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Transcranial direct current stimulation of bilateral dorsolateral prefrontal cortex eliminates creativity impairment induced by acute stress

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ABSTRACT

The creativity impairment under acute stress may be closely related to the down-regulation of the prefrontal cortex function caused by stress-related neurotransmitters and hormones. In the current study, we explored whether transcranial direct current stimulation (tDCS) over bilateral dorsolateral prefrontal cortex (DLPFC) eliminated stress-induced creativity impairment and the potential mechanism from the perspective of stress response recovery. Seventy participants were randomly allocated to a group undergoing the activation of right DLPFC and the deactivation of left DLPFC (R+L−; $N = 35$), and a group of sham stimulation (sham; $N = 35$). Participants received tDCS after the stress induction, and then completed the Alternative Uses Task (AUT) and the Remote Association Task (RAT) during the stimulation. The stress response was indicated using heart rate, cortisol, and emotion changes. Results showed that R+L− stimulation facilitated the recovery of anxious state compared to sham stimulation. We also found that the decreased value of AUT scores after stress in the R+L− group was significantly lower than that in the sham group. Moreover, further analysis revealed state anxiety mediated the effect of tDCS on the flexibility component of the AUT. We concluded that bilateral tDCS over the DLPFC is efficient in alleviating stress-induced creativity impairment, which may correlate with greater recovery of state anxiety. Our findings provide causal evidence for the neurophysiological mechanisms by which stress affects creativity, as well as clinical suggestions for stress-related psychiatric disorders prevention and intervention.

1. Introduction

It seems to be a consensus that we exist in a society that is full of volatility, uncertainty, complexity, and ambiguity, which makes stress exposure become people's natural state of life. As an example, the COVID-19 epidemic outbreak spread rapidly around the world, and triggered mild to extreme stress symptoms in healthy people (Wang et al., 2020). Meanwhile, the incidence of post-traumatic stress disorders continued to increase (Tan et al., 2020). Human creative activities are facing major challenges. Both organizations and individuals are often required to retain creative vitality to produce creative solutions and decisions when exposing to stress (Bartscht, 2015). Hence, looking into effective interventions for boosting creativity under stress is of great significance in the current context.

Creativity is the ability to generate novel (i.e., original, unexpected) and appropriate (i.e., useful, adaptive) ideas, solutions, or products within a given situation (Amabile, 1983; Sternberg and Lubart, 1999). Creative thinking includes two forms: divergent thinking and convergent thinking (Guilford, 1967). Divergent thinking is a process of idea generation requiring the exploration of as many original problem-solving answers as possible, and it's typically measured by fluency, flexibility, and originality (Kaufman and Sternberg, 2010; Runco, 1991). Convergent thinking, on the other hand, is the process of organizing ideas and information according to a set of logical steps to get a correct

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solution (Guilford, 1950). Increasing evidence suggesting acute stress significantly impaired the two forms of creative thinking process (Duan et al., 2020a, 2020b; Duan et al., 2019; Wang et al., 2019). Specifically, stress can inhibit participants from generating more ideas in divergent thinking tasks and reduce correctness in convergent thinking tasks by impairing cognitive flexibility (Alexander et al., 2007; Duan et al., 2020a).

Acute stress is often defined as the organism's adaptive physiological and psychological responses in reaction to unpredictable, uncontrollable, and threatening stressors (Byron et al., 2010; Selye, 1936). Under the condition of acute stress, the body's homeostasis is rapidly out of balance, accompanied by a series of non-specific physiological reactions. The sympathetic nervous system (SNS) and hypothalamic pituitary adrenal (HPA) axis are activated, releasing catecholamines (i.e. dopamine and norepinephrine) and glucocorticoids (mainly cortisol) (Chrousos, 2009). Activation of the SNS and HPA axis is an important neuropharmacological basis for creativity impairment under stress (Beversdorf, 2019). The neurotransmitters and hormones released by their activation can change our emotions, thoughts, and actions by directly or indirectly affecting the central nervous system (Shansky and Lipps, 2013).

As the most stress-sensitive brain region, animal researches have revealed that activity of the prefrontal cortex (PFC) is suppressed by the excessive dose of neurotransmitters and hormones release under the condition of psychological stress (Arnsten, 2009, 2015). The inactivity was also observed in the PFC when the healthy volunteers conducted a working memory task after acute stress exposure (Qin et al., 2009). The PFC regulates emotional processing, decision-making, and other high-level cognitive functions through extensive connections with other brain regions (Alvarez and Emory, 2006; Coan and Allen, 2004; Collins and Koechlin, 2012; Fuster, 1991; Harmon-Jones et al., 2010). Importantly, specific prefrontal brain regions such as the ventrolateral prefrontal cortex (vlPFC), the inferior frontal gyrus (IFG), and the dorsolateral prefrontal area (DLPFC) are widely involved in creative cognitive processing (Dietrich, 2004; Gonen-Yaacovi et al., 2013; Vartanian and Goel, 2007). According to the twofold model of creativity, creative cognitive processing is generated by the two phases of generation and evaluation (Ivancovsky et al., 2019). PFC is the core of the executive control network and contributes to the cyclic motion between these two phases (Kleinmintz et al., 2019). Inhibition of the PFC may diminish the generation of novel conceptual association and evaluation of the adaptive ideas (review in Chrysikou, 2019; Wang et al., 2019). There is a typical case that patients with frontotemporal dementia or Parkinson's disease, who have damage to specific PFC regions, show a reduction in creativity performance.(de Souza et al., 2010; Drago et al., 2009). While stress-related neuromodulators impair PFC regulation, amygdala function is strengthened (Van Oort et al., 2017). As a consequence, the brain activity changes from "top-down" regulated by the PFC to "bottom-up" regulated by the sensory cortex. For attention regulation, this switch can make individuals more inclined to habitual motor responding, but not innovative behavior (Arnsten, 2009; Arnsten and Goldman-Rakic, 1998). Moreover, the activation of amygdala function also leads to the experience of negative emotions and the inhibition of emotional regulation (Banks et al., 2007), which can weaken creativity performance indirectly (Davis, 2009; Ivcevic and Brackett, 2015). Taken together, the weakening effect of acute stress on creativity may be closely linked to the down-regulation of PFC structure and function. We speculated that modulation of PFC activity through noninvasive brain intervention can improve the performance of creativity under acute stress.

Transcranial direct current stimulation (tDCS) is a safe and noninvasive transcranial stimulation technique applied in modulating the level of cortical excitability. It utilizes anode and cathode electrodes to deliver a low-amplitude direct current to specific brain areas (Nitsche and Paulus, 2000).

