The HPA and SAM axis mediate the impairment of creativity under stress

Xiaoyu Guo[1], Yifan Wang[1], Yuecui Kan[1], Meilin Wu[1], Linden Ball[2], and HAIJUN DUAN[1]

[1]Shaanxi Normal University
[2]University of Central Lancashire

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Abstract

With the ever-changing social environment, individual creativity is facing a severe challenge induced by stress. However, little is known about the physiological mechanisms by which acute stress affects creative cognitive processing. The current study explored the effects of neuroendocrine response on creativity under stress and its underlying cognitive flexibility mechanisms. The Enzyme-Linked Immuno Sorbent Assay was used to assess salivary cortisol, which acted as a marker of stress-induced activation of the hypothalamic-pituitary-adrenal (HPA) axis. Eye blink rate (EBR) and pupil diameter were measured as respective indicators of dopamine and noradrenaline released by activation of the sympathetic-adrenal medullary (SAM) axis. The Wisconsin Card Task (WCST) measured cognitive flexibility, while the Alternative Uses Task (AUT) and the Remote Association Task (RAT) measured separately divergent and convergent thinking in creativity. Results showed higher cortisol increments following acute stress induction in the stress group compared to the control group. Ocular results showed that the stress manipulation significantly increased EBR and pupil diameter compared to controls, reflecting increased SAM activity. Further analysis revealed that stress-released cortisol impaired the originality component of the AUT by increasing perspective errors of the WCST. Serial mediation analyses showed that both EBR and pupil diameter were also associated with increased perspective errors leading to poor originality on the AUT. These findings confirm that physiological arousal under stress can impair divergent thinking through the regulation of different neuroendocrine pathways, in which the deterioration of flexible switching plays an important mediating role.

The HPA and SAM axis mediate the impairment of creativity under stress

Guo Xiaoyu[a,1], Wang Yifan[a,1], Kan Yuecui[b], Wu Meilin[a], Linden J. Ball[c,*], Duan Haijun[a,*]

[a] Key Laboratory of Modern Teaching Technology, Ministry of Education, Shaanxi Normal University, Xi'an, China

[b] School of Psychology, Shaanxi Normal University, Xi'an, China

[c] School of Psychology & Computer Science, University of Central Lancashire, Preston, UK

Corresponding to: Duan Haijun, Key Laboratory of Modern Teaching Technology, Ministry of Education, Shaanxi Normal University, 199 South Chang'an Road, Xi'an 710062, China; Linden J. Ball, School of Psychology University of Central Lancashire Preston Lancashire PR2 8BX, UK

Email address: duanhj@126.com; LBall@uclan.ac.uk

Tel: 86-18966707988; +44 (0)1772 893421

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[1] Equal Contribution

* Corresponding Author

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Abstract: With the ever-changing social environment, individual creativity is facing a severe challenge induced by stress. However, little is known about the physiological mechanisms by which acute stress affects creative cognitive processing. The current study explored the effects of neuroendocrine response on creativity under stress and its underlying cognitive flexibility mechanisms. The Enzyme-Linked Immuno Sorbent Assay was used to assess salivary cortisol, which acted as a marker of stress-induced activation of the hypothalamic-pituitary-adrenal (HPA) axis. Eye blink rate (EBR) and pupil diameter were measured as respective indicators of dopamine and noradrenaline released by activation of the sympathetic-adrenal medullary (SAM) axis. The Wisconsin Card Task (WCST) measured cognitive flexibility, while the Alternative Uses Task (AUT) and the Remote Association Task (RAT) measured separately divergent and convergent thinking in creativity. Results showed higher cortisol increments following acute stress induction in the stress group compared to the control group. Ocular results showed that the stress manipulation significantly increased EBR and pupil diameter compared to controls, reflecting increased SAM activity. Further analysis revealed that stress-released cortisol impaired the originality component of the AUT by increasing perspective errors of the WCST. Serial mediation analyses showed that both EBR and pupil diameter were also associated with increased perspective errors leading to poor originality on the AUT. These findings confirm that physiological arousal under stress can impair divergent thinking through the regulation of different neuroendocrine pathways, in which the deterioration of flexible switching plays an important mediating role.

Keywords: acute stress, hormones, neuroendocrine, cognitive flexibility, creativity**1. Introduction**

Creativity, as a unique gift of human beings, has become the core competence and key talent in the 21st century (Ananiadou & Claro, 2009; Heilman, 2016). Creativity is defined as the ability to generate novel output in an appropriately useful manner (Sternberg & Lubart, 1996). Nowadays, with the advent of the VUCA (Volatile, Uncertain, Complex, and Ambiguous) era, stress has become a regular part of life and work that people have to face. Creative problem-solving under stress seems to be the norm for organizations and individuals. In recent years, researchers have made some explorations into the relationship between stress and creativity (Alexander et al., 2007; Chrousos, 2009; Ulrich-Lai & Herman, 2009; Villarejo et al., 2012). However, the physiological mechanisms by which stress affects creativity processes remain incompletely revealed.

Upregulated activity of the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic-adrenal-medullary (SAM) axis under acute stress is a central effect of such stress (Chrousos, 2009; Ulrich-Lai & Herman, 2009). Under stressful situations, the SAM pathway immediately stimulates the amygdala in the central nervous system and rapidly activates the adrenal medulla via the hypothalamus. This causes catecholamines (i.e., dopamine and norepinephrine) to be released, which induces sympathetic excitement in the peripheral nervous system (Arnsten, 2009). It is manifested by an increase in heart rate, blood pressure, skin electrical levels, and salivary alpha-amylase (sAA) concentration, which speeds metabolic breakdown and saves energy for the body's response to stressful stimuli (Villarejo et al., 2012). At the same time, activation of the HPA axis results in the release of corticotrophin-releasing hormone (CRH) and vasopressin from the hypothalamus. These neuropeptides stimulate the release of the adrenocorticotropic hormone (ACTH) in the anterior pituitary (Pariante & Lightman, 2008). ACTH activates the adrenal cortex to release glucocorticoid hormones, which help the body restore homeostasis by mobilizing the body's readily available resources (Allen et al., 2014). Therefore, catecholamines and glucocorticoids are valid biochemical indicators to assess the stress response (Fogelman & Canli, 2018; Walker et al, 2017). They can influence creative activities that require divergent thinking, attention and memory by directly or indirectly regulating the central nervous

system (Sanchez-Ruiz et al, 2015; Shansky & Lipps, 2013).

