dysfunction and other physiological-psychological responses.

Enhanced PFC function may protect against impairments in creativity under stressful conditions. Previous studies have stimulated the dlPFC and FPC through tDCS to demonstrate that activation of PFC subregions can effectively enhance the novelty index and analogical transfer in creative problem-solving (Lundie et al., 2022; Huang et al., 2023). High prefrontal functional connectivity can support higher levels of cognitive flexibility and imaginative abilities, directing active exploration to complete the process of creative idea generation (Chen et al., 2014; Beaty et al., 2018; Li et al., 2023). Meanwhile, effective functional connectivity enables individuals to maintain goal maintenance and engage in flexible cognitive control in an alert state (Meno & Esposito, 2022), allowing for autonomous monitoring of creative cognition under stress.

In summary, the present study aimed to investigate whether a tDCS intervention before stress could prevent impairment in creativity by alleviating the stress-induced neurophysiological response. The relatively left-lateralized activation was achieved by tDCS activating the left dlPFC and suppressing the right dlPFC. To explore the underlying mechanism whereby PFC functioning via tDCS might affect stress responses and creativity performance, functional near-infrared spectroscopy (fNIRS) was utilized to detect hemoglobin fluctuations during stress as an indicator of the intrinsic neural activity in the PFC. fNIRS requires a more liberal imaging environment compared to other neuroimage techniques. It is simple to combine with tDCS and allows for the manipulation of realistic social pressure as a stress-induction technique. We predicted that tDCS would result in a significant enhancement in the activation and functional connectivity of the PFC compared to a normal stress state. It was also predicted that the stimulated group would have weaker physical and psychological responses to stress and perform better in a creative task.

2 Methods

2.1 Participants

Ninety healthy female college students (age: *M*=19.5 years, *SD*=1.24) were recruited in the present study. Gender-specific differences in the brain and cerebrospinal fluid can influence the induced electric field and thus interfere with the tDCS effectiveness (Meiron & Lavidor, 2013; Mezger et al., 2021). Different genders also demonstrate differential stress responses in HPA axis, neural activity and behavioral performance (Wang et al., 2007; Van den Bos et al., 2009; Kalia et al., 2018; Nitschke et al., 2022; Wallace and Myers, 2023). Females generally exhibit greater susceptibility to stress and are vulnerable to more physical and psychological symptoms than males (Kudielka & Kirschbaum, 2005; Brydges et al., 2020). Therefore, the experiment only focused on female participants to avoid confounding the results with gender variations. A statistical power analysis was calculated using G*Power 3.1.9.7 (Faul et al., 2007). According to the experimental design, a total sample size of 90 could achieve 95% power when the estimated effect size is 0.25 and the Type I error is 0.01 ($\alpha = 0.01$).

People with a history of heart disease, hypertension, or other long-term health problems were excluded from the experiment. All participants had a body mass index between 18 kg/m^2 and 27 kg/m^2 and were not taking contraception, drugs, or caffeine for the three days before the experiment. The menstrual cycle was also avoided as it may affect individual stress responses (Ossewaarde et al., 2010).

All participants signed an informed consent form after being informed of the detailed procedure of the experiment. They were paid monetarily after completing the whole experiment. The study adhered to the principles of the Helsinki Declaration (World Medical Association, 2013) and was ethically approved by the Academic Committee of the Ministry of Education of Shaanxi Normal University's Key Laboratory of Modern Teaching Technology in China.

2.2 Experimental procedure and Tasks

2.2.1 Study design and Procedures

We used a sham-controlled, stress-controlled study design with the factors being stress condition (Stress vs. Control) and tDCS condition (Active vs. Sham). Three groups were designed,

including a group undergoing the stress induction with the sham stimulation (SS), one group undergoing the stress induction with the active stimulation that activated the left dlPFC and deactivated the right dlPFC (SA), and one group undergoing the control manipulation with the sham stimulation as a comparison to the stress conditions and true stimulation (CS). Participants were allocated to one of three groups at random (30 participants per group). The pre-post design was performed to control the individual differences in creativity.

Concerning the fluctuation of endogenous cortisol levels, all data collection in this study were undertaken between 14:00 and 18:00. Participants rested for a while to ensure that indicators such as cortisol and heart rate returned to a stable baseline state. During this period, the State-Trait Anxiety Inventory (STAI-T: Spielberger et al., 1999) and the Beck Depression Inventory-II (BDI-II: Beck et al., 1996) were completed to exclude the interference on the experimental results arising from the presence of depressive and anxiety symptoms. After participants passed the practice trials, the pre-test Alternative Uses Task (AUT) was completed to provide a baseline measure of creative performance. Following this, tDCS was administered for 20 min. After 15 min of preparation for fNIRS data acquisition, the Trier Social Stress Test (TSST) or corresponding control test was carried out, during which fNIRS data were acquired. Next, the post-test AUT was completed after the stress induction. A monitoring device was worn by the participants throughout the test session to collect the changes in heart rate (HR) throughout the test session. Questionnaires regarding emotion changes were collected at T1, T2, T3, and T4 time points, as were salivary samples to enable the measurement of cortisol changes (Figure 1).

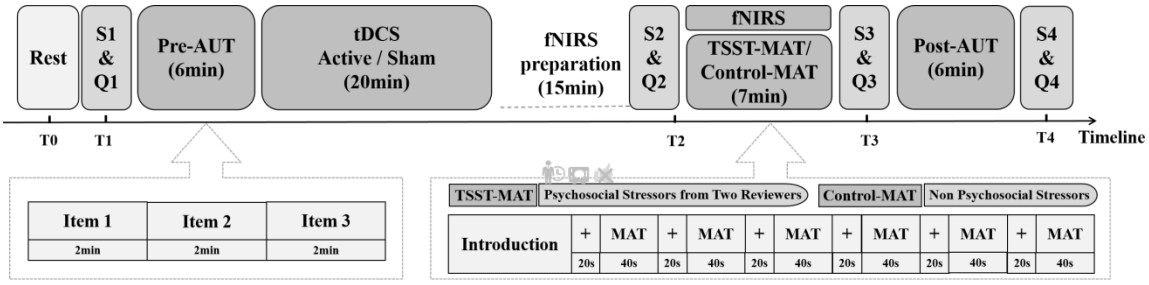

Figure 1. Diagram of the experimental protocol and overall timeline. The salivary samples were collected at S1/S2/S3/S4. The questionnaires about emotion changes were completed at Q1/Q2/Q3/Q4. AUT: Alternative Uses Task; tDCS: Transcranial Direct Current Stimulation; MAT: Mental Arithmetic Task.

2.2.2 Stress induction task

The Mental Arithmetic Task (MAT) in the Trier Social Stress Test (TSST) was applied to elicit a stressful state (Kirschbaum et al., 1993; Zhao et al., 2022; Kan et al., 2019). Previous studies suggest that an arithmetic paradigm is better to extract more accurate fNIRS signals by excluding the interference of irrelevant factors while also effectively inducing an elevated degree of stress state (Al-Shargie et al., 2017; Alyan, Saad, and Kamel, 2021; Alyan, Saad, Kamel, et al., 2021; Rosenbaum, Hilsendegen, et al., 2018; Rosenbaum, Thomas, et al., 2018).

The MAT in the present study consisted of six blocks (Rosenbaum, Hilsendegen et al., 2018; Rosenbaum, Thomas et al., 2018). Each block was designed for 40 s computation and 20 s pauses, with the entire task lasting a total of 6 min. Participants were asked to subtract 17 sequentially from the number on the screen (i.e. six different starting points between 2023 and 323) and to report the results orally. The six numeric starting points were presented randomly. During the pause phase, the center of the screen presented a "+" fixation point lasting for the 20 s. Psychosocial pressure was imposed on the participants during the task. Two interviewers in white coats entered the laboratory and sat across from the participants. Participants were informed that the interviewers would judge and score their performance during the task, and they were instructed to stand and face the two interviewers to give their mental arithmetic answers. When participants gave an incorrect answer, the interviewer immediately interrupted them with harsh instructions and required them to start over. The interviewer also put time pressure on the participants based on the speed of their answers, constantly asking them to answer more quickly. Any affirmative feedback was delivered to the participants throughout the experiment. To increase the level of psychosocial stress, a video camera was placed in the participant's line of sight. Participants were informed that all their verbal and non-verbal behavior would be recorded for the interviewer's overall assessment of their performance.

The control condition used the same MA task but without any psychosocial stress manipulation. Participants only had to follow the instructions to complete the arithmetic task, during which no two interviewers were present and no video camera was used to record their performance. They were asked to calculate the answers as accurately as possible but could be told the correct answer without any negative feedback when an incorrect answer was given.