In the stress state, tDCS was confirmed to prevent stress-induced cognitive deficits by activating the PFC area. Bogdanov and Schwabe (2016) applied online stimulation via anode over the right DLPFC after stress, and the results showed better working memory performance. Meanwhile, extensive studies have shown that acute stress response can be alleviated by tDCS. For example, researchers observed that anodal stimulation over the right medial PFC by tDCS reduced lower stress-induced cortisol release compared to the cathodal condition (Antal et al., 2014). Also, activation of the left DLPFC induced a lower heart rate and a lower subjective reported anxiety level in healthy individuals during stress induction (Carnevali et al., 2020). Even though these aforementioned studies used tDCS before and during stress induction and found inconsistent results depending on the stimulation target areas, they confirmed that tDCS could be a promising tool benefiting the recovery of the stress response. Given that stress responses can impact various cognitive processes of creativity (Akinola et al., 2019; Yeh et al., 2015), this advantage may help alleviate the impairment of acute stress on creativity.

In a non-stress state, tDCS has been widely used in the improvement and recovery of creativity (Leite et al., 2013; Lucchiari et al., 2018), increasing the possibility of recovering from creativity impairment under stress. A balance hypothesis shows that right PFC activation and left PFC suppression can promote creativity. In line with this hypothesis, highly creative individuals are associated with the lower structural integrity of the left PFC (Jung et al., 2010) and the greater volume of gray matter in the right PFC (Takeuchi et al., 2010). Most brain stimulation studies also support this hypothesis, which proved creativity is more facilitated by a balance of activation between two frontal hemispheres (i.e. higher right frontal activation than left frontal activation). For example, Mayseless and Shamay-Tsoory (2015) revealed that anodal tDCS over the right IFG combined with cathodal tDCS over the left IFG improved creativity, whereas neither the reverse stimulation nor separate stimulation did not affect creative production. Khalil et al. (2020) have also shown that a similar tDCS protocol could improve creativity through weakening cognitive inhibition. The neural mechanism underlying the beneficial influence of tDCS on creativity has been further investigated by using the electroencephalographic technique. Results showed that the improvement of creativity performance was significantly positively associated with the increase of resting-state EEG beta power in the right frontal area (Hertenstein et al., 2019). Unilateral stimulation produces similar facilitation effects on creative performance. Erickson et al. (2017) conducted activation of the right DLPFC and found the increased semantically remote responses. Lifshitz-Ben-Basat and Mashal (2021) revealed that cathodal stimulation of the left angular gyrus, part of the frontotemporal network, enhancing novel metaphor generation through the inhibition of the control network. In addition, some direct evidence showed that cathodal stimuli over the left DLPFC and vlPFC were able to produce more creative ideas (Chrysikou et al., 2013; Chrysikou et al., 2021; Colombo et al., 2015). However, other studies still proved that left-hemisphere activation plays an equally important role in creativity tasks, especially in convergent thinking tasks (Cerruti and Schlaug, 2009; Metuki et al., 2012; Zmigrod et al., 2015). Therefore, stimulation effects depend on the interaction between task demand, stimulation polarity, stimulation location and external environment (Weinberger et al., 2017). Whether right-hemispheric activation and left-hemispheric suppression have the same beneficial effect on creative thinking under acute stress remains to be further investigated.

The main purpose of this study was to investigate whether one single session of tDCS could reduce creativity impairments induced by acute stress, and whether the effect of tDCS on creativity performance is partially mediated by the recovery of the stress response. tDCS in the present study was applied to bilateral DLPFC regions, and the stimulation conditions were divided into two types: the active group (the anode over the right DLPFC and the cathode over the left DLPFC) and the sham group. The DLPFC was chosen as the target region because it was an essential brain region regulating creativity (Beaty et al., 2015), and was also involved in the stress responses caused by the neuroendocrine

system (Antal et al., 2014; Carnevali et al., 2020). As previously mentioned, left-side versus right-side suppression improves creativity performance. In addition, the right hemisphere (especially right dlPFC) is more likely to deactivate by stress-related neuromodulators (Cerqueira et al., 2008; Luettgau et al., 2018). Therefore, we speculated that anode stimulation of the right DLPFC combined with cathode stimulation of the left DLPFC could effectively recover the damage of creativity caused by stress while accelerating the recovery of the stress response.

2. Methods

2.1. Participants

Seventy healthy female students (age: $M = 19.6$, $SD = 1.55$) from Shaanxi Normal University participated in the study. In order to eliminate the confusion caused by gender differences in physiological and subjective stress response, the experiment only focused on female participants (Van den Bos et al., 2009; Duan et al., 2020b). People with a body mass index of <18 kg/m^2 or >27 kg/m^2, as well as hormonal contraceptive intake, drug use, alcohol use, acute diseases, or a lifelong history of any psychiatric, were excluded from the study. Participants in the experiment have been asked to come to the formal experiment during non-menstrual periods. In addition, they were instructed to avoid strenuous exercise, food or drinks (except water) within 3 h before the experiment, and ensure to get 7 h of adequate sleep.

Participants were randomly assigned to a group undergoing activation of the right DLPFC and deactivation of the left DLPFC (R+L−; $N = 35$), and a group of sham stimulation (sham; $N = 35$). Following a thorough explanation of the experimental protocols, they signed an informed consent document. At the end of testing, they received monetary compensation. The study was approved by the Academic Committee of the Ministry of Education of the Key Laboratory of Modern Teaching Technology, Shaanxi Normal University in China, and pursued the principles of the Declaration of Helsinki (World Medical Association, 2013).

2.2. Procedure

Participants were tested in two days with an interval of about a week. The time of each test session was from 2:00 to 6:00 P.M. for controlling the individual difference caused by the circadian rhythms (Izawa et al., 2010). On the first day, the participants completed the trait version of the State-Trait Anxiety Inventory (STAI-T) (Speilberger and Sydeman, 1994) and the Beck Depression Inventory-II (BDI-II) (Beck et al., 1996), to prevent the potential group differences caused by depressive and anxiety symptoms from affecting the experimental results. Participants then completed the Alternative uses task (AUT) and Remote association task (RAT) to obtain baseline levels of creativity. The order of the two tasks was counterbalanced across participants. An opportunity was given to practice the two tasks before the formal experiment.

On the second session, the E4 real-time wristwatch was worn to collect the changes in heart rate throughout the test session. The whole experimental procedure is shown in Fig. 1. Firstly, participants were asked to complete the positive and negative affect schedule (PANAS) (Watson et al., 1988) and the state version of the State-Trait Anxiety Inventory (STAI-S) for measuring the baseline of subjective stress parameters. The first salivary sample (S1) was then collected before stress induction. Subsequently, participants performed Trier Social Stress Test (TSST). After TSST, they completed again the measurement of subjective stress parameters, and we collected the second salivary samples (S2). Ten minutes after the end of stress, tDCS was administered for 20 min. The salivary samples (S3) were collected 5 min after tDCS stimulation. At the same time, the participants began to complete the post-test of RAT and AUT (maximum duration: 15 min). Two parallel versions of AUT and RAT were prepared and counterbalanced between pre-test and post-test. The third measurement of subjective stress parameters was completed and a salivary sample (S4) was collected after the stimulation was over. For tracking continuously the changes in cortisol, salivary samples (S5) were taken again 10 min after the stimulation.