Evidence has demonstrated that the cortisol generated by HPA axis activation is critical to behavioral and neuroendocrinological adaptations to acute stress (Yeh et al., 2015). However, to our knowledge, no research has examined the influence of stress-induced cortisol levels on creative processing. Cortisol has the ability to cross the blood-brain barrier and enter the brain, where it binds to glucocorticoid receptors in the hippocampus, prefrontal cortex (PFC) and amygdala (Lovallo & Buchanan, 2016). These brain regions play important roles in executive function and are associated with fundamental executive processes such as working memory, flexibility, cognitive function, and the processing of novelty (Blackford et al., 2010; D'Esposito & Postle, 2015; Plessow et al., 2011). Accordingly, the relationship between stress-induced cortisol and creativity may be established through some cerebral mechanisms and mediated by executive functions.

Cognitive flexibility, as a stress-sensitive cognitive function, has a close relationship with creativity (Chakravarty, 2010; Heilman, 2016). Plessow (2011) investigated the effects of acute psychosocial stress on dynamic control adjustments, using the Trier Social Stress Test (TSST) to induce stress responses and a selective attention task to measure individual cognitive flexibility. The results revealed that stressed participants showed tonically increased goal shielding at the expense of decreased cognitive flexibility. Moreover, the stress effects on cognitive functions were not presented immediately after the stress experience but developed gradually over time, paralleling the time course of the HPA stress response. In the present research, we predicted that the altered cognitive flexibility resulting from HPA axis activation is an essential mediation mechanism for how stress affects creativity. In the reported study, salivary cortisol was used as an indicator of HPA under stress.

Dopamine (DA) and norepinephrine (NE) are SAM axis indicators closely associated with creativity. Increased central dopaminergic activity under stress leads to a high release of DA (Abercrombie et al., 1989; Neri et al., 1995; Thierry et al., 1976). Multiple dopaminergic pathways could affect excitatory signaling within the frontal-hippocampal network, involving a range of cognitive functions involving creative processing (Dave et al., 2021). We predicted that DA release may play an important role in the effect of stress on creativity. Neuropharmacological research has shown that DA may improve creative performance. For example, striatal DA seems to be associated with specific dimensions of divergent thinking performance, especially with the categorical diversity (flexibility) of ideas (Dodds et al., 2008). Moreover, novel stimuli have been shown directly to influence DA release in the brain, which promotes cognitive flexibility and facilitates the onset of the epiphany phase of creative tasks (Wingo et al., 2016; Zhang et al., 2020). However, some studies have indicated that DA secretion can impair creativity. High-intensity stress leads to excessive DA release in the prefrontal lobe, showing attentional rigidity and inflexibility (Cools & D'Esposito, 2011), which may be detrimental to creative performance (Boot et al., 2017).

We assumed that stress can not only affect individual creativity directly by altering brain activity and regulating the DA levels, but that it can also affect individual creative performance by altering cognitive flexibility. Direct measurements of DA are mostly performed in animal experiments via blood measurements, which are used less for humans in the laboratory. Spontaneous eye blink rate (EBR) has been verified by numerous findings to be a reliable biomarker of DA in the central nervous system. According to Kaminer et al. (2011), DA inhibits the trigeminal complex via effects on the nucleus raphe magnus, increasing spontaneous blinking. Moreover, clinical observations in patients with DA-related dysfunctions, such as schizophrenics. Indicate that they have both elevated EBRs (Freed, 1980) and elevated striatal DA uptake. Furthermore, pharmacological research in nonhuman primates has demonstrated that the dopaminergic agonists and antagonists, respectively, increase and reduce EBRs (Kleven & Koek, 1996). Decades of research have shown that spontaneous EBR is a well-established clinical marker (Shukla, 1985; Jongkees & Colzato, 2016) thought to index striatal DA production, with higher EBR predicting higher DA function. In the present research, spontaneous EBR was employed as a reliable method of assessing DA function.

Norepinephrine (NE) is one of the brain's most important neurotransmitters and has a critical role in modulating the brain's arousal (Heilman, 2016). The locus coeruleus-norepinephrine (LC-NE) system releases

large amounts of NE under stressful conditions. Like DA, NE plays an important role in how acute stress affects creative processing. NE increases the brain's signal-to-noise-ratio, which enhances attention and reduces intrinsic associative activity (Hasselmo et al, 1997). In such a state, cognitive flexibility is reduced and creative performance is impaired (Beversdorf et al., 2002). Thus, acute stress states could lead to elevated NE levels so as ultimately to affect creativity by altering cognitive flexibility. However, the laboratory measurement of NE is still a methodological challenge. In this regard, pupil diameter as an ocular measure could provide insight into neuromodulatory activity, which is strongly connected with the enhanced activity of noradrenergic neurons in the locus coeruleus (de Rooij et al., 2011; Murphy et al., 2011). A strong correlation between baseline pupil diameter and tonic locus coeruleus firing rate has been observed in monkeys during task performance involving 90 min target detection (Rajkowski et al., 1993). Human experimentation has also demonstrated that the pupil diameter at rest is relatively large when individuals are hyperaroused (Unsworth et al., 2019). Moreover, pupil dilation indicates higher noradrenergic activity and is associated with enhanced arousal and alertness (Knapen et al., 2016; Pajkossy et al., 2018). In the current study, pupil diameter was used as an indirect indicator of noradrenergic activity.

To sum up, the present study aimed to elucidate the cognitive flexibility mechanism by which acute stress affects creativity from a neuroendocrine perspective by using enzyme-linked immunosorbent assay (ELISA) and eye-tracking techniques. The arousal of the HPA axis was indicated by salivary cortisol concentrations. Eye blink rate and pupil diameter were used as indicators of DA and NE activity, reflecting the activation of the SAM axis under acute stress conditions. The stress condition was manipulated with the Montreal Imaging Stress Task (MIST), and the corresponding psychological and physiological indexes were collected to confirm that the acute stress induction was successful. Measures reflecting the activation of these biological stress systems alongside the behavioral measures were included in serial mediation models in order to illuminate the neuroendocrine pathways contributing to creative degradation under stress. We expected that impaired creativity under stress results from degraded cognitive flexibility mediated by HPA and SAM activation.