2.2.3 Alternative Uses Task

The Alternative Uses Task (AUT) was used to measure creative performance (Duan et al., 2019;

Wang et al., 2019; Wang et al., 2022). Participants were instructed to report orally as many uses for daily necessities as feasible within two minutes. The two versions of the task each consisted of three items (AUT1: newspaper, bucket, and shoes; AUT2: umbrella, paper clip, and can), which were randomly balanced across participants between the pre-test and post-test. The two versions of the AUTs with similar difficulties have been shown to be the equivalent tasks (Supplementary, S3) (Wang et al., 2022).

2.3 tDCS parameters

The DC-STIMULATOR MC stimulation apparatus (Neuroconn, Germany) was used in this study. tDCS was performed through two graphite electrode sheets (25 cm^2, 5×5 cm), which were contained in a sponge moistened with saline (NaCl 0.9%). The anode was placed over the left dlPFC and the cathode was placed over the right dlPFC. Based on the EEG 10-20 system and associated MRI localization studies, the anode center was located at the F3 position, and the cathode center was located at the F4 position (Allaert et al., 2022; Borwick et al., 2020; Brunelin and Fecteau, 2021; Huang et al., 2022) (Figure 2 A-B.).

The active group was stimulated for 20 min with constant current stimulation of 1.5 mA, plus a 30s fade-in and a 30s fade-out. The sham group received only one stimulation cycle with a 30s fade-in and a 30s fade-out, followed by no current stimulation. In this way, participants felt current stimulation but they failed to induce effective cortical excitability, which effectively excluded the placebo effect present in the active group. The stimulation conditions were kept strictly confidential for the participants and were operated by specific experimental personnel who were not involved in the other stage of the experiment. Participants completed a sensitivity questionnaire to assess tDCS safety and the quality of blinding, which evaluated the incidence and severity of the typical stimulation symptoms (Brunoni et al., 2011).

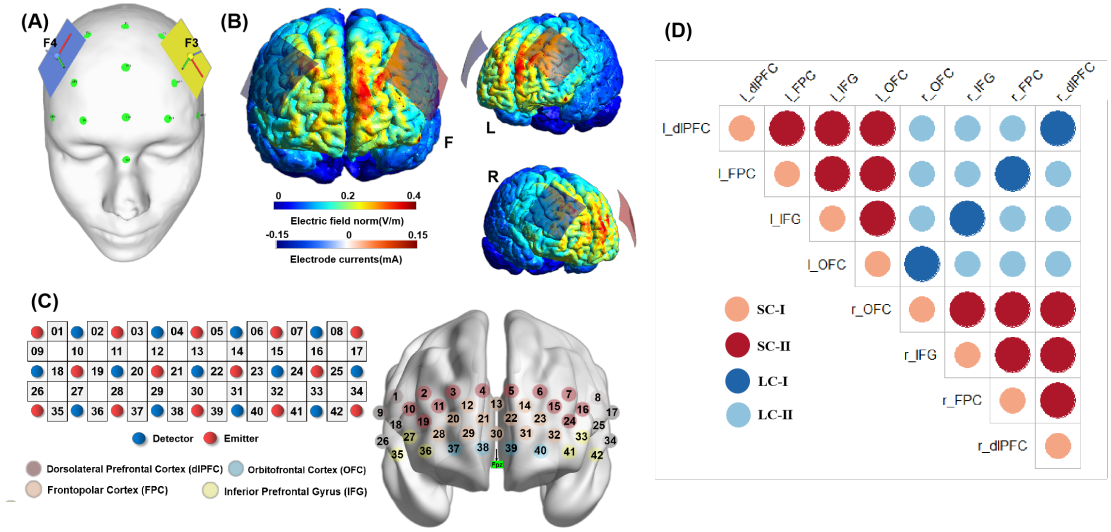

Figure 2. Diagram of the tDCS manipulation and the fNIRS optode probes. (A) The placement location of anode and cathode electrodes. (B) The distribution of the stimulated electric field was performed with SimNibs. (C) 42 fNIRS channels composed of 14 emitters and 13 detectors. The center point of the bottom row of optode probes was located in Fpz. Configuration of the regions of interest was located according to the MNI coordinates. (D) Thirty-six pairs and four clusters composed of 8 ROIs. L, left sagittal plane; R, right sagittal plane; F, frontal coronal plane; SC: short-distance connectivity; LC: long-distance connectivity.

2.4 Data acquisition

2.4.1 Physiological and psychological data acquisition

Physiological stress indicators included heart rate and cortisol, which were used to assess the activity of the SNS and HPA pathways, respectively. The BIOPAC MP150 (BIOPAC, Goleta, CA) was used to record heart rate, and saliva cortisol samples were obtained using Olivetti collection equipment (Salivette, Sarstedt 51.1534.500, Germany) to determine cortisol concentration. The participants chewed the swabs in the salivette for 1 min and then placed them in the saliva collection device. All saliva samples were stored frozen at -20 ℃.

The Positive and Negative Affect Schedule (PANAS) and the state version of the State-Trait Anxiety Inventory (STAI-S) were used to evaluate the effect of the stressors on mental state. The 10 items from PANAS measuring the negative mood were chosen to reflect the immediate negative emotional intensity, while the 20 items from STAI-S were chosen to reflect the degree of state

anxiety at a particular moment.

2.4.2 fNIRS data acquisition

The LABNIRS system (Shimadzu Company, Japan) with three wavelengths of 780 nm, 805 nm, and 830 nm was utilized for data acquisition. The concentration of oxyhemoglobin (HbO), deoxyhemoglobin (HbR), and total hemoglobin (HbT) were determined. The sampling rate was configured to 10 Hz. We applied one 3 × 9 optode probe patch containing 14 emitters and 13 detectors. The two types of optode probes were spaced 3 cm apart, making up 42 recording channels covering the PFC.

Referencing the international 10-20 system, the center point of the bottom row of optode probes was located in Fpz. With NZ, CZ, AL, and AR as reference points, the spatial positions of all optodes and channels were recorded by a 3D magnetic space digitizer (FASTRAK; Polhemus, USA). Then, the Brodmann partition based on the MNI coordinate was further converted by the NIRS-SPM MATLAB package (Supplementary, S1). Results confirmed that the channels cover a large area of the PFC region. According to the Brodmann partition, we further determined four subregions of the PFC, including the dlPFC, FPC, IFG, and OFC. These subregions were further divided into the left and right hemispheres, constituting eight regions of interest (ROIs). The brain regions and channel configurations were visualized by the BrainNet Viewer (Figure 2C).

2.5 Data analysis

2.5.1 Physiological data analysis

Saliva samples were centrifuged for 20 min (3000 rpm) at 2-8 °C to enable the collection of 0.5-1.5 mL of supernatant. The supernatant was taken for the assay of cortisol concentration by Enzyme-Linked Immuno Sorbent Assay (Zhuocai, China). The average heart rate was calculated by AcqKnowledge 5.0 software. To assess the overall increase in physiological indicators over a time period, the area under the curve with respect to increasing (AUCi) was determined based on the values measured at specific time points. The formula of AUCi was defined below.

$$AUCg = \left(\sum_{i=1}^{n-1} \frac{\left(m_{(i+1)} + m_i\right) \cdot t_i}{2} \right)$$

$$AUCi = AUCg - \left(m_1 \cdot \sum_{i=1}^{n-1} t_i \right)$$

In the formula above, *m, t,* and *n* respectively denote the values at one measurement point, the time distance between the measurements, and the total number of the measurement interval. AUCi is derived from the area under the curve with respect to ground (AUCg), which can reflect the overall amount of change in the variable. AUCg is the sum of the area under the curve for each period. AUCi that increases relative to the baseline level is calculated by AUCg removing the area between zeros and the first measure for all time points.

2.5.2 fNIRS data analysis

Processing The fNIRS data were processed and analyzed using MATLAB and NIRS_SPM. The raw density signals from near-infrared lights were transformed to the concentration changes of HbO, HbR, and HbT by the modified Beer-Lambert Law. Compared with HbR, the HbO signal has a higher signal-to-noise ratio and is more sensitive to cerebral blood flow changes (Rostrup et al., 2002; Hoshi, 2003; Lindenberger et al., 2009). Therefore, the HbO signal was further processed in this study. The hemodynamic response function (HRF) first smoothed the NIRS data and corrected the temporal autocorrelation (Friston et al., 2000). Then, a Wavelet-MDL detrending method based on the discrete wavelet transform was applied to remove the global trend and uncorrelated noise at distinct scales (e.g. motion, blood pressure, breathing, and other physiological noises) (Jang et al., 2009; Ye et al., 2009). Baseline corrections were conducted on HbO data for all blocks by subtracting the mean value of the 20 s initial time before the task from each task-related data point.