2.3. Measures

2.3.1. Stress paradigm

In this experiment, we used TSST as the psychological stress-inducing method (Kirschbaum et al., 1993). TSST included two sessions: public speaking and mental arithmetic. In the public speaking session, participants were required to complete a five-minute job interview speech to two interviewers. If the free speech was <5 min, the interviewers would ask questions according to the standard questions prepared in advance (e.g., “Why do you think you are qualified for this job?”, “What are your strengths compared to other competitors?”, “What are your major disadvantages?” etc.). Subsequently, participants began a five-minute mental arithmetic task. They were asked to orally report the result of subtracting 17 from 2023 consecutively in a fast and accurate way. When the calculation was wrong, the interviewers interrupted the participants and instructed them to start again from 2023. During the whole experiment, the interviewers remained neutral and indifferent and do not give any oral or non-verbal feedback. The camera pointed directly at the participants’ faces and recorded their verbal and non-verbal performance.

The induction of acute stress was evaluated by physiological and psychological indicators. On a physiological level, SNS activity was evaluated using the heart rate collected by Empatica E4 real-time wristwatch (Empatica Inc., Milano, Italy). In addition, salivary cortisol (sC) was used to quantify HPA axis activity. The saliva samples were collected by Olivetti collection devices (Salivette, Sarstedt 51.1534.500, Germany) at several time points across the experiment. All saliva samples were stored at −23 °C in a freezer and determined cortisol concentration by Enzyme-Linked Immuno Sorbent Assay (Zhuocai, China).

On a psychological level, the scores in PANAS and STAI-S were used to evaluate the effect of stress on emotion and anxiety. The PANAS consists of two 10-item self-report scales that respectively measure the positive affect and negative affect. Participants rated the current emotional intensity on a 5-point Likert scale. Higher scores indicate higher emotional activation. The STAI-S consists of 20 items measuring state anxiety symptoms and requires participants to describe how they feel at a particular moment on a 4-point Likert scale.

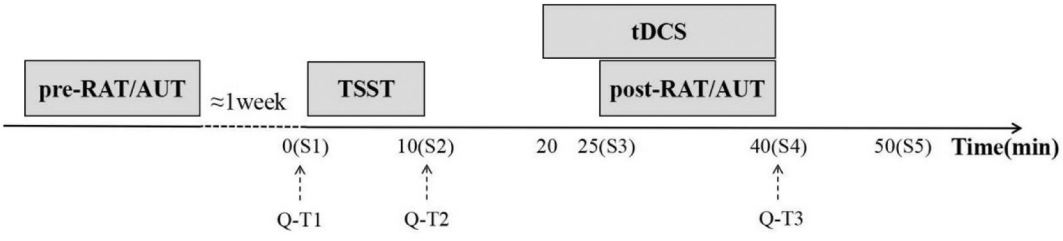

Fig. 1. Schematic illustration of the experimental design and procedure.

2.3.2. Alternative uses task (AUT)

AUT is a commonly used test for measuring divergent thinking. Participants were asked to give oral reports on the use of three daily necessities as much as possible within 2 min. Items in the two lists (list1: newspaper, bucket, and shoes; list2: umbrella, paper clip, and can) were randomly presented in the experimental session. The performance of the AUT was measured by fluency, flexibility, and originality. According to the standard scoring method (Radel et al., 2015), the fluency score was denoted as the total number of effective and reasonable answers given, with one point for each answer. Comparatively, the flexibility score was computed from the number of categories in the given answers. The originality score was calculated by the answer frequency of occurrence in the answer pool. If the frequency of an answer was <1%, it got 2 points. If the percentage was between 1% and 5%, it got 1 point. If the percentage was >5%, no score was given. The responses of the participants were rated by two professional raters in the creative field who were blind to the experimental condition. The Internal Consistency Coefficient (ICC) was also acceptable (ICC: 0.993 for fluency, 0.859 for flexibility, 0.880 for originality).

2.3.3. Remote association task (RAT)

A modified Chinese version of RAT was used to evaluate convergent thinking (Duan et al., 2020a). During the RAT, each question consists of three Chinese characters, such as "灯(light)", "宝(treasure)" and "铁(iron)". Participants were asked to come up with a Chinese character that could be combined with each of the first three characters to create a reasonable word, such as "塔(tower)". The pretest and the post-test included 20 different groups of items. The maximum response time for each item was set to 27 s for restricting that participants complete creativity tasks within the time of stimulation. To eliminate interference at the language level, all the words were from the high-frequency words in the dictionary of modern Chinese word frequency (1989). Previous studies have shown satisfactory internal consistency in the updated RAT.

2.4. tDCS parameters

tDCS was conducted using DC-STIMULATOR MC in a single-blind and sham-controlled manner (NeuroConn, Germany). According to the International EEG 10–20 system, the anode in R+L− group was placed on the right DLPFC (position F4), and the cathode was placed on the left DLPFC (position F3) (see Fig. 2). Constant current stimulation of 1.5 mA was applied through saline-soaked sponges (25cm^2, 5 × 5 cm). In the R+L− group, the current faded in and out for 30 s, lasting for 20 min. In the sham group, there was no current stimulation after 30s fade-in and 30s fade-out. A questionnaire was used to measure the difference in tDCS sensitivity between the two groups (Brunoni et al., 2011). It measures the incidence and severity of various responses to tDCS, such as tingling, itching, burning sensation, etc. Higher scores indicate a more intense sensation of the stimulation.

3. Results

3.1. Baseline parameters and control variables

An independent-sample *t*-test was conducted to compare the differences in the baseline assessment and control parameters between the two groups. As seen in Table 1, no significant group differences were observed. To be specific, no significant differences for state anxiety and depressive symptoms were noted between the two groups, excluding these factors to explain the results. For baseline physiological and subjective stress parameters, the two groups showed similar HR, salivary cortisol concentrations, and emotional activation before stress induction. Results also found that there was no significant difference in creativity performance. In particular, no significant difference between the two groups in tDCS sensitivity questionnaire scores, indicating that active and sham stimuli cannot be distinguished by participants in the sham group. In other words, participants were blind to the condition they underwent.

Table 1
Baseline parameters and control variables.