2. Methods

2.1. Participants

A total of 63 healthy, undergraduates with a mean age of 19.46 years (SD = 1.82, female = 36) were recruited for the present study. All participants were prescreened using the State-Trait Anxiety Inventory (T-AI score >45) and the Beck Depression Inventory (BDI-II score > 15), as well as for abnormal BMI (>28 or <18), regular intake of medicine, use of hormonal contraceptives (current; female participants only), consumption of alcohol or coffee, and existence of chronic or acute illnesses. Two participants were excluded from the final analysis: one quit during the stress induction procedure and another was withdrawn because of computer failure. The final sample comprised 60 individuals (female = 31,M_{age}=19.57, SD = 1.84) who met the inclusion criteria and completed all the tests.

To determine sample size, a statistical power analysis was conducted based on a medium effect size (Cohen's f = 0.25), which suggested that 54 participants were required in order to detect the hypothesized effect at α= 0.05 and β = 0.95. Participants provided written informed consent and all procedures were conducted following the Declaration of Helsinki. Prior to the experiment, participants were asked not to eat, exercise, or consume caffeine for 2 hours. Randomly chosen groups of participants were allocated to either the stress condition (n = 31) or the control condition (n = 32).

The study pursued the principles of the Declaration of Helsinki (World Medical Association, 2013) and was approved by the Academic Committee of the Ministry of Education of the Key Laboratory of Modern Teaching Technology, Shaanxi Normal University in China. Prior to the experiment, all participants were required to provide written informed consent. And each participant received payment as a token of appreciation for their participation in the study.

2.2. Procedure

Two visits to the laboratory were scheduled for participants, with a two-week gap between each session.

At the first visit, the participants finished a demographics questionnaire, the Beck Depression Inventory-II (BDI-II), and the State-Trait Anxiety Inventory (STAI-T). Baseline measurements of cognitive flexibility were also administered using the Wisconsin Card Sorting Test (WCST) to keep any group differences from influencing experimental results.

To reduce cortisol and EBR changes, the second laboratory visit was arranged between 14:00 and 18:00 (Barbato et al., 2000). Upon arrival, participants measured spontaneous EBR and pupil diameter for 3 min during the baseline state (Ocular 1). They then completed the Remote Association Task (RAT) and Alternative Uses Task (AUT) tests before the acute stress induction. Following the completion of the Montreal Imaging Stress Tasks (MIST) or the control task, Ocular 2 was assessed while the participant was continuously thinking about either an angry or a calm memory. Subsequently, participants performed the post-test WCST and the post-test AUT.

Twenty min after the end of AUT, Ocular 3 was administered for 3 min. After Ocular 3, the participant started to complete the post-test RAT. Spirit-10 wireless telemetry biofeedback instruments (Mind Media, B.V. Netherlands) were used to measure heart rate throughout the experiment. Electrodes were applied to the chest for an electrocardiogram (ECG), and BioTrace+ was used to evaluate the ECG data at a sample rate of 2048 Hz. The spontaneous EBR and pupil diameter were measured during the MIST task and Ocular tasks. The saliva samples were taken at the time points of T, and the STAI-S and PANAS were evaluated at the time points of S (see Fig. 1).

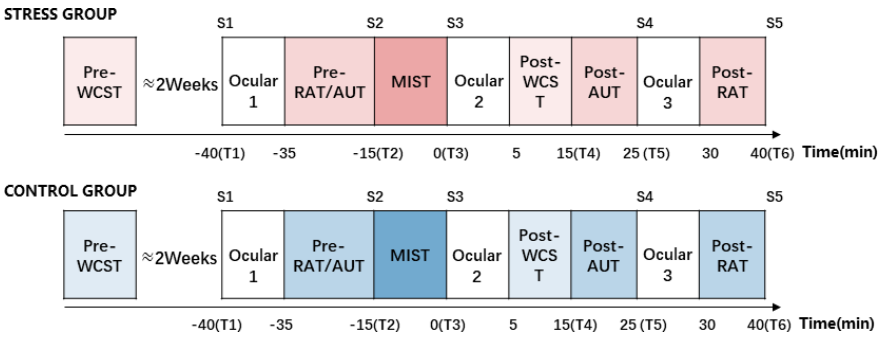

Fig. 1. Schematic illustration of the experiment design and procedure.

2.3. Acute stress induction

To induce acute stress, the Montreal Imaging Stress Task (MIST) was employed. This task is a validated paradigm to increase negative affect and levels of cortisol (Dedovic et al., 2009). Participants were asked to complete the mental arithmetic task shown on the screen. This task consists of two sessions: a training session with 15 trials and an experimental session with 75 trials. This study involved the random selection of math problems of varying difficulty: the easiest problems only had three one-digit integers and used addition or subtraction only (e.g., 2+9-7); the medium difficulty problems had three integers, two of which were two-digit numbers, and used multiplication (e.g., 3*12-29); the hardest problems had four integers, three of which were two-digit numbers, and used multiplication and division operations (e.g., 14*16/4-52).

In the stress condition, the difficulty and time limit of the mental arithmetic tasks exceeded the participant's psychological ability, and the negative feedback from the computer further increased their stress. A participant's reaction time and correct response rate were continuously recorded throughout the experiment. If a participant answered a series of three consecutive problems correctly, the time limit reduced to 10% less than the participant's average response time; conversely, the time limit increased by 10%. Every time a participant completed the arithmetic test, the appropriate feedback ("correct" or "incorrect"), response time and cumulative correct response rate were presented. If no response was submitted within the allotted time, the feedback "timeout" was shown. At the same time, participants received negative feedback from

the investigator on their performance compared to a fictitious user who exhibited high-performing behavior. In the control condition, participants were instructed to complete the task as quickly and accurately as possible, but the investigator also makes it clear that this was a control condition, therefore performance was not being evaluated. Similarly difficult mental arithmetic tasks were completed by the participants in the control condition, but there were no time restrictions, aural cues, or disapproving comments from the software or investigator.