Activation analysis Based on the general linear model (GLM), the beta values for the 42 channels were analyzed to reflect the level of neural activation by the NIRS_SPM package. The

$$Y = X\beta + \varepsilon$$

$$\beta = X^{-1}Y$$

Where Y, X, β, and ε respectively denote the pre-processed data, the design matrices, the unknown corresponding hemodynamic response signal strength, and the error term. GLM provides the standard linear estimate of the hemodynamic response. The estimated hemodynamic response function (HRF), which was convolved in the boxcar function, was incorporated into the regressor of design matrix X (Uga et al., 2014). The matrix β was obtained from the inverse X matrix and Y

using the least squares estimation method.

Functional connection analysis The functional connection strength was calculated using the magnitude squared coherence. This method is a frequency domain functional connectivity measure, measuring the relationship of time-invariant relationship between two-time series signals at the specific frequency range. It is expressed using the formula below.

$$Coh_{xy}(\lambda) = \frac{\left|f_{xy}(f)\right|^2}{f_{xx}(f)f_{yy}(f)}$$

$f_{xx}(f)$ and $f_{yy}(f)$ denote respectively the power spectral density of two signals for a frequency f, and $f_{xy}(f)$ denotes the cross-spectral density of x and y. The MATLAB function "mscohere" performed the coherence computation. A frequency range of 0.009~0.1 Hz was selected. HbO signals in the cerebral region demonstrated high coherence within this frequency range, and measurement and physiological artifacts could be efficiently removed (Sasai et al., 2011; Sakakibara et al., 2016).

To begin, the task-related coherence values between the 42 channel pairs were determined by averaging the hemodynamic response from the six trails. After converting the coherence values to the normal distribution variable z using Fisher's r-to-z transformation, all channel-to-channel pairs involved in the ROI pairs were averaged based on the brain region localization of the channels. Eight ROI gave rise to 36 region-to-region functional connections, including 8 intra-ROI connections and 28 inter-ROI connections (Figure 2D.). Intra-ROI connections were connections between channels covered within one single ROI, and inter-ROI connections were all possible channel connections between two different ROIs.

To further clarify the effect of tDCS and stress on the intra-hemispheric and inter-hemispheric connectivity between the PFC region, we distinguished two clusters of short-distance connectivity and two clusters of long-distance connectivity referencing the method from Zhu (2017). Short-distance connections reflected the strength of connections within the hemispheres, including intra-hemispheric connections within the 8 ROIs (SC-I), as well as intra-hemispheric connections between different ROIs belonging to the same hemisphere (SC-II). Long-distance connections reflected the strength of inter-hemispheric connections, including inter-hemispheric connections between the left and right hemispheres of the symmetrical ROIs (LC-I), and inter-hemispheric connections between the left and right hemispheres of the asymmetrical ROIs (LC-II). The

coherence average of the four functional connectivity clusters was calculated to further examine the overall functional connectivity differences in PFC between groups.

2.5.3 Behavioral data analysis

Creative performance was assessed by scores relating to the fluency, flexibility, and originality dimensions, which were rated in accordance with the classic standard scoring method (Radel et al., 2015). The fluency score was the total number of appropriate and reasonable answers, with each answer counting as one point. The flexibility score was determined by the total number of categories of the provided answers, with one point for the same use. The originality score was calculated by the frequency with which a certain response appeared in the answer pool. More specifically, two points were scored when the percentage was less than 1%. One point was scored when the percentage fell between 1% and 5%. No points were awarded when the percentage was higher than 5%. Two experts in the field of creativity research simultaneously rated the answers given by each participant. The final scores for the three dimensions were the average scores from the two raters. The Internal Consistency Coefficient (ICC) between the two raters was verified to be reliable (fluency ICC = 0.998, flexibility ICC = 0.946, originality ICC = 0.865).

2.5.4 Statistical analysis

Statistical analyses were performed using *F*-tests with SPSS25.0 to evaluate the difference between the three groups on physical stress responses, psychological responses, the beta value of PFC activation, the z value of functional connectivity within the PFC, and creativity. FDR was used to conduct multiple comparison correction for *F*-tests for the fNIRS channels and their functional connection pairs. The Bonferroni method was used to perform post hoc tests after *F*-tests. The relationships between tDCS condition, brain activity and creativity were assessed by calculating Pearson's correlation coefficients after FDR correction and by undertaking a mediation analysis for multi-categorical independent variable.

3 Results

3.1 Testing for baseline characteristics and tDCS blinding

The baseline characteristics of each group are shown in Table 1. Results from a one-way

ANOVA showed no significant differences between the three groups at baseline in anxiety symptoms, depressive symptoms, baseline physiological stress parameters, baseline physiological parameters, and baseline creativity performance. The presence of individual differences in the experimental results therefore was dismissed. A Chi-square test was conducted to test the blinding of the stimulation. Results showed that 82.2% of the participants reported they received an active current stimulus. More importantly, there was no significant difference in the number of participants who perceived the stimulation between the three groups. The differences in the scores on the tDCS sensitivity questionnaire were also not significant between any of the three groups. Those results suggested that sham stimulation cannot be distinguished by participants and that our blinding manipulation was valid.

Table 1. The baseline characteristic and tDCS blinding among groups

	Group			**Statistics**	
	CS (*n* = 30)	**SS (*n* = 30)**	**SA (*n* = 30)**	***F*/χ^2**	***p***
BDI-II	6.73±5.67	10.17±9.62	7.9±6.29	1.67	.194
STAI-T	42.27±6.53	44.67±10.26	42.17±5.79	0.99	.375
Baseline physiological stress parameters					
Heart Rate	81.28±11.83	81.14±9.61	81.51±10.80	0.01	.991
Salivary cortisol	5.75±3.19	5.84±2.23	5.94±2.39	0.36	.964
Baseline psychological stress parameters					
STAI-S	39.80±7.44	43.17±9.89	40.03±8.32	1.43	.245
PANAS-N	14.57±4.80	15.77±5.26	15.53±4.61	0.51	.604
Baseline creativity tasks					
AUT-fluency	23.88±7.17	25.32±8.54	28.08±8.11	2.16	.122
AUT-flexibility	18.27±4.38	18.85±5.66	20.43±5.65	1.36	.262
AUT-originality	11.92±2.87	11.23±5.04	11.25±6.65	0.18	.839
tDCS blinding					
Active stimulation perception	26(4)	23(7)	25(5)	1.05	.591
tDCS sensitivity	16.30±4.20	15.23±6.37	17.5±4.02	1.56	.217

Note: Data are reported as mean ± standard deviation. CS: control condition with sham stimulation; SS: stress condition with sham stimulation; SA: stress condition with active stimulation. BDI-II: Beck Depression Inventory-II; STAI-T: trait version of the State-Trait Anxiety Inventory; PANAS-N: the negative dimension of the Positive and Negative Affect Schedule; STAI-S: state version of the State-Trait Anxiety Inventory; AUT: Alternative Uses Task; tDCS: Transcranial Direct Current

Stimulation.

3.2 Effect of tDCS on stress-induced physiological responses

A 3×4 mixed measures ANOVA with Group (SA, SS, CS) as a between-participants factor and Time (T1, T2, T3 and T4) as a within-participants factor was conducted on the data relating to average heart rate and salivary cortisol. Results showed the presence of a significant interaction effect between Time × Group, F (6, 261) = 13.72, $p < 0.001$, $\eta_p^2 = 0.240$. Following simple effect analyses it was found that the heart rate in the SS group was significantly higher than that in the CS group at T3 ($p = 0.001$). Moreover, the heart rate at T3 was also significantly higher than that at T2 ($p < 0.001$) and T1 ($p < 0.001$) in the SS group (Figure 3A). These results indicated a successful induction of stress. The difference in heart rate at T3 between the SA and CS groups was not statistically significant, which may be the consequence of tDCS. We further calculated the AUCi of heart rate increase every three minutes after the onset of the stress manipulation. A one-way ANOVA showed that the increase in heart rate in the SA ($p = 0.020$) and CS groups ($p < 0.001$) was significantly lower than that in the SS group, F (2, 87) = 8.80, $p < 0.001$, $\eta_p^2 = 0.168$ (Figure 3B).