	Sham (n = 35)	R+L− (n = 35)	t	p
BDI-II	6.69 ± 5.89	7.31 ± 6.58	−0.42	0.675
STAI-T	41.71 ± 8.77	41.40 ± 8.40	0.15	0.879
Baseline physiological stress parameters				
HR	82.03 ± 10.41	82.29 ± 10.05	−0.11	0.917
Salivary cortisol	5.69 ± 1.16	5.69 ± 1.37	−0.03	0.976
Baseline subjective stress parameters				
STAI-S	37.06 ± 7.98	36.43 ± 7.06	0.35	0.728
PANAS-N	11.71 ± 2.53	12.63 ± 5.24	−0.93	0.356
PANAS-P	21.00 ± 7.46	21.45 ± 8.58	−0.24	0.813
Baseline creativity tasks				
RAT accuracy	51.43 ± 13.64	51.00 ± 13.38	0.13	0.895
AUT-fluency	25.71 ± 8.33	22.49 ± 8.30	1.63	0.109
AUT-flexibility	18.43 ± 6.09	16.49 ± 5.71	−1.38	0.173
AUT-originality	16.36 ± 10.47	13.46 ± 9.26	1.23	0.224
tDCS sensation	16.11 ± 4.29	16.03 ± 3.74	−0.09	0.929

Data are reported as mean ± standard deviation. R+L−: anodal stimulation over the right DLPFC combined with cathodal stimulation over the left DLPFC. BDI-II: Beck Depression Inventory-II; STAI-T: State-Trait Anxiety Inventory, Trait version; HR: heart rate; STAI-S: State-Trait Anxiety Inventory, State version; PANAS-N: Positive and Negative Affect Schedule, Negative dimension; PANAS-P: Positive and Negative Affect Schedule, Positive dimension; AUT: Alternative uses task; RAT: Remote association task; tDCS: Transcranial Direct Current Stimulation.

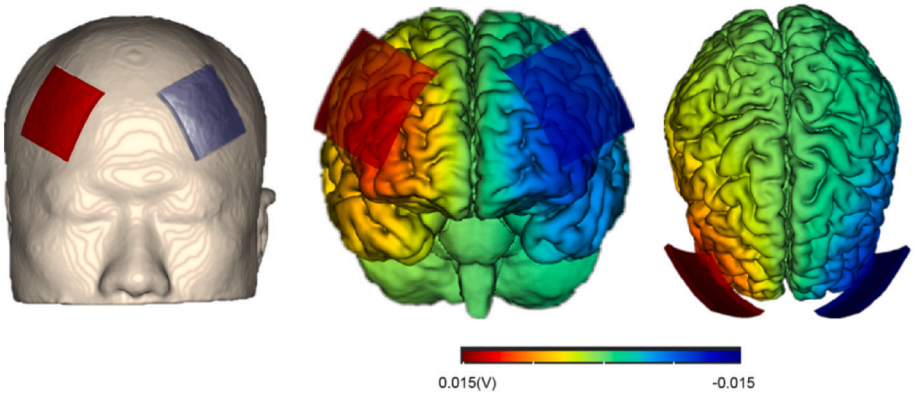

Fig. 2. Schematic diagram of tDCS montage and electric field simulation. The anode was located over the right DLPFC and the cathode was positioned over the left DLPFC. The electric field simulation for the tDCS montage was performed by the NEUROPHET tES LAB 3.0 software.

3.2. Physiological stress parameters

A 2 × 7 mixed measures ANOVA with one between-group factor (CONDITION: R+L−, Sham) and one repeated factor (TIME: 0, 5, 10, 15, 20, 25, 50 min in relation to TSST onset) was conducted on HR. Results revealed a significant main effect of TIME, F (6, 408) = 70.79, $p < 0.001$, $\eta_p^2 = 0.510$. Bonferroni-adjusted post-hoc t-tests found that the initial value ($M = 82.16$, $SD = 10.16$) of HR was significantly lower than that of 5 min ($M = 92.93$, $SD = 13.70$) ($p < 0.001$), 10 min ($M = 97.11$, $SD = 15.15$) ($p < 0.001$) and 15 min ($M = 86.06$, $SD = 10.71$) ($p = 0.029$) after stress exposure, indicating a successful stress induction. However, HR already returned to the initial value before tDCS (20 min after stress exposure), verifying that tDCS did not regulate the recovery of heart rate in two groups (see Fig. 3A). Additionally, no significant main effect of CONDITION and interaction effect of CONDITION × TIME were found [CONDITION: F (1, 68) = 0.062, $p = 0.804$ $\eta_p^2 = 0.001$; CONDITION × TIME: F (6, 408) = 0.421, $p = 0.865$ $\eta_p^2 = 0.006$].

For salivary cortisol concentrations, a 2 × 5 mixed measures ANOVA with one between-group factor (CONDITION: R+L−, Sham) and one repeated factor (TIME: 0, 10, 35, 40, 50 min in relation to TSST onset) was conducted. There was a significant main effect of TIME on salivary cortisol concentrations, F (4, 272) = 68.74, $p < 0.001$, $\eta_p^2 = 0.503$. Bonferroni-adjusted post-hoc t-tests found lower value of cortisol concentrations at baseline ($M = 5.69$, $SD = 1.26$) compared to those at 10 min ($M = 6.54$, $SD = 1.33$), 35 min ($M = 7.73$, $SD = 1.32$), 40 min ($M = 8.95$, $SD = 1.32$), 50 min ($M = 7.95$, $SD = 1.2$) obtained after TSST onset (All $ps < 0.001$). These results revealed that salivary cortisol significantly increased in response to TSST, indicating successful stress induction. However, no significant interaction effect of TIME × CONDITION and the main effect of CONDITION were observed [CONDITION: F (1, 68) = 0.62, $p = 0.435$ $\eta_p^2 = 0.009$; CONDITION × TIME: F (6, 272) = 0.589, $p = 0.445$ $\eta_p^2 = 0.009$]. In order to further examine whether there was any difference in the overall changes of salivary cortisol between the two tDCS conditions, an independent sample t-test was used on the AUCi (area under the curve with respect to increasing, AUCi). Results showed no significant difference between the groups [t (68) = −0.41, $p = 0.682$; the sham group: $M = 90.02$, $SD = 59.83$; the R+L− group: $M = 96.58$, $SD = 72.66$] (see Fig. 3B).

3.3. Subjective stress parameters

To examine indicators of successful stress induction and the effect of tDCS on stress response recovery, a mixed-design ANOVA with one repeated measures factor (TIME: Q-T1, Q-T2, Q-T3 in relation to TSST onset) and one between-group factor (CONDITION: R+L−, Sham) was respectively conducted on PANAS scores (negative affect and positive affect) and STAI-S scores.