In both the stress and control conditions, a 500 ms fixation cross appeared on the screen at the beginning of each trial and was followed by a mental arithmetic test. After the participant entered the answer or reached the time limit, the corresponding feedback appeared on the screen for 2000 ms. The pupil diameter was continuously sampled at 1000 Hz during the experimental phase of the MIST/control task.

2.4. Ocular measurement

Eye data were measured using an Eyelink 1000 Plus (SR Research, Mississauga, ON, Canada). An elliptical fitting pupil detection technique was used to record data from the left eye at 1000 Hz. The lighting in the laboratory was kept consistent throughout the experiment to control ambient brightness. Visual stimuli were shown at a screen resolution of 1440 x 900 pixels (60 Hz refresh rate) at a distance of 60 cm from the eyes to the LCD monitor. A 9-point calibration and validation procedure was used to calibrate gaze position and pupil measurement. Spontaneous EBR and pupil diameter were measured during the MIST task and Ocular tasks

2.4.1. Eye blink rate

As spontaneous EBR remains steady during the day but increases in the evening (at about 20:30, see Barbato et al., 2000), no EBR was recorded after 18:00. Participants were also urged not to smoke before their arrival. Throughout the experiment, the spontaneous EBR was measured three times for each participant. At the start of each Ocular task, a nine-point eye-movement calibration was performed, which was followed by a light gray screen with a central fixation cross for 3 min. Participants were sat comfortably alone in the room and asked not to gaze, but just to look casually at the fixation cross in a relaxed state. The individual EBR (blinks/min) was calculated by dividing the total number of eye blinks during the 3 min measurement interval by the duration (in minutes). Eye blinks were marked by the Eyelink online event parser using a proprietary algorithm based on several consecutive missing pupil samples, which was independently demonstrated to identify blinks accurately (Ehinger et al., 2019). The blinks that were outside of the normal range of blink duration were removed to assure data quality in blink measurements (less than 80 ms or more than 900 ms, as reported by Ehinger et al., 2019).

2.4.2. Pupillometry

Pupil diameter was measured during the MIST task and Ocular tasks. When using video-based eye trackers, pupil diameter distorts as a consequence of the position of the eyes. Therefore, this study excluded the data that fell outside of a two-degree visual angle square that was centered on the fixation point as well as the samples that fell during blink and saccade events. In the MIST task, for each trial and each participant, the baseline pupil diameter was determined as the mean pupil diameter measured 300 ms before the mental arithmetic test onset. To account for individual variability in pupil size, the baseline pupil size was deducted from the mean pupil diameter during each experiment (Langer et al., 2022). The area under the curve concerning increase (AUCi, see Kuchinke et al., 2011) following the arithmetic test onset was determined as a measure of the total pupillary increase in response to the presentation of the mental arithmetic (Langer et al., 2020). Pupil dilations were averaged across each trial. In Ocular tasks, the individual pupil diameter was calculated by averaging during the 3 min measurement period.

2.5. Physiological measures

Prior research has introduced that salivary cortisol is an effective measure of hypothalamic-pituitary-adrenal (HPA) axis activity (Arafah et al., 2007; Dorn et al., 2007). In this study, Salivettes® (Sarstedt 51.1534.500, Germany) were used to collect saliva samples, and the salivary cortisol in these samples was assessed by

enzyme-linked immunosorbent assay (Zhuocai, China). Upon arrival at the laboratory, participants were instructed to rinse their mouth with clear water and discard the first saliva sample. The experimenter then inserted a cotton swab from the sampling device into the participant's mouth using tweezers, instructing he/she to hold it in the mouth for one minute before spitting it back into the sampling device. All saliva samples were stored in a freezer at -20 until assay, with intra- and inter-assay variability both below 10%.

The heart rate data in this study were measured using the Spirit-10 wireless telemetry biofeedback system. This system was connected to a computer in a control room, which amplified the collected physiological signals and displayed them on the computer. Electrocardiogram (ECG) electrodes were placed on the participant's chest, and ECG data were analyzed using BioTrace+ (Mind Media, BV Netherlands) at a sampling rate of 2048 Hz. Heart rate recordings were time-matched with salivary cortisol sampling, with each sample collected over a period of 5 minutes.

2.6. Assessment instruments

2.6.1. Alternative Uses Task (AUT)

The Alternative Uses Task (AUT) is a popular test for assessing divergent thinking. Participants were asked to give verbal reports on as many non-conventional uses as possible for three everyday objects within two minutes. Two lists of objects were used for each experimental session (pre-test: newspaper, bucket, and umbrella; post-test: paper clip, can and shoes). Each AUT's score was evaluated in terms of fluency, flexibility, and originality (Guilford, 1950). The fluency score was determined as the total number of responses; the flexibility score as the number of response categories; and the originality score as the frequency of occurrence of a certain response across participants. According to Radel et al. (2015), a response frequency percentage of less than 1% received 2 points, a frequency of 1% to 5% received 1 point, and a frequency of more than 5% received 0 points. Two experienced coders of creativity tasks examined the responses of the participants and their inter-rater reliability was satisfactory (ICC: 0.993 for fluency, 0.859 for flexibility, 0.880 for originality).

2.6.2. Remote Association Task (RAT)

An adapted Chinese version of the Remote Association Task (RAT) was implemented to assess convergent thinking (Duan et al., 2020). During the task, participants were presented with three Chinese characters and were asked to generate a Chinese character that could combine with each of the shown three characters to produce a reasonable word. For example, one of the RAT questions was: "board, hole, color", and the answer is: "black" which can be combined into "blackboard, black hole, and black color". Each question was randomly presented for a maximum of 20 s. Once the participant figured out the answer, he or she could immediately press the keyboard (space key) to report it. The pre-test and post-test contained 20 different item groups with solution rates ranging from 40% to 65%. To prevent interference at the linguistic level, all of the words were chosen from the Modern Chinese Frequency Dictionary (1989). Previous research has found that the revised RAT has adequate internal consistency.