Concerning the concentration of salivary cortisol, we also found a significant interaction effect of Time × Group, F (6, 261) = 13.53, $p < 0.001$, $\eta_p^2 = 0.237$. Further simple effects analyses showed that the cortisol concentration in the SS and SA stress groups at T3 (SA: $p = 0.005$; SS: $p < 0.001$) and T4 (SA: $p < 0.001$; SS: $p < 0.001$) was significantly higher than that in CS group (Figure 3C). No group differences were observed between the SS and SA groups after stress induction. We also applied a one-way ANOVA on the calculated AUCi for the collected salivary cortisol. Results revealed that the AUCi in the SA ($p < 0.001$) and SS ($p < 0.001$) groups were significantly higher than that in the control group, F (2, 87) = 23.88, $p < 0.001$, $\eta_p^2 = 0.237$ (Figure 3D).

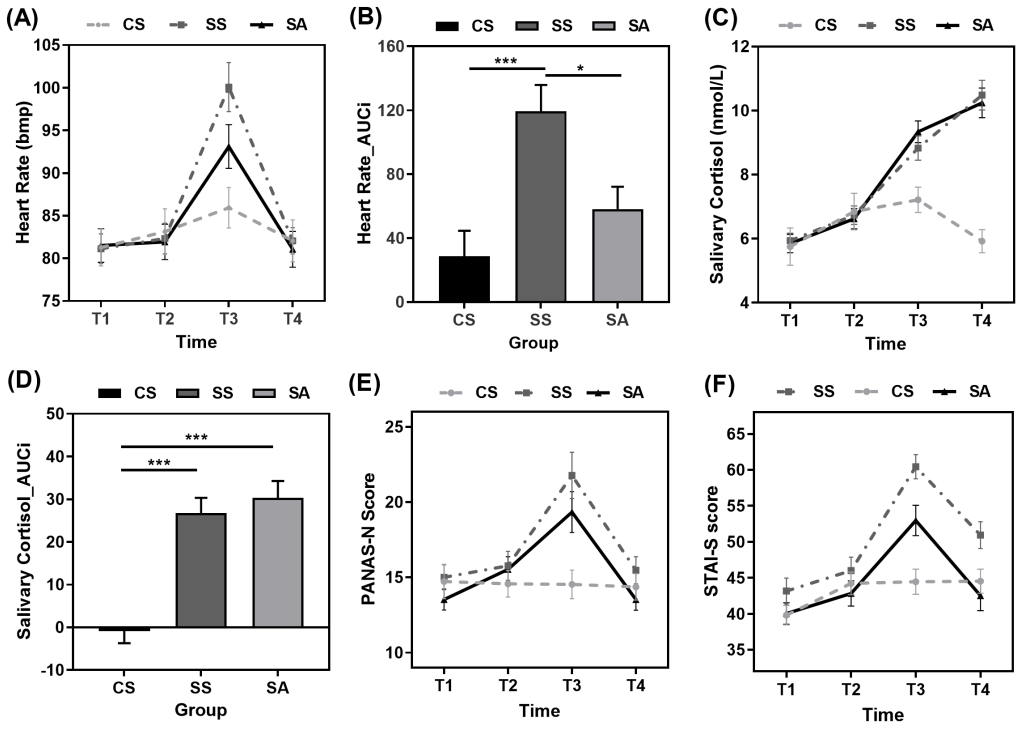

Figure 3. Physiological and psychological stress responses. (A) The mean heart rate change at all collected time-point. (B) The corresponding AUCi for heart rate. (C) The mean salivary cortisol changes at all collected time points. (D) The corresponding AUCi for salivary cortisol. Error bars represent standard errors of the mean. (E) The negative affect scores at all collected time-points. (F) The state anxiety score at all collected time-point. CS: control condition with sham stimulation; SS: stress condition with sham stimulation; SA: stress condition with active stimulation. $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p < 0.001$.

3.3 Effect of tDCS on stress-induced psychological responses

To measure indicators of successful stress induction and the effect of tDCS on psychological stress responses (Figure 3E and 3F), a mixed-design ANOVA was employed on the psychological stress parameters with one within-participants factor (Time: T1, T2, T3, T4) and one between-participants factor (Group: SA, SS, CS).

The significant interaction effect of Time × Group was observed both with the negative mood measure, F (6, 261) = 5.79, $p < 0.001$, $\eta_p^2 = 0.117$, and for the state anxiety measure, F (6, 261) = 7.14, $p < 0.001$, $\eta_p^2 = 0.141$. Further simple effects analyses showed that the SA group and SS group that received stress induction had significantly higher negative emotion scores at T3 than at T2 (SA:

p = 0.008; SS: p < 0.001) and T1 (SA: p < 0.001; SS: p < 0.001). However, the CS group, as a control condition for stress, had no significant difference. Similarly, simple effects analyses also showed that the state anxiety scores of the SA and SS groups at T3 were higher than those at T2 (SA: p < 0.001; SS: p < 0.001) and T1 (SA: p < 0.001; SS: p < 0.001), while no significant changes were observed in the CS group. These results confirmed the effective induction of stress states.

The simple effects analyses also revealed significant differences in state anxiety levels between the two stress-conditioned groups at T3 and T4. To further examine the moderating effect of tDCS on psychological responses to stress, we conducted a one-way ANCOVA on the state anxiety scores at T3 and T4, with the three groups as a between-participants factor, and the scores at T2 before stress as covariates. The results showed a significant group difference [T3: F (2, 86) = 22.69, p < 0.001, η_p^2 = 0.345; T4: F (2, 86) = 4.49, p = 0.014, η_p^2 = 0.094]. Bonferroni-adjusted pairwise comparison tests indicated that the SA group had a significantly lower level of state anxiety at T3 than the SS group (p = 0.044), although both the SA (p < 0.001) and SS (p < 0.001) groups had significantly higher scores than the control group. For the scores at T4, the Bonferroni-adjusted pairwise comparison test showed that the level of state anxiety in the SA group was not significantly different from that of the control group, and both the control group (p = 0.077) and SA groups (p = 0.017) had higher scores compared to the SS group. The above results demonstrated the effectiveness of tDCS in alleviating stress-induced anxiety and accelerating the recovery of negative emotion.

3.4 Effect of tDCS on stress-induced PFC activation

A series of one-way ANOVAs using Group (SA, SS, CS) as a between-participants factor were conducted on the beta values for all channels (Figure 4). Results found that the main effect of Group by FDR correction was significant at the right dlPFC [CH3: F (2, 87) = 5.90, p_{FDR} = 0.028, η_p^2 = 0.119; CH4: F (2, 87) = 6.08, p_{FDR} = 0.025, η_p^2 = 0.123), left dlPFC [CH5: F (2, 87) = 13.76, p_{FDR} < 0.001, η_p^2 = 0.240], and FPC [CH12: F (2, 87) = 8.50, p_{FDR} < 0.001, η_p^2 = 0.163; CH13: F (2, 87) = 6.70, p_{FDR} = 0.021, η_p^2 = 0.133; CH22: F (2, 87) = 7.10, p_{FDR} = 0.014, η_p^2 = 0.140, CH23: F (2, 87) = 5.53, p_{FDR} = 0.030, η_p^2 = 0.113]. Subsequently, the Bonferroni-adjusted pairwise comparison tests were conducted on the beta value of the significant channels. The results showed that the beta values on CH3 (SA: p = 0.038; CS: p = 0.005), CH4 (SA: p = 0.003; CS: p = 0.052), CH5 (SA: p =

0.001; CS: $p < 0.001$), CH12 (SA: $p < 0.001$; CS: $p = 0.032$), CH13 (SA: $p = 0.015$; CS: $p = 0.003$), CH22 (SA: $p = 0.001$; CS: $p = 0.035$) were significantly greater in both the SA and CS groups than in the SS group. The beta value of the SS group on CH23 was significantly lower than that of the SA group ($p = 0.003$) but not lower than that of the CS group. The differences in PFC activation on these channels between the SA and CS groups were not significant (all $p > 0.3$).

We then conducted a one-way ANOVA on the averaged beta values for each ROI to further confirm the impact of active stimulation on enhanced brain activation under stress. A significant main effect of Group was observed at both the right PFC [F (2, 87) = 4.91, $p = 0.010$, $\eta_p^2 = 0.101$] and the left PFC [F (2, 87) = 4.79, $p = 0.011$, $\eta_p^2 = 0.099$]. Bonferroni-adjusted pairwise comparison tests showed the average beta values on the right PFC were significantly greater in the CS than that in the SS group ($p = 0.047$). The beta value of the SA group was significantly higher than that of the SS group on the right PFC ($p = 0.010$) and the left PFC ($p = 0.003$). Likewise, there were no significant differences in these regions between the SA and CA groups.