Concerning emotion change throughout the experiment, results showed a significant main effect of TIME on positive mood scores, F (2, 136) = 23.01, $p < 0.001$, $\eta_p^2 = 0.253$. Following Bonferroni-adjusted post-hoc t-tests found a higher positive affect score at Q-T1 ($M = 21.23$, $SD = 7.99$) compared to that at Q-T2 ($M = 18.66$, $SD = 7.68$), Q-T3 ($M = 17.10$, $SD = 7.16$) (All $ps < 0.001$) obtained after TSST (see Fig. 4A). We also found that the main effect of TIME was significant on negative affect scores, F (2, 136) = 47.55, $p < 0.001$, $\eta_p^2 = 0.412$. Following Bonferroni-adjusted post-hoc t-tests revealed a lower initial value of negative affect at Q-T1 ($M = 12.17$, $SD = 4.11$) than that at Q-T2 ($M = 17.39$, $SD = 5.61$) ($p < 0.001$), and no significant difference between negative affect scores at Q-T1 and Q-T3 ($M = 12.14$, $SD = 5.86$) (see Fig. 4B). Moreover, there was no significant interaction effect of TIME × CONDITION both on positive and negation emotion [positive affect score: F (1, 136) = 0.73, $p = 0.486$, $\eta_p^2 = 0.011$; negative affect score: F (1, 136) = 1.26, $p = 0.287$, $\eta_p^2 = 0.018$]. In order to further verify the effect of tDCS on the recovery of positive and negative emotions after stress, we conducted the analysis of covariance (ANCOVA) with the scores after stimulation as the dependent variable and the scores before and after stress as the covariate, no significant results were reported [positive affect score: F (1, 66) = 0.22, $p = 0.638$, $\eta_p^2 = 0.003$; negative affect score: F (1, 66) = 2.22, $p = 0.141$, $\eta_p^2 = 0.033$].

Concerning the state anxiety change, a two-way repeated ANOVA applied on STAI-S scores revealed a significant main effect of TIME, F (2, 136) = 139.97, $p < 0.001$, $\eta_p^2 = 0.673$. Following Bonferroni-adjusted post-hoc t-tests reported higher state anxiety level at Q-T2 ($M = 51.64$, $SD = 10.06$) than that at Q-T1 ($M = 36.74$, $SD = 7.48$) and Q-T3 ($M = 38.84$, $SD = 8.87$) (All $ps < 0.001$), and there was a significant difference between state anxiety level at Q-T1 and Q-T3 ($p = 0.042$). Interestingly, results also showed a significant TIME × CONDITON interaction effect, F (2, 136) = 5.48, $p = 0.005$, $\eta_p^2 = 0.075$. Subsequent simple-effect analysis revealed that the state anxiety scores of the two groups were similar on the baseline psychological measurement and just after TSST. After the tDCS procedure, the R+L− group ($M = 35.77$, $SD = 7.22$) reported significantly lower levels of state anxiety compared to the sham group ($M = 41.91$, $SD = 9.39$) ($p = 0.003$). To further examine the recovery effect of tDCS on state anxiety response, we conducted ANCOVA for state anxiety scores with tDCS condition as a between-group factor, and the scores before and after stress as covariates. Results showed a significant group difference, F (1, 66) = 15.00, $p < 0.001$, $\eta_p^2 = 0.185$, indicating that real stimulation promoted the recovery of

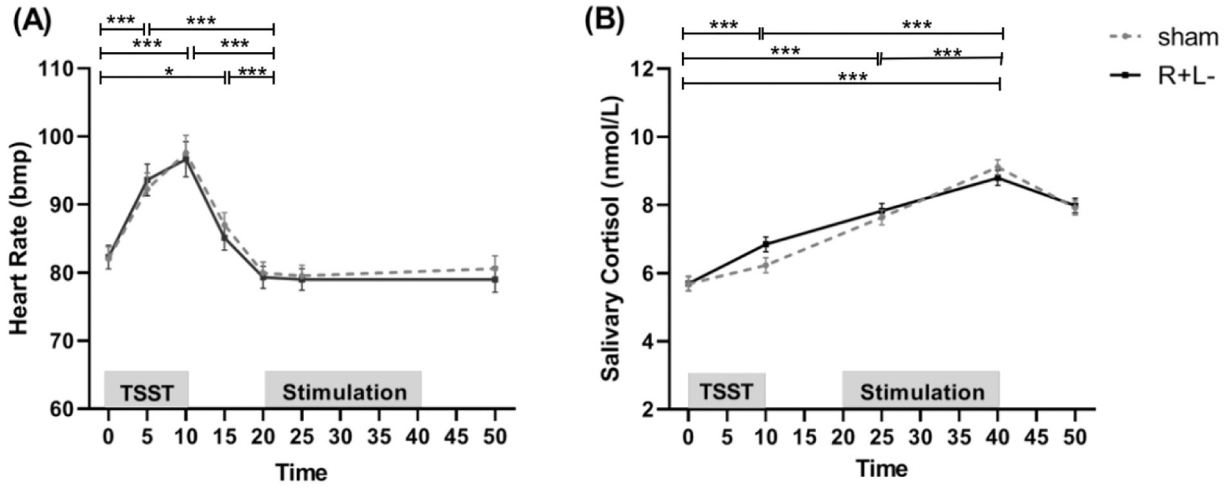

Fig. 3. Physiological stress parameters. Data are as mean ± standard errors. (A) The mean salivary cortisol levels following stress and tDCS manipulation. (B) The salivary cortisol levels following stress and tDCS manipulation. *$p < 0.05$, ***$p < 0.001$.

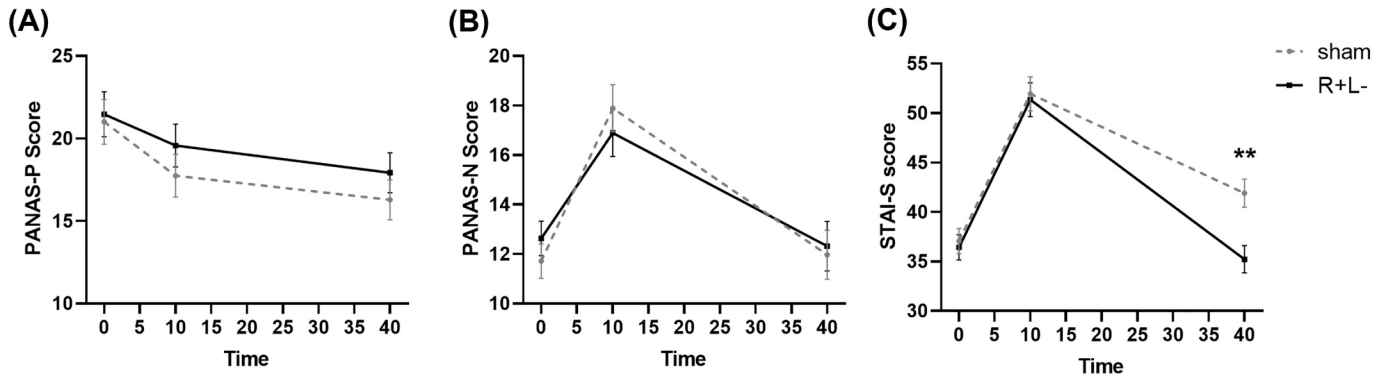

Fig. 4. Subjective stress parameters. (A) the mean positive affect scores in R+L− and sham groups; (B) the mean negative affect scores in R+L− and sham groups. (C) the mean state anxiety scores in R+L− and sham groups. Data are as mean ± standard errors, $^{**}p < 0.01$.

state anxiety response faster (see Fig. 4C).