2.6.3. Wisconsin Card Sorting Test (WCST)

Cognitive flexibility was assessed using a computerized version of WCST-64 (Kongs et al., 1993). Each trial required participants to sort test cards according to one of three possible categories: number (1-4), shape (triangle, circle, cross, star), or color (red, blue, yellow, green). Every time participants made a choice, feedback was displayed on the screen in the form of "correct" or "wrong". Since the sorting rules were not be instructed, participants needed to discover the rules themselves through the feedback provided. Whenever participants correctly sorted a series of ten cards, the rule changed. Each participant completed 64 trials and finished 1 to 6 sorting sequences depending on their performance. Although the WCST-64 provides several measures as indicators of cognitive flexibility, the primary outcome of interest within the present study was perseverative errors, which indicate a continued application of a card sorting rule that is no longer appropriate instead of shifting to the use of a new rule (Miyake et al., 2000). Prior studies have noted that perseverative errors on the WCST are the outcome most affected by acute stress, consistent with earlier studies showing that perseverative errors point to a lack of cognitive flexibility (Kalia et al., 2018; Nyhus &

Barcelo, 2009).

3. Results

3.1. Biochemical stress parameters

A mixed-design ANOVA with Time (T1 to T6 time points) as a within-participant factor and Group (control group vs. stress group) as a between-participant factor was conducted on the collected salivary cortisol. Results (see Figure 2) showed significant main effects of Time, F (5, 305) = 6.07, $p < .001$,$\eta_p^2 = 0.09$, and of Group, F (1, 61) = 26.06, $p< .001$, $\eta_p^2 = 0.30$. A significant interaction effect of Time x Group was also observed, F (5, 305) = 9.92,$p < .001$, $\eta_p^2 = 0.14$. Simple effects analyses (Bonferroni corrected) found that salivary cortisol levels in the stress group were significantly higher than that in the control group at T3 (p = .002), T4 (p = .001), T5 ($p< .001$), and T6 ($p < .001$). Salivary cortisol concentrations taken after the MIST in the stress group were also significantly higher than those at baseline, supporting the notion that stress was successfully induced.

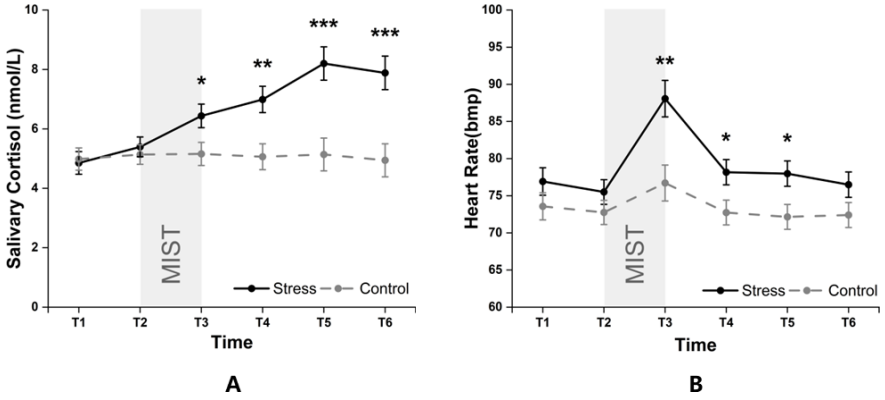

Fig. 2. Biochemical stress parameters. Data are mean ± standard errors. (A) The mean salivary cortisol in the stress and control groups. (B) The heart rate in the stress and control groups. $^{*}p< .05$, $^{***}p < .001$.

For heart rate, a 2 × 6 mixed-measures ANOVA was conducted with one within-group factor Time (T1 to T6 time points) and one between-group factor Group (control group vs. stress group). The results revealed that the main effect of Time was significant, F (5, 305) = 15.86,$p < .001$, $\eta_p^2 = 0.21$. The main effect of Group was also significant, F (1, 61) = 6.85, $p = .011$,$\eta_p^2 = 0.10$. In addition, the interaction of Group × Time was significant, F (5, 305) = 15.95, $p < .001$,$\eta_p^2 = 0.21$ (see Figure 2). Across the groups, simple effects analyses (Bonferroni corrected) revealed that the stressed participants showed significantly higher heart rates after completing the MIST session than the control participants at T3 ($p< .001$), T4 (p = .027), and T5 (p = .020).

3.2. Psychological stress parameters

The effects of the stress induction on STAI-S score, negative affect scores and positive affect scores were analyzed by mixed-measures ANOVAs, with the factors Time (S1 to S5 time points) and Group (control group vs. stress group).

For the STAI-S scores (see Figure 3A), the results showed significant main effects of Group, F (1, 61) = 13.179, $p < .001$, $\eta_p^2 = 0.18$, and Time, F (4, 244) = 10.34,$p < .001$, $\eta_p^2 = 0.15$ (see Figure 3A). The interaction of Time × Group was also significant, F (4, 244) = 6.83, $p < .001$, $\eta_p^2 = 0.10$. Simple effect tests (Bonferroni corrected) showed that the control groups had significantly lower STAI-S scores than the stress group at the time points of S3 ($p < .001$), S4 (p = .010), and S5 ($p < .001$).

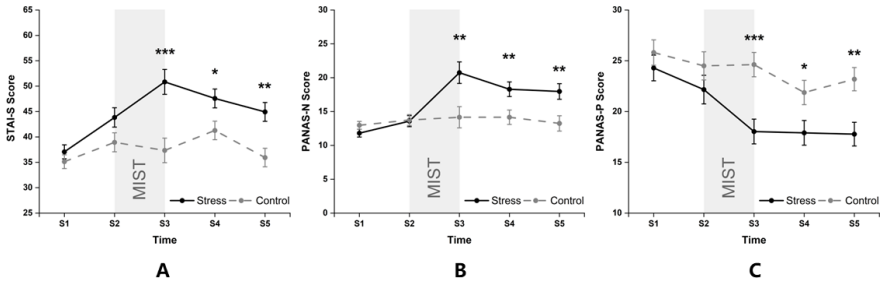

Fig. 3. Psychological stress parameters. (A) The mean state anxiety scores in the stress and control groups. (B) The mean negative affect scores in the stress and control groups. (C) The mean positive affect scores in the stress and control groups.$^{*}p < .05,^{***}p < .001$.