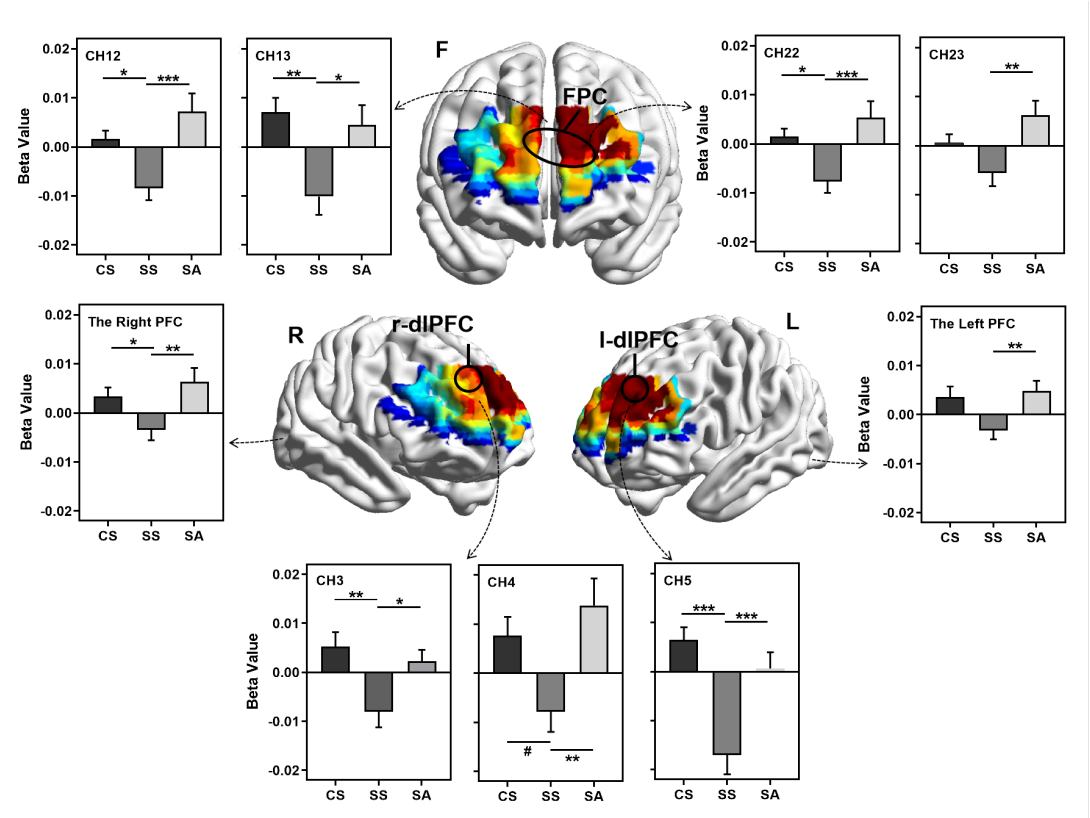

Figure 4. PFC activation results are induced by stress and control manipulation. L, left sagittal plane; R, right sagittal plane; F, coronal plane. Error bars represent standard errors of the mean. CS: control

condition with sham stimulation; SS: stress condition with sham stimulation; SA: stress condition with active stimulation. $^{\#}p<0.10$, $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p < 0.001$.

3.5 Effect of tDCS on stress-induced functional connection within PFC

A series of one-way ANOVAs using Group (SA, SS, SC) as a between-participants factor were conducted on the stress-related functional connectivity between seed regions (Figure 5). After FDR correction, there was a marginally significant main effect of Group in l-dlPFC_l-FPC [F (2, 87) = 6.82, p = 0.054, η_p^2 = 0.135], l-dlPFC_l-IFG [F (2, 87) = 6.17, p = 0.054, η_p^2 = 0.124], l-dlPFC_r-dlPFC [F (2, 87) = 5.17, p = 0.066, η_p^2 = 0.106], l-FPC_l-IFG [F (2, 87) = 5.66, p = 0.060, η_p^2 = 0.115], l-IFG_l-OFC [F (2, 87) = 4.74, p = 0.066, η_p^2 = 0.098], and l-IFG_r-FPC [F (2, 87) = 4.83, p = 0.066, η_p^2 = 0.100]. Bonferroni-adjusted pairwise comparison tests revealed that the connection strength of the CS group was significantly stronger than that of the SS group (l-dlPFC_l-FPC: p = 0.004, l-dlPFC_l-IFG: p = 0.004, l-dlPFC_r-dlPFC: p = 0.006, l-FPC_l-IFG: p = 0.004, l-IFG_l-OFC: p = 0.010, l-IFG_r-FPC: p = 0.008). Importantly, except for the ROI between l-FPC and l-IFG (p = 0.031), none of the connection strengths between the CS and SA groups were significant. Moreover, the result of l-dlPFCl-FPC in the SA group was found to be significantly higher than that in the SS group (p = 0.010).

To reveal more specifically the difference induced by tDCS in the whole functional connectivity between the left and right hemispheres, a further series of one-way ANOVAs were conducted on the four clusters of connectivities in the SA, SS and SC groups. An obvious clustering effect can be seen in SC-I [F (2, 87) = 4.04, p = 0.021, η_p^2 = 0.085], SC-II [F (2, 87) = 4.74, p = 0.011, η_p^2 = 0.098], LC-I [F (2, 87) = 5.47, p = 0.006, η_p^2 = 0.112], and LC-II [F (2, 87) = 4.86, p = 0.010, η_p^2 = 0.100]. Subsequent pairwise comparison tests revealed that intra-hemispheric connectivity and symmetrically inter-hemispheric connectivity were both stronger in the CS (SC-I: p = 0.037, SC-II: p = 0.015, LC-I: p = 0.011, LC-II: p = 0.012) and SA groups (SC-I: p = 0.061, SC-II: p = 0.060, LC-I: p = 0.024, LC-II: p = 0.062) than in the SS group. The difference between the CS and SA groups was not significant. These results suggested that tDCS improved the disorganized pattern of PFC functional connectivity under acute stress.