3.4. Creativity tasks

To examine the effect of tDCS on creativity performance under stress, a mixed-design ANOVA with one repeated-measures factor (TIME: Pre-test vs. Post-test) and one between-group factor (CONDITION: R+L− vs. Sham) was conducted on AUT scores and RAT accuracy.

Concerning AUT fluency, we found a significant interaction effect of TIME × CONDITON, F (1, 68) = 12.42, p = 0.001, η_p^2 = 0.154. Following simple-effect revealed that the post-test score (M = 22.49, SD = 8.55) in the sham group was significantly lower than the pre-test score (M = 25.71, SD = 8.33) (p = 0.001). Moreover, R+L− group's post-test score (M = 23.83, SD = 8.28) was higher than the pre-test score (M = 22.49, SD = 8.30), although it didn't reach a significant level (p = 0.148) (see Fig. 5B). No significant main effect of TIME or CONDITION were observed [TIME: F (1, 68) = 0.25, p = 0.620, η_p^2 = 0.004; CONDITION: F (1, 68) = 2.11, p = 0.151, η_p^2 = 0.030]. In order to further examine

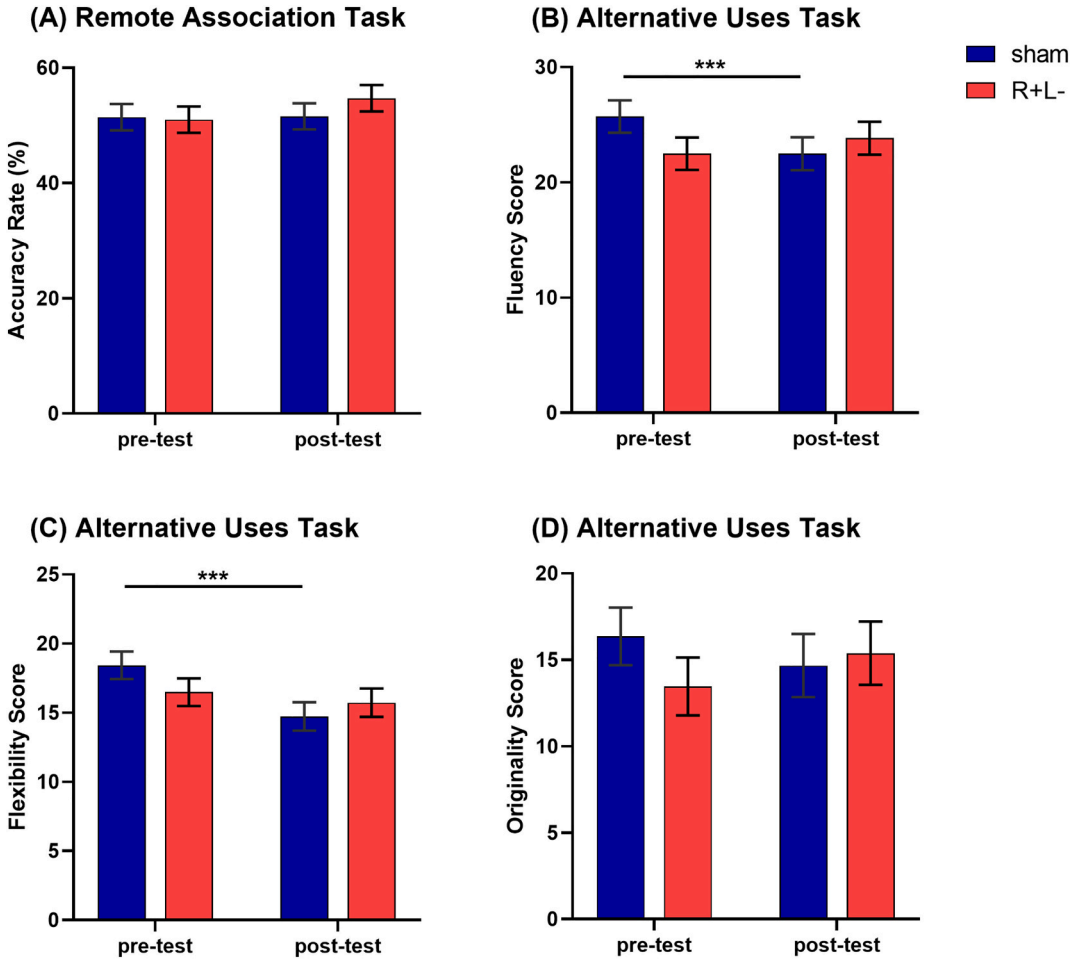

Fig. 5. Mean scores of creativity tasks prior to and after the stress induction task across two tDCS conditions. (A) Mean accuracy rate of Remote Association Task (B) Flexibility scores of Alternative Uses Task; (C) Fluency scores of Alternative Uses Task; (D) Originality scores of Remote Association Task. Data are as mean ± standard errors, $^{***}p < 0.001$.

whether there was a difference in the change of fluency scores between two tDCS conditions, an independent sample *t*-test was conducted on the change of fluency between pre-test and post-test (post-test score minus pretest score). Results showed a significant difference between the groups, revealing that the decrease value in the sham group ($M = -3.23$, $SD = 4.87$) was significantly greater than that in the R+L− group ($M = 1.34$, $SD = 5.93$) [t (68) $= -3.45$, $p = 0.001$].