Q1

A mixed-measures ANOVA for the negative affect scores (see Figure 3B), showed that there were significant main effects of Group, F (1, 61) = 6.05, p = .017, η_p^2 = 0.09, and Time,F (4, 244) = 13.07, $p < .001$, η_p^2 = 0.18. The interaction of Time and Group was also significant,F (4, 244) =8.59, $p < .001$, η_p^2 = 0.12. Comparing the stress group to the control group using simple effects analyses (Bonferroni corrected), revealed that the MIST task significantly increased negative affect at the time points of S3 (p = .005), S4 (p = .008), and S5 (p = .004). A mixed-measures ANOVA for the positive affect scores (see Figure 3C), showed significant main effects of Time, F (4, 244) = 21.85,$p < .001$, η_p^2 = 0.26, and Group,F (1, 61) = 4.73, p = .034, η_p^2 = 0.07. The interaction of Time and Group was also significant, F (4, 244) = 4.81, p = .003, η_p^2= 0.07. Simple effect tests (Bonferroni corrected) revealed that positive affect in the stress group was significantly lower than that in the control group at S3 (p = .001), S4 (p = .049), and S5 (p = .005).

3. 3. Eye blink rate

A mixed-design ANOVA with Time (Ocular 1, Ocular 2, and Ocular 3) as a within-participant factor and Group (stress group vs. control group) as a between-participant factor was conducted on the recorded EBR (see Figure 4A). No main effects of Time, F (2, 122) = 0.62, p = .538, η_p^2 = 0.01, or Group, F (1, 61) = 2.56,p = .115, η_p^2 = 0.04, emerged as significant. There was, however, a significant interaction effect of Time × Group,F (2, 122) =3.41, p = .036, η_p^2 = 0.05. Subsequent simple effect analysis (Bonferroni corrected) further revealed that the EBR in the stress group was significantly higher than that in the control group at the time point of Ocular 2 (p = .032).

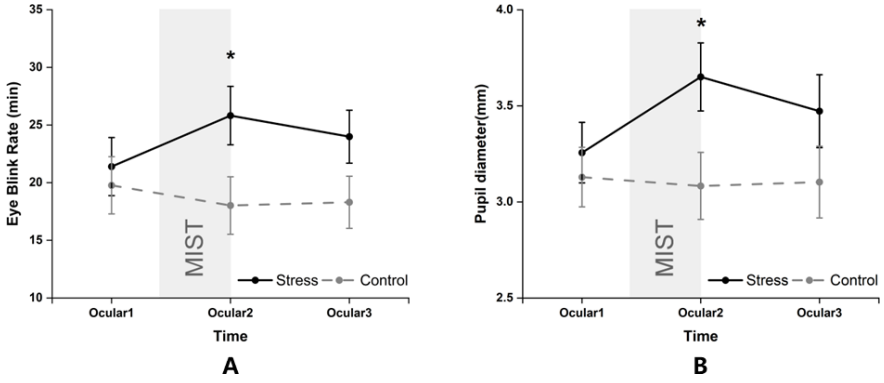

Fig. 4. Ocular measurement results. (A) the mean eye blink rate in the stress and control groups. (B) The mean pupil diameter in the stress and control groups. $^{*}p < 0.05,^{***}p < .001$.

3. 4. Pupil diameter

The effect of stress induction on the average pupil diameter (see Figure 4B) was analyzed using a mixed-measures ANOVA with the factors Time (Ocular 1, Ocular 2, and Ocular 3) and Group (control group vs. stress group). No significant main effects of Time, F (2, 122) = 2.82,p = .007, η_p^2 = 0.04, or Group, F (1, 61) = 2.36, p = .130, η_p^2 = 0.04 were found. However, the interaction effect of Time × Group was significant, F (2, 122) = 4.52, p = 0.016, η_p^2 = 0.07. Simple effects analyses (Bonferroni corrected) indicated that the pupil diameter in the stress group was significantly larger than that in the control group at the time point of Ocular 2 (p = .026).

To determine whether the pupil diameter changed during acute stress induction, an independent sample t-test was performed on the AUCi of pupil dilation. Significant differences in pupil dilation between the groups were observed, t (61) = 3.07, p = .003. The result revealed that calculating mental arithmetic tasks led to a significant increase in pupil dilation, confirming that pupil diameter varies with stressful arousal.

3. 5. Creativity tasks

Mixed-design ANOVAs with Time (pre-test vs. post-test) as a within-participant factor and Group (control group vs. stress group) as a between-participant factor, were conducted on AUT scores (fluency, flexibility, and originality) and RAT scores (accuracy rate). Data are depicted in Figure 5A.

For AUT fluency, no significant main effects of Time, F (1, 61) =0.92, p = .342, η_p^2 = 0.02, or Group, F (1, 61) = 0.91, p = .343, η_p^2 = 0.02 were observed, but there was a significant Time × Group interaction, F (1, 61) = 6.50, p = .013, η_p^2 = 0.10. Simple effects analyses (Bonferroni corrected) showed that the post-test score in the control group was significantly higher than the pre-test score (p= .015).

For AUT flexibility, there no significant main effects of Time,F (1, 61) = 0.235, p = .630, η_p^2 = 0.004, or Group, F (1, 61) = 0.711, p = .403, η_p^2 = 0.01. In addition, no significant Time × Group interaction was observed,F (1, 61) = 3.61, p = .062, η_p^2 = 0.06.

For AUT originality, a significant main effect of Group was observed,F (1, 61) = 9.568, p = .003, η_p^2 = 0.14, although the main effect of Time was not significant, F (1, 61) = 0.001, p = .972, η_p^2 < 0.001. However, a significant Time × Group interaction occurred, F (1, 61) = 21.66,p < .001, η_p^2 = 0.26. The simple effects tests (Bonferroni corrected) revealed that the post-test score in the stress group was significantly lower than pre-test score (p = .002).