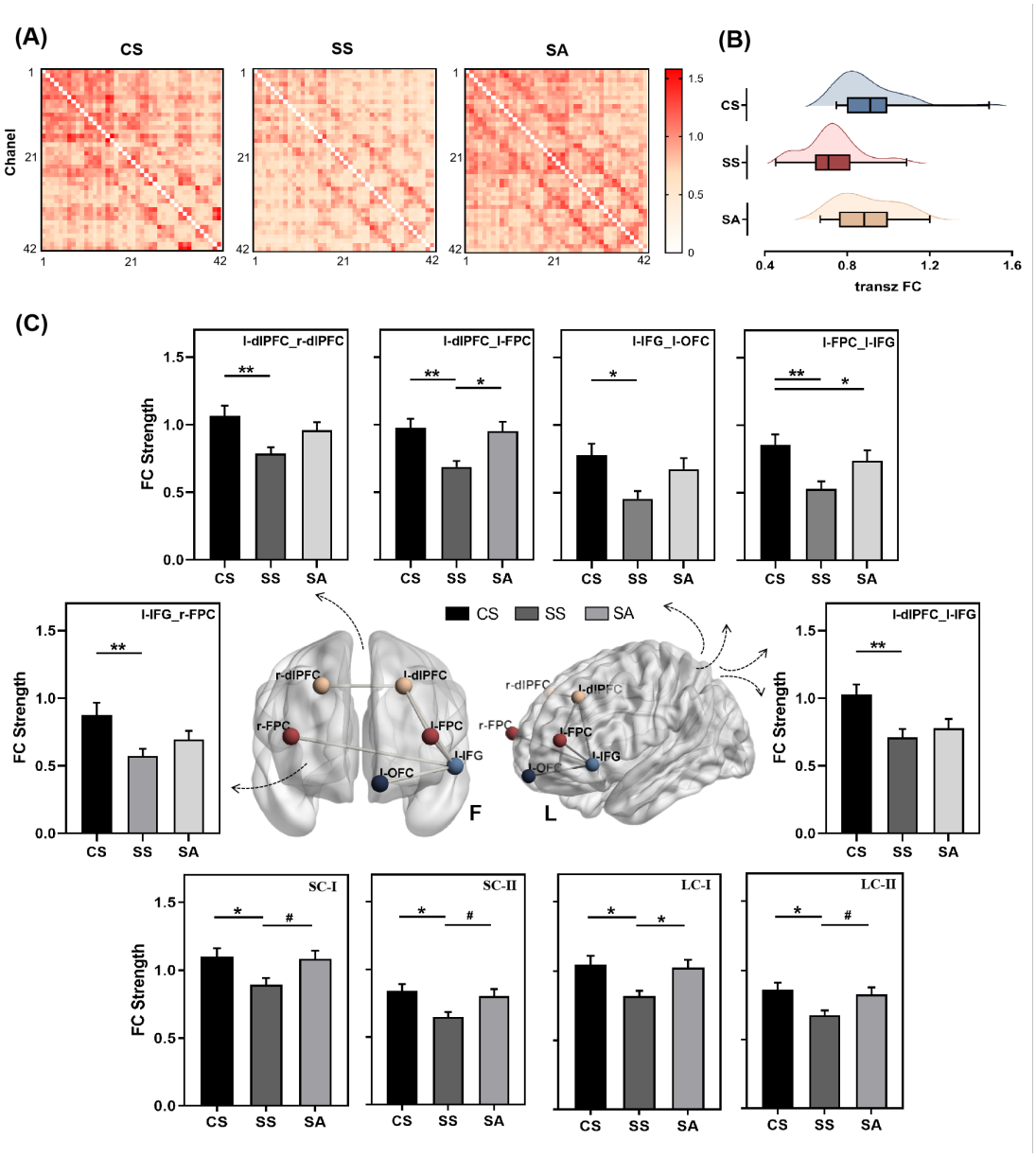

Figure 5. Results of functional connectivity strength induced by the stress and control manipulations. (A) Functional connectivity strength. Grouped-averaged connectivity matrix map of PFC. (B) Distribution of mean connectivity change. (C) Grouped-averaged functional connection strength of four clusters and significant ROI pairs after FDR correction. Error bars represent standard errors of the mean. CS: control condition with sham stimulation; SS: stress condition with sham stimulation; SA: stress condition with active stimulation. $^{\#}p<0.10$, $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$. L, left sagittal plane; F, coronal plane.

3.6 Differences in creativity before and after stress

To test the changes in creative performance between groups, a two-way mixed design ANOVA

was conducted on AUT scores with Time (pre-test, post-test) as the within-participants variable and Group (SA, SS, SC) as the between-participants variable.

In relation to AUT scores (Figure 6), a significant interaction effect of Time × Group was found [Fluency: F (2, 87) = 6.35, p = 0.003, η_p^2 = 0.127; Flexibility: F (2, 87) = 3.92, p = 0.023, η_p^2 = 0.083; Originality: F (2, 87) = 4.753, p = 0.011, η_p^2 = 0.098]. Subsequent simple effects analyses revealed that the post-test score in the SS group was significantly lower than the pre-test score (Fluency: p < 0.001; Flexibility: p = 0.004; Originality: p < 0.001). However, there was no significant difference between the pre-test score and post-test scores in the active stimulation group (Fluency: p = 0.552; Flexibility: p = 0.673; Originality: p = 0.652) and the control group (Fluency: p = 0.966; Flexibility: p = 0.655; Originality: p = 0.203). Furthermore, an ANCOVA analysis showed that the post-test score of the SS group was significantly lower than that of the SA group (Fluency: p = 0.003; Flexibility: p = 0.022; Originality: p = 0.032) and the CS group (Fluency: p = 0.022; Flexibility: p = 0.058; Originality: p = 0.002). The difference between SA and CS was not significant [Fluency: F (2, 86) = 4.48, p = 0.014, η_p^2 = 0.094; Flexibility: F (2, 86) = 4.48, p = 0.014, η_p^2 = 0.094; F (2, 86) = 4.48, p = 0.014, η_p^2 = 0.094].

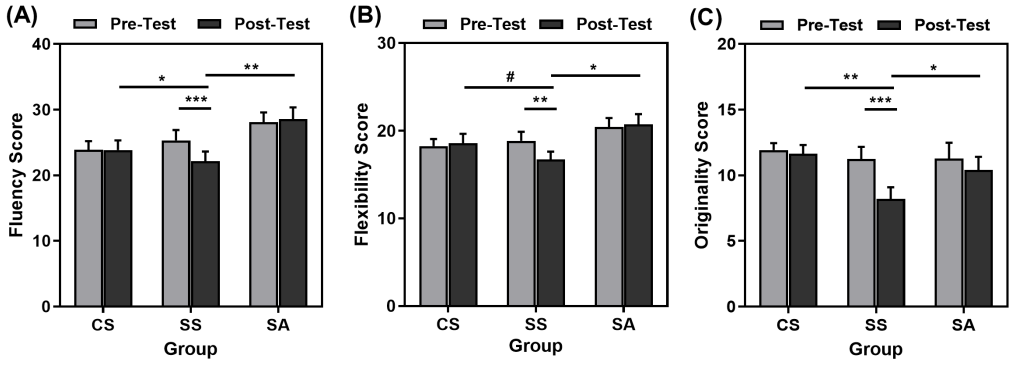

Figure 6. Pre-test and post-test AUT performance for the dimensions of fluency (A), flexibility (B), and originality (C). Error bars represent standard errors of the mean. CS: control condition with sham stimulation; SS: stress condition with sham stimulation; SS: stress condition with active stimulation. $^{\#}p$<0.10, $^{*}p$<0.05, $^{**}p$<0.01, $^{***}p$ < 0.001.

3.7 Correlation analysis of brain responses and creativity

The correlation analysis between cortical activation and AUT scores revealed that the change in originality scores was positively corrected with beta values in the left dlPFC (CH5: r = 0.332, p

= 0.042) (Figure 7A). The correlation analysis between cortical activation and the state anxiety scores revealed that higher beta values in the left dlPFC were associated with the lower enhancement of anxiety under stress (score at T3 minus score at T1)(CH5: $r = -0.310$, $p = 0.024$) and the higher recovery of anxiety after stress (score at T4 minus score at T3)(CH5: $r = 0.316$, $p = 0.016$) (Figure 7F.).

The average connection strength among SC-I ($r = 0.275$, $p = 0.009$), SC-II ($r = 0.305$, $p = 0.004$), LC-I ($r = 0.326$, $p = 0.004$), and LC-II ($r = 0.337$, $p = 0.004$) was positively correlated with changes in fluency scores (Figure 7B-7E). In addition, connection strength showed a correlation with physiological and psychological indicators of stress. Higher connectivity strength was associated with lower enhancement of anxiety (l-dlPFC_l-IFG: $r = -0.302$, $p = 0.012$; l-dlPFC_r-dlPFC: $r = -0.324$, $p = 0.012$; l-FPC_l-IFG: $r = -0.219$, $p = 0.076$) and negative mood (l-dlPFC_l-IFG: $r = -0.351$, $p = 0.006$; l-dlPFC_r-dlPFC: $r = -0.246$, $p = 0.040$; l-FPC_l-IFG: $r = -0.301$, $p = 0.012$; l-IFG_r-FPC: $r = -0.226$, $p = 0.048$) after stress induction. Higher connectivity strength was associated with the AUCi values of heart rate (l-dlPFC_l-IFG: $r = -0.280$, $p = 0.048$; l-dlPFC_r-dlPFC: $r = -0.230$, $p = 0.087$) (Figure 7G-7I).