Concerning the flexibility of AUT, results also revealed a significant main effect of TIME was observed, F (1, 68) $= 29.76$, $p < 0.001$, $\eta_p^2 = 0.304$, with the post-test score being lower compared to the pre-test score. A significant interaction effect of TIME × CONDITON was also reported, F (1, 68) $= 12.98$, $p = 0.001$, $\eta_p^2 = 0.160$. The following simple-effect analysis revealed that post-test scores ($M = 14.73$, $SD = 6.46$) in sham group was significantly lower than pre-test scores ($M = 18.43$, $SD = 6.09$) ($p < 0.001$). Likewise, R+L− group's post-test scores ($M = 15.73$, $SD = 5.62$) were lower than pre-test scores ($M = 16.49$, $SD = 5.71$), but it didn't reach a significant level ($p = 0.194$) (see Fig. 5C). No significant main effect of CONDITION were observed, F (1, 68) $= 0.12$, $p = 0.732$, $\eta_p^2 = 0.002$. An independent sample *t*-test was used on the change of flexibility between the pre-test and post-test to examine a difference of change between two tDCS conditions. Results showed a significant difference between the groups, indicating that the decrease value in the sham group ($M = -3.70$, $SD = 3.16$) was significantly greater than that in the R+L− group ($M = -0.76$, $SD = 3.66$) [t (68) $= -3.60$, $p = 0.001$].

Concerning the originality of AUT, a significant interaction effect of TIME × CONDITON was also reported, F (1, 68) $= 5.57$, $p = 0.021$, $\eta_p^2 = 0.076$. The following simple-effect analysis revealed that post-test score ($M = 14.67$, $SD = 10.96$) in the sham group was lower than pre-test score ($M = 16.36$, $SD = 10.47$) ($p = 0.124$). There was a marginally significant difference between pre-test score ($M = 13.46$, $SD = 9.26$) and post-test score ($M = 15.39$, $SD = 10.65$) in R+L− group ($p = 0.079$) (see Fig. 5D). No significant main effect of TIME or CONDITION were observed [TIME: F (1, 68) $= 0.22$, $p = 0.644$, $\eta_p^2 = 0.003$; CONDITION: F (1, 68) $= 0.03$, $p = 0.875$, $\eta_p^2 = 0.000$]. An independent sample *t*-test was further conducted on the change of originality between the pre-test and post-test to examine a difference of change between two tDCS conditions. Results showed a significant difference between the groups, indicating that the decrease value in the sham group ($M = -1.69$, $SD = 5.93$) was significantly greater than that in the R+L− group ($M = 2.17$, $SD = 6.95$) [t (68) $= -2.50$, $p = 0.015$].

Concerning the accuracy rate of the RAT, as shown in Fig. 5A, no significant differences were found on the main effect of tDCS CONDITON [F (1, 68) $= 0.31$, $p = 0.578$, $\eta_p^2 = 0.005$], the main effect of TIME [F (1, 68) $= 0.82$, $p = 0.367$, $\eta_p^2 = 0.012$], and the interaction effect of TIME × CONDITON [F (1, 68) $= 0.70$, $p = 0.404$, $\eta_p^2 = 0.010$].

3.5. Mediation model test

As described above, there was no significant decrease in the divergent thinking task in R+L− group, and the state anxiety after real stimulation was significantly lower than that of the control group. Thus, we further verified the mediated role of state anxiety on the relationship between tDCS manipulation and creativity performance under stress by using PROCESS v3.0 add-on to SPSS 22.0 (Hayes, 2017). The 95% confidence interval (C.I.) was examined by 5000 bootstrap samples. The mediated model was tested with the tDCS condition as the independent variables, the changes of state anxiety scores after TSST (score at Q-T3 minus score at Q-T2) as the mediating variable, and the changes of creative task performance (fluency, flexibility, and originality of the AUT) between pre-test and post-test (post-test score minus pretest score) as dependent variables.

The correlations between all variables are presented in Table 2. Results showed that higher flexibility ($r = -0.362$, $p = 0.002$) of AUT was significantly associated with lower state anxiety symptoms. Furthermore, the state anxiety mediated the effect of tDCS on the flexibility component of AUT, taking up 60.73% of the total effect, while the 95% CI was [0.0321–1.3797]. As depicted in Fig. 6, the condition of real stimulation facilitated the recovery of anxious state, which in turn, was related to the lower impairment of creativity performance.

Table 2
Pearson correlation coefficients between tDCS condition, creativity performance, and state anxiety.

Variables	1	2	3	4	5
1. tDCS condition	–	−0.316**	0.393**	0.400**	0.290*
2. State anxiety		–	−0.235	−0.362**	−0.152
3. AUT-fluency			–	0.817**	0.580**
4. AUT-flexibility				–	0.659**
5. AUT-originality					–

* $p < 0.05$.
** $p < 0.01$.

4. Discussion

The present study aimed to investigate the effect of online frontal tDCS on creativity performance under acute stress and its possible underlying mechanism. Results showed that active tDCS over bilateral dlPFC facilitates the recovery of state anxiety after stress compared to sham. The same tDCS protocol also eliminated stress-induced creativity impairment in AUT. Moreover, the effect of tDCS on creativity is partial mediated by recovery of the state anxiety. To our knowledge, the present study made the first attempt to explore the effect of tDCS on modulating stress-induced creativity change, and further revealed the possible mechanism from the perspective of recovery of the stress response.

4.1. The effect of acute stress on creativity

In accordance with most of our prior researches (Duan et al., 2020a; Duan et al., 2019; Wang et al., 2019), the present results demonstrated that acute stress disrupted the performance of creativity, and this impact appeared to be greater for the divergent thinking (AUT) than the convergent thinking (RAT). Divergent thinking required more exploration in the problem space to generate more than one solution. Therefore, it benefits from the modulation of cognitive flexibility. In contrast, convergent thinking aims to find one analytical solution based on analytical thinking. Therefore, it involves more cognitive persistence and focus (Zhang et al., 2020). One possible explanation of our results was that acute stress increases dopamine levels at PFC, which may enhance cognitive persistence and thus facilitate more systematic ideas in RAT (Boot et al., 2017). Correspondingly, the improvement of cognitive persistence means the lack of cognitive flexibility, resulting in the inflexibility of individual attention, focusing on the irrelevant stimuli, which hinders the generation of original solutions in AUT (Cools and D'Esposito, 2011).

We also reported that tDCS over bilateral DLPFC modulated creativity performance in the stressed state. These results complemented and extended recent studies revealing that tDCS prevented stress-induced cognitive function impairment (Bogdanov and Schwabe, 2016;

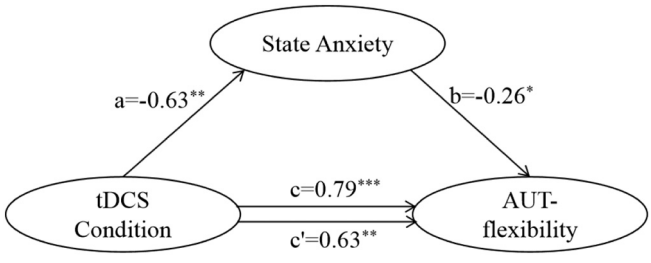

Fig. 6. Diagram of mediator model. *$p < 0.05$, **$p < 0.01$.