For RAT accuracy rate (see Figure 5B), no significant main effect of Time, F (1, 61) =1.01, p = .320, η_p^2 = 0.02, or Group, F (1, 61) = 0.74, p = .394, η_p^2 = 0.01, were observed. In addition, the interaction effect of Time × Group was not significant, F (1, 61) = 1.35, p = .249,η_p^2 = 0.02.

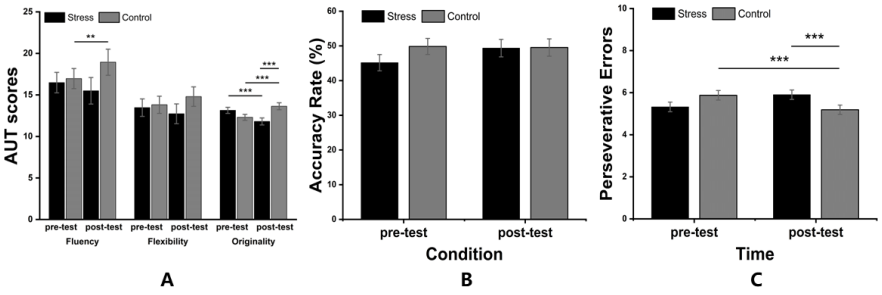

Fig. 5. Behavioral performance. (A) The mean AUT scores in the stress and control groups. (B) The mean RAT accuracy rate in the stress and control groups. (C) The mean perseverative errors in the WCST in the stress and control groups. $^{*}p < .05$,$^{***}p < .001$.

3. 6. Cognitive Flexibility Performance

Mixed-measures ANOVAs with the within-subject factor of Time (pre-test and post-test) and the between-subject factor of Group (control group vs. stress group) were computed for the interference effect on WCST perseverative errors. No significant main effects emerged for Time, F (1, 61) = 0.06, p = .816, $\eta_p^2 < 0.01$ or Group, F (1, 61) = 0.13, p = .716, $\eta_p^2 < 0.01$. However, a significant Time × Group interaction was observed, F (1, 61) = 7.71, p = .007, $\eta_p^2 = 0.11$ (see Figure 5C). Simple effects analyses (Bonferroni corrected) revealed that the post-test score in the control group was significantly lower than the pre-test score (p = .036).

3. 7. Serial mediation model test

To explore the function of HPA and SAM activation in stress-related alterations in creativity and cognitive performance, three serial mediation models were performed with PROCESS v4.0. The 95% bias-corrected confidence intervals (CIs) were generated employing 5000 bootstrapping samples. The aim of the first model was to provide evidence for the mediation of stress-induced HPA activation on creativity. The second and third models were performed to verify the role of the SAM axis in stress-influenced creativity. Before the serial mediation model test, bivariate Pearson correlation analyses were conducted on the physiological, cognitive, and behavioral outcomes (see Table 1).

Table 1 Pearson correlation coefficients between group condition, cortisol results, ocular results, cognitive flexibility, and creativity performance.

Variables	1	2	3	4	5	6	7	8
1. Group condition	-	-.461***	-.306*	-.315*	-.335***	.310*	.236	.507**
2. AUCIi of cortisol		1	.451***	.545**	.380**	-.374**	-.416**	-.256*
3. AUCi of EBR			1	.504**	.380**	-.211	-.309*	-.312*
4. AUCi of pupil diameter				1	.411**	-.287*	-.336**	-.270*
5. WCST perseverative errors					1	-.346**	-.382**	-.545**
6. AUT- fluency						1	.840**	.457**
7. AUT- flexibility							1	.448**
8. AUT- originality								1

The first serial mediation analysis was used to investigate the role of HPA activation in stress-related changes in creativity and cognitive performance. This model was tested with Group (stress group or control group) as the independent variable, the cortisol AUCi (T1 to T6) as the first mediating variable, the changes in cognitive flexibility performance (the post-WCST score minus pre-WCST score) as the second mediating variable and the variations of creative task performance (changes in fluency, flexibility, and originality of the AUT) between pre-test and post-test (post-test score minus pretest score) as dependent variables. The results supported a serial mediation model (see Figure 6): stress condition was associated with higher HPA activation, which reduced cognitive flexibility, leading to worse creativity performance (parameter $a_1 \times d \times b_2$ = 0.296, [0.029, 0.897]).

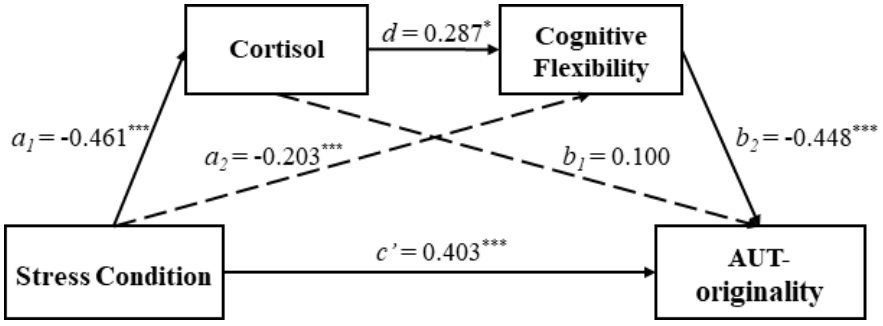

Fig. 6. Serial mediation model 1. Serial mediation analysis of cortisol levels and cognitive flexibility performance on the association between stress and creative performance. The dotted line represents the non-significant path coefficients. $^{*}p < .05$, $^{***}p < .001$.

The second serial mediation model examined whether stress-related dopaminergic system activation could influence creativity by mediating cognitive flexibility. Hence, the serial mediation model was tested with Group (stress or control) as the independent variables, EBR AUCi (Ocular 1 to 3) as the first mediating variable, the change in perseverative errors (the post-WCST score minus pre-WCST score) as the second mediating variable and the variations of creative task performance (changes in fluency, flexibility, and originality of the AUT) as dependent variables. The analysis indicated that the indirect effect of cognitive flexibility was significant (parameter $a_2 \times b_2 = 0.492$, [0.014, 1.116]), suggesting mediation by cognitive flexibility (see Figure 7). A significant effect of stress on creativity via dopaminergic system activation and cognitive flexibility was also discovered (parameter $a_1 \times d \times b_2 = 0.191$, [0.048, 0.526]), consistent with a serial mediation through DA activity followed by cognitive flexibility.

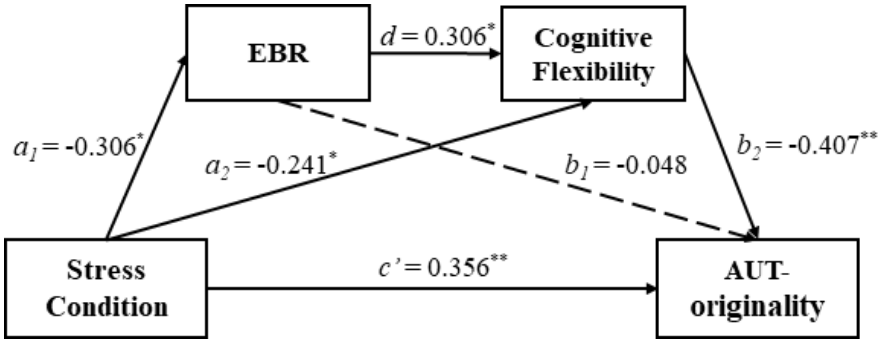

Fig. 7. Serial mediation model 2. Serial mediation analysis of dopamine levels and cognitive flexibility performance on the association between stress and creative performance. The dotted line represents the non-significant path coefficients. $^{*}p < .05$, $^{***}p < .001$.

The third serial mediation model examined whether the noradrenergic system activation can influence individual creativity by mediating cognitive flexibility under acute stress. Group (stress or control) was entered as an independent variable, the AUCi of pupil diameter (Ocular 1 to 3) and the cognitive flexibility performance changes (the post-WCST score minus pre-WCST score) were entered as potential parallel mediators, and the variations of creative task performance (changes in fluency, flexibility, and originality of the AUT) between pre-test and post-test (post-test score minus pretest score) were entered as dependent variables. The results only showed that the stress condition enhanced the LC-NE activity (pupil dilation AUCi), which was related to decreased cognitive flexibility (the changes of WCST performance) leading to worse creative performance (originality of AUT). As we expected, the results support a serial mediation: stress was associated with NE activation, which reduced cognitive flexibility, leading to worse creative performance. Indeed, the bias-corrected bootstrap confidence interval for the indirect stress condition – NE activity – cognitive flexibility – individual creativity (parameter $a_1 \times d \times b_2 = 0.230$) was above zero (0.034, 0.738).

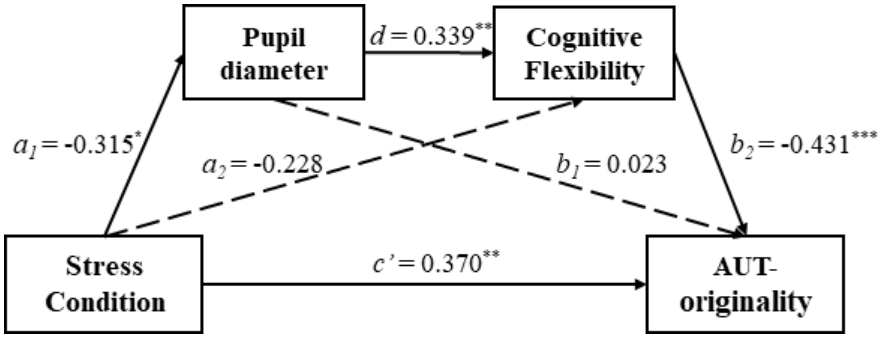

Fig. 8. Serial mediation model 3. Serial mediation analysis of noradrenaline levels and cognitive flexibility performance on the association between stress and creative performance. The dotted line represents the non-significant path coefficients. $^{*}p < .05, ^{***}p < .001$.

4. Discussion

The current study aimed to determine the underlying physiological processes and cognitive mechanisms of stress-related impairment of creativity from a neuroendocrine perspective. We explored the effects of HPA axis and SAM axis activation on creativity under stress through an experimental study using reliable biomarkers. Importantly, the mediating role of cognitive flexibility in the physiological response associated with creative processing has been corroborated. In Model 1, we assessed concurrent effects of stress on HPA activation (measured through salivary cortisol), cognitive flexibility, and creativity. In Model 2 and Model 3, the concurrent effects of stress on cognitive flexibility, creativity and SAM activation were investigated. SAM activation was responded to by the activity of dopamine (measured through eye blink rate) and noradrenaline (measured through pupil diameter). Results demonstrated that stress facilitated HPA and SAM activation, which impaired cognitive flexibility, leading to reduced creative performance. Through testing the serial mediation models in this study, a more comprehensive framework was constructed based on the changes in hormones and neurotransmitters under stress.

4.1. Stress-induced modulation of HPA activation on creativity

The current study investigated the role of the HPA axis in the process of acute stress affecting creative performance. Various studies have indicated that activation of the HPA axis under stress results in the release of the glucocorticoid hormone cortisol (Dedovic et al., 2009; Munck et al., 1984). This evidence is consistent with our findings that the salivary cortisol levels of participants increased after the MIST task. The results of the serial mediation analysis showed that the impairment of creativity under stress was mediated by the increase of cortisol concentration and degraded cognitive flexibility.

High cortisol levels have been shown to prevent the coordination between the salience network's subregions and the central executive network (Hu et al., 2019; Zhang et al, 2019). The salience network is involved in filtering relevant interoceptive and emotional information (Dosenbach et al., 2007; Menon, 2011). The central executive network is engaged in the manipulation of working memory and decision-making (Fox et al., 2006; Knudsen, 2007; Menon & Uddin, 2010). Stress-induced cortisol would enhance the salience monitoring function of the salience network, but the central executive network cannot respond effectively to the control demands launched by the salience network (Hu et al., 2019; Zhang et al., 2022), which is associated with enhanced emotional responses and decreased executive functions (Laredo et al., 2015; Plessow