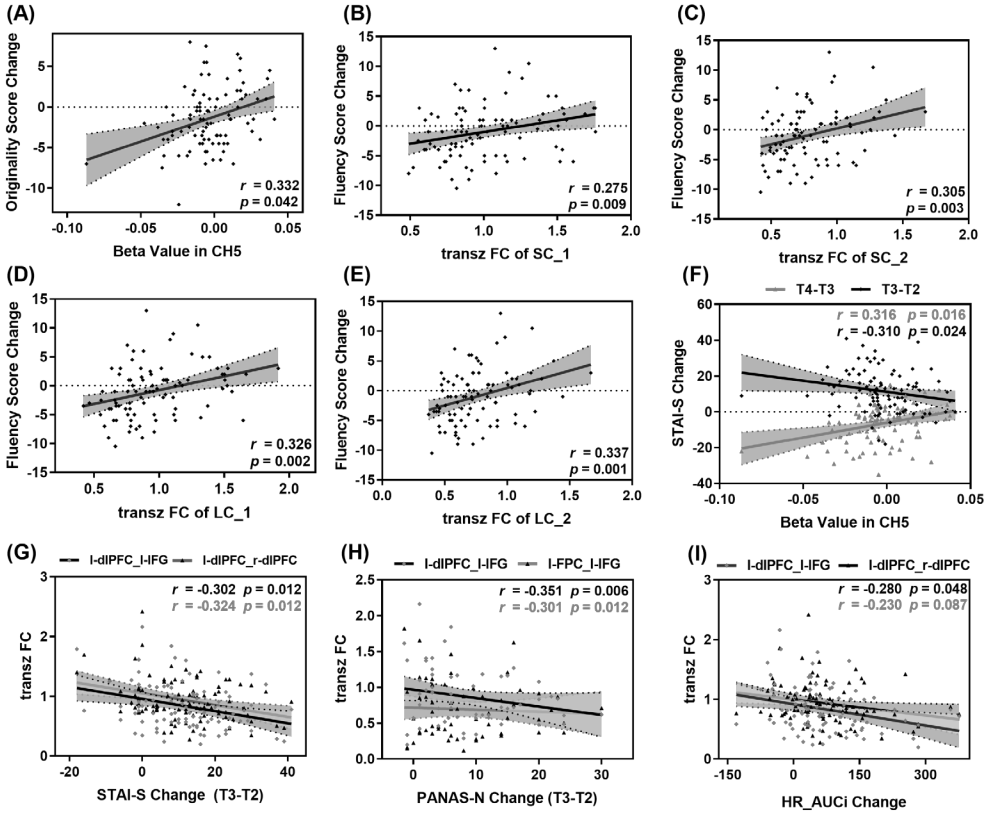

Figure 7. Scatter plots of the PFC activity and behavioral indicators with regression lines and

confidence bands. (A)-(F) Relationship between the PFC activity and creativity performance, (G)-(J) Relationship between the PFC activity and stress response with respect to emotion and heart rate.

To further explore the mediating role of brain activity in tDCS influencing creative performance, a mediation analysis for a multi-categorical independent variable was implemented (Hayes and Preacher, 2014). With the CS condition as the reference level, the SS and SA groups were coded as dummy variables, the mediating variable was the beta value for PFC activation and functional connectivity after z-transformation, and the dependent variable was the change in different dimension in relation to creativity. As seen in Table 2 and Figure 8, the mediating effect in the SS group was significant, suggesting stress diminishes creativity by reducing PFC activation and functional connectivity. In contrast, the negative effect of stress on both PFC activation and functional connectivity was not significant in the SA group when the control group was set as a comparison. These results demonstrate that tDCS effectively alleviated PFC dysfunction under stress and thus prevented impaired creativity.

Table 2. Mediation effect of brain responses on the association between stress conditions and creativity performance.

CS as a comparison group	SS			SA		
	Effect	95% CI		Effect	95% CI	
		Lower	Upper		Lower	Upper
Conditions→CH5 →AUT-Originality	-0.27	-0.556	-0.040	-0.07	-0.224	0.022
Conditions→SC-I →AUT-fluency	-0.12	-0.298	-0.003	-0.01	-0.117	0.118
Conditions→SC-II →AUT-fluency	-0.16	-0.245	-0.017	-0.03	-0.156	0.098
Conditions→LC-I →AUT-fluency	-0.17	-0.369	-0.030	-0.02	-0.165	0.125
Conditions→LC-II →AUT-fluency	-0.19	-0.377	-0.038	-0.04	-0.196	0.109

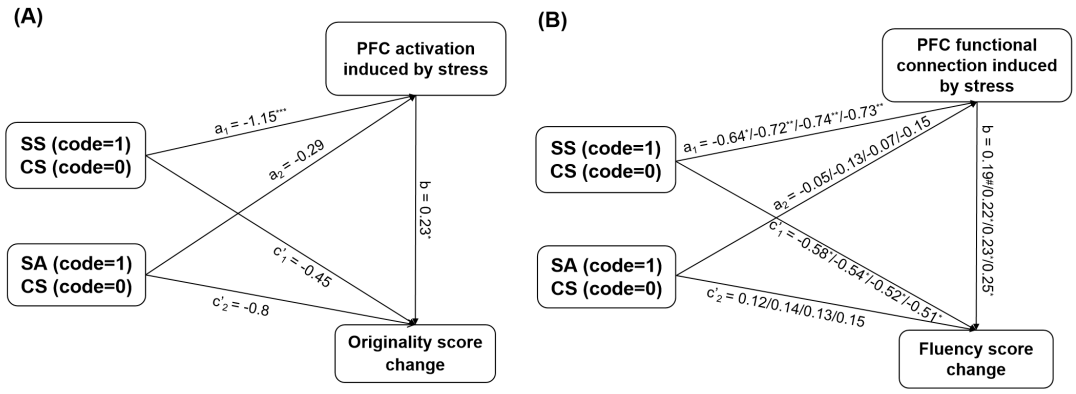

Figure 8. Diagrammatic representation of the mediation model. (A) Mediation analysis of beta values in the PFC on the association between the SS and SA groups and the change in originality scores compared with the control group without the stress manipulation (CH5). (B) Mediation analysis of functional connectivity after z transformation on the association between the SS and SA groups and change in fluency scores compared with the control group without the stress manipulation (SC-I/SC-II/LC-I/LC-II). $^{\#}p<0.10$, $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p < 0.001$. CS: control condition with sham stimulation; SS: stress condition with sham stimulation; SA: stress condition with active stimulation.

4 Discussion

The purpose of this study was to investigate how activation of the left dlPFC induced by tDCS affects the stress response and subsequent creative performance. By applying the fNIRS to record cerebral hemodynamic parameters, underlying neural mechanisms were made clear. The results showed that active stimulation effectively alleviated the stress response on HR and emotion, while also preventing a stress-induced impairment in creativity performance. fNIRS results indicated that tDCS improved the level of cortex activation in the dlPFC and FPC, as well as the strength of inter-hemispheric and intra-hemispheric functional connectivity within the PFC. In addition, the neural activity of the PFC was correlated with the changes in creativity scores and stress responses. These results not only provided causal evidence about the relationship between the left dlPFC and acute stress responses but also demonstrated that the ameliorating effect of tDCS on creativity impairment can be achieved by preventing PFC dysfunction during stress.

4.1 The hindering effect of stress on PFC function

Consistent with previous studies, stress reduced activation and connection strength in the PFC

(Qin et al., 2009; Al-Shargie et al., 2017; Alyan, Saad, and Kamel, 2021; Al-Shargie et al., 2022; Alyan, Saad, and Kamel et al., 2021; dos Santos et al., 2022). As mentioned above, this dysregulated state may be due to the detrimental effects of the extensive release of catecholamines in the PFC that is induced by stress. Numerous animal studies have demonstrated the inverted U-shaped curve relationship between catecholamine release and prefrontal activity. Moderate catecholamine release could increase cortical excitability, facilitating neurons to process information (Datta and Arnsten, 2019). However, the excessive release of prefrontal catecholamines under stress would abandon high-affinity receptors leading to an inhibitory pattern of neural firing (Birnbaum et al., 2004; Arnsten, 2009). In contrast, the release of catecholamines has been found to enhance amygdala function to support fear and vigilance responses to threatening stimuli (Ferry et al., 1999; Roozendaal et al., 2002). The brain shifts from cautious and thoughtful top-down processing dominated by the PFC to impulsive and sensory-driven bottom-up processing dominated by the amygdala (Ossewaarde et al., 2011; Arnsten, 2015). Neural resources are found to be reallocated to the salience network with the amygdala as the key structure (Van Marle et al., 2010; Hermans et al., 2014). fMRI evidence has suggested that decoupling between the amygdala and dlPFC under stress enhances the negative memory bias (Luo et al., 2018; Moses et al., 2023). This dynamic shift helps speed up the ability to avoid threatening situations but is detrimental to thinking and reasoning, including complex creative cognitive processing.

According to the neurovisceral integration model, the PFC is both essential to the activation of the SNS and the inhibition of vagal activity (Thayer and Lane, 2009). The “offline” state of the PFC under stress could be relieved by its spontaneous limbic system regulation. Consequently, groups with some levels of prior resting-state PFC activation before stress exhibited lower degrees of psychological, and physiological changes during stress (Datta and Arnsten, 2019), which provides directional support and a clear rationale for brain interventions.

4.2 Modulation of stress-induced PFC dysfunction by tDCS

tDCS can induce changes in cortical synaptic transmission (Hoogendam et al., 2010), and this preconditioning produces neurobiological after-effects to influence changes in neural activity in subsequent tasks (Cirillo et al., 2017). In line with previous brain stimulation research (Brunoni et al., 2013; Remue et al., 2016; Carnevali et al., 2020), the present study found that the activation preponderance of the left dlPFC before stress alleviated both physiological and psychological stress

responses in the present study. More importantly, left-dominant brain activation effectively improved activity and connectivity in the PFC a during stressful task. These results further supported the asymmetry hypothesis concerning the stress response, and elucidated the regulatory role played by the left dlPFC in suppressing adverse neural responses to stress.