Brunelin and Fecteau, 2020). More importantly, our study also provided indirect evidence to prove that DLPFC was a critical brain region regulating the influence of acute stress on creativity.

4.2. Modulation of tDCS on creativity under acute stress

A series of prior tDCS investigations have shown the positive relationship between the tDCS modulation over two prefrontal hemispheres and creativity performance in the non-stressed state (Lucchiari et al., 2018), which may be one potential explanation for the relative boost of creativity under stress observed in this study. In agreement with the balance hypothesis suggesting right-hemispheric superiority in creativity (Chi and Snyder, 2011), we found that right DLPFC activation combined with left DLPFC inhibition eliminated creativity impairment caused by stress. The activation of the right PFC has been observed in different types of creativity tests (Howard-Jones et al., 2005; Takeuchi et al., 2012). The more gray matter volume on the right PFC, the higher the creativity level (Takeuchi et al., 2010). The left PFC has been implicated in cognitive control including working memory, goal-direction behavior, and cognitive inhibition (Beaty et al., 2019; Kleinmintz et al., 2018). The deactivation of this area can reduce inhibitory control, and further have a 'releasing' effect benefiting creativity. For example, Chrysikou et al. (2013) has proved the enhancement of creativity by the cathodal stimulation across DLPFC. Patients with the lesions of left PFC also found the same effect (Shamay-Tsoory et al., 2011). Nevertheless, this advantage was usually observed only in divergent thinking (AUT), but not convergent thinking (RAT). We increased the activity of the right PFC while decreasing the activity of the left PFC found similar results, in line with the other tDCS studies (Hertenstein et al., 2019; Khalil et al., 2020; Mayseless and Shamay-Tsoory, 2015). One possible explanation is that RAT is a more complex verbal problem-solving task than AUT, which requires keeping three words and their associated associations at the same time, so that its working memory demands are higher (Zhang et al., 2020). The inhibition of left PFC cannot meet those demands and maintain the convergent focus on a single answer. Therefore, it is reliable to activate left DLPFC or other left PFC regions for implementing persistence and facilitating convergent thinking (Cerruti and Schlaug, 2009; Zmigrod et al., 2015).

Besides the facilitation of cognitive processing of creativity, anxiety relief may be another underlying mechanism of the effect of tDCS on creativity under acute stress. Anxiety induced by stress is an avoidance-related motivational state, which narrows the scope of conceptual attention and enhances analytical thinking, but impairs creative generation (Derryberry and Reed, 1998). These behavioral results are closely associated with the greater activation of the left hemisphere than the right hemisphere. Therefore, shifting the activation balance from the left to the right can release the attentional limitation caused by avoidance motivation and thus bolster creativity (Derryberry and Reed, 1998; Friedman and Förster, 2005).

4.3. Modulation of tDCS on state anxiety induced by acute stress

One interesting finding is that R+L− group exhibited lower state anxiety scores after active stimulation, indicating faster recovery from negative emotion. It may be attributed to the fact that the increased neural excitability in the right DLPFC could effectively regulate negative emotional experiences. The prior study addressed that the anxiety states generally showed weaker activation of top-down cognitive control, which may be caused by the reduction of lateral PFC activity (Bishop et al., 2004). Increasing DLPFC activation could down-regulate negative emotions through a top-down modulation of the activity of the amygdala (Eippert et al., 2007; Ochsner et al., 2004), in which the right DLPFC played a major role (Feeser et al., 2014; Ochsner et al., 2012; Pripfl and Lamm, 2015).

However, the findings were inconsistent with the prior studies using left DLPFC as the main target stimulation region to decrease negative emotion perception in emotional processing (Fregni et al., 2020; Pena-Gomez et al., 2011). Nevertheless, an increasing number of studies in healthy volunteers revealed that activation on left DLPFC cannot improve a negative emotional state (Garcia et al., 2020; Clarke et al., 2020b; Plazier et al., 2012), and may even lead to increase anxiety reactivity (Clarke et al., 2020a). Recent meta-analytic studies also reported that there was no discernible difference in the efficacy of brain stimulation over different PFC hemispheres on the stress-induced emotional responses (Smits et al., 2020). Therefore, it is important to further explore the interaction of various target PFC regions during emotional processing for improving the reliability of the tDCS intervention, and by extension, optimizing the clinical treatment for psychiatric illness.

4.4. Limitations and future directions

There are several limitations in the present study. To begin with, the regulation of catecholamine concentrations in the brain by tDCS cannot be overlooked. Using human biomarker measurement techniques such as pupillometry and eye blink rate, future research may look into the mediating effect of catecholamine changes between tDCS and stress-induced creativity impairment. Secondly, creative cognition is related to brain networks interaction (Beaty et al., 2016). It's possible that tDCS stimulates brain regions other than the DLPFC because of its poor spatial resolution (Keeser et al., 2011). Therefore, future work is expected to integrate with neuroimaging techniques for deeply revealing the role of the brain network connection and other brain areas in the effect of tDCS on creativity under acute stress. Thirdly, in order to exclude the response variability in tDCS and stress caused by sex differences, all the participants in the experiment were females. Therefore, the results obtained in this study need to be further verified in male participants. A fourth limitation is the loss of experimenter blindness, which may create a bias against the performance of different groups of participants. Future research should adopt a more strict double-blinding design to repeat the results. Finally, the directionality of brain stimulation on creativity and acute stress may be modulated by the potential individual baseline, such as personalities, genes, trait anxiety, etc. (Dennison et al., 2019; Xiang et al., 2021). Based on the inverted U-shaped curve, tDCS may hinder the creativity performance of the individuals with a high baseline level by exceeding the moderate activation level, while tDCS may promote the creativity performance of the individuals with a low baseline level by reaching the moderate activation level. The regulatory effect of the individual baseline between tDCS and creativity under acute stress should be further explored by expanding the sample size.

5. Conclusion

In conclusion, our results revealed that one single session of tDCS over the bilateral DLPFC prevented stress-induced creativity deficits, and anxiety relief may be one potential mechanism of this effect. Our findings present indirect causal evidence the down-regulation of PFC under acute stress is a key neurophysiological process resulting in creativity deficit. At the same time, based on the existing literature, our study makes a significant step forward. On the one hand, it provides a theoretical foundation for the intervention of stress-related diseases like anxiety and depression, and more effective clinical advice for the selection of stimulation targets and stimulation parameters of tDCS. On the other hand, the current research also emphasizes that the intervention of frontal area cortical activity can effectively prevent the decreased creativity under acute stress, which may bring some inspiration for the cultivation of creative talents and the improvement of organizational innovation ability.

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