The right PFC is considered to be the main brain region dominating the activation of stress-related systems (Tanida et al., 2004; Cerqueira et al., 2008; Ishikawa et al., 2014; Macefield et al., 2023). When stress responses were repeatedly elicited through fearful faces alone, participants showed a sustained activation of the right dlPFC, reflecting the distress signal generated by the stress response (Fischer et al., 2002; Sinha et al., 2016). Further studies have revealed that right-sided dominant activation lateralization in healthy populations produces a greater heart rate response (Tanida et al., 2004; Ishikawa et al., 2014). This right PFC-dominated activation is a common resting state in patients with mental disorders related to stress, who generally exhibit a more intense stress response (Strigo et al., 2010; Yin et al., 2011; Zhu et al., 2017). It was explained at molecular level that enhanced NE input was an important reason for the greater sensitivity to fight-flight responses in participants with right PFC dominance (Jung et al., 2019). DA is also preferentially input to the right PFC cortex during stress (Sullivan and Szechtman, 1995; Lupinsky et al., 2010), which is more likely to cause dysfunction in this region (Fonzo et al., 2016). As further evidence, in the present study, we found the right PFC was deactivated to a greater extent than it was in the control group. Deactivation of the right dlPFC before stress may also reduce the degree of SNS arousal to some extent, decreasing excessive input of catecholamines and thus prevent deactivation of the FPC in response to stress.

The left dlPFC has been shown to suppress physiological stress responses through connections with the medial PFC (Barbas and Pandya, 1989). Era et al. (2021) observed sustained autonomic and neuroendocrine activation, as well as higher task-related subjective stress perception, by inhibiting left dlPFC activity in healthy subjects through continuous theta burst stimulation. Patients with anxiety disorders also exhibited the loss of regulation in the left dlPFC under stress, which might be a key factor in restricted higher cognitive control (Koric et al., 2012). During the stress recovery phase, a significant enhancement in the connectivity network between the left dlPFC and the FPC has been demonstrated (Al-Shargie et al., 2022). The present study observed stronger functional connectivity between the left dlPFC, FPC, IFG, and OFC, further demonstrating the

causal relationship between the left PFC and stress response regulation.

The relatively left-lateralized activation has been shown to decrease GABA concentration and increase glutamatergic transmissions, which activate to promote Ca^{2+} flow to produce early the late long-term potentiation (LTP) (Stagg et al., 2009; Cirillo et al., 2017; Yamada et al., 2021). Enhanced LTP can enhance information processing efficiency by promoting the efficiency of neurotransmission in cortical circuits (Jung et al., 2019; Yu et al., 2019). Meanwhile, unilateral or bilateral stimulation of the PFC could induce connectivity reduction and enhancement within and beyond the stimulation regions (Krause et al. 2017; Ren et al., 2021). Both changes in cortical excitability and connectivity strength reflect more flexible resource allocation and information encoding in brain networks, which may strengthen stress regulation of the left dlPFC to prevent bilateral PFC dysfunction and restore dominant control of the PFC under stress condition.

4.3 Effects of restored PFC function under stress on stress responses and creativity

As previously stated, prefrontal dysregulation under stress results in regulation of the salience network centered on the amygdala. The majority of prior research has addressed the mechanism of bottom-up control from the amygdala to the right PFC, particularly the dlPFC (Johnstone et al., 2007; Cerqueira et al., 2008; Zhang et al., 2019; Warren et al., 2020). It was found in the present study that the stimulated group had a greater degree of activation and internal connectivity in the PFC compared to the sham group under stress condition, which may enhance top-down regulation to cope with these stress conditions and thus alleviate the subsequent impairment of creativity.

Specifically, activation of the right dlPFC that was observed in this study further supports its down-regulated role on emotional responses (Delgado et al., 2008; Ray and Zald, 2012; Feeser et al., 2014; Pripfl and Lamm, 2015). Meanwhile, activation of the left dlPFC enhances cognitive control and reduces rumination in cognitive reappraisal (Baeken et al., 2017; Takamura et al., 2020). Therefore, the synergistic effect of the bilateral dlPFC contributed to higher emotional flexibility, motivating effective emotion regulation strategies to reduce the undesirable effects of negative emotions. This explanation supported the results of the relatively lower negative mood and anxiety states in the stimulation. Further, more positive emotion states can reduce the subjective psychological perception of stress, which in turn enhances creativity by stimulating approach motivation and boosting cognitive flexibility (Baas et al., 2008; Ivcevic and Brackett, 2015).

In addition to improvements in emotional stress responses, enhanced PFC activation and connectivity indicated effective mobilization of cognitive resources to cope with creative tasks under stressful conditions. According to the findings of this study, the stimulated group had higher activation of two subregions including the bilateral dlPFC and FPC (Ellamil et al., 2012; Green et al., 2012). The dlPFC is a core brain region for executive control that facilitates the generation of original ideas by integrating, evaluating, and validating information (Sun et al., 2016), whereas the FPC enables creative integration across semantic distances (Green et al., 2015). Poor creativity is frequently observed in patients with frontotemporal dementia (de Souza et al., 2010). Therefore, the activated states of the stimulation and control groups in both of these regions were able to support creative cognitive processing.

Moreover, the enhanced short-distance connectivity and long-distance connectivity between subregions of the PFC reflected the fact that individuals had a higher neural network reorganization ability to adapt to the stress condition. Specifically, left-right PFC dysregulation and decoupling is an important feature of the stress state (Liston et al., 2009). However, stronger functional connectivity strength in the PFC is required to facilitate creative cognitive processing (Beaty et al., 2014; Beaty et al., 2018; Chen et al., 2018). Thus, tDCS-induced high connectivity helps individuals re-establish new homeostasis and rapidly reorganize neural resources that are required to maintain levels of creativity.

Notably, although some studies have found effective regulation of the HPA axis by the left dlPFC (Baeken et al., 2014; Remue et al., 2016; Hernaus et al., 2018), no equivalent effect of left dlPFC activation under stress was found in the present study. Similarly, tDCS activation on the left side of dlPFC also did not reveal significant differences in cortisol release by HPA after stress induction (Carnevali et al., 2020; De Wandel et al., 2023). Importantly, the cortisol arousal level one day after the experiment, which could represent the potentially long-lasting effects of the HPA axis, appeared significantly increased (Carnevali et al., 2020). The regulatory effects of glucocorticoids released from the HPA axis last longer and exhibit delayed effects (Campos-Cardoso et al., 2023). Therefore, a single tDCS stimulation before stress may not produce rapid modulation of the HAP axis in the short term. It is necessary to further explore the top-down intervention method regulating the activity of the HPA axis under acute stress to reduce the possibility of stress pathogenicity.

4.4 Limitations and future directions

There are several limitations to the present study. First, the present study assumed that the SNS and the HPA axis played a potential inhibitory role in cognitive functioning under stress. In the future, biological markers or pathopharmacological means should be used to reveal and verify the different physiological mechanisms involving catecholamine and glucocorticoid in the influence of stress on creativity. In addition, exploring the modulatory effects of tDCS on neurotransmitters and hormone release deserves more in-depth exploration. Second, only female participants and healthy participants were included in this study to avoid misleading results caused by large differences between groups. Future research should expand the sample group to verify the stability of tDCS intervention effects. Third, the neural and cognitive mechanisms should be further investigated to predict more precisely the directionality of the tDCS treatment and increase its efficacy. At the neural level, both stress and creative cognitive processing require synergy between different brain networks. Future studies need to further reveal the brain mechanisms of tDCS by exploring the dynamic casual relationships among brain networks. At the cognitive level, the cognitive pathways by which tDCS affects creativity under stress can be further explored in conjunction with cortical and psychophysiological changes.

5 Conclusion

In conclusion, the current study revealed that tDCS-induced left-lateralized dlPFC activation can effectively alleviate the stress response as well as the impairment of creativity under stress. It has been demonstrated that a direct causal relationship exists between PFC activity and stress reactions through tDCS modulation before stress, and the neurophysiological mechanism of PFC dysfunction in the effect of stress on creativity. These results represent a major contribution to supporting the brain asymmetry hypothesis of stress, while also deepening our understanding of the etiology of mental disorders. By guiding and optimizing the application of tDCS, our study can provide empirical evidence as well as a theoretical basis for the cultivation of innovative talents and the pursuit of interventions to ameliorate stress-related mental disorders.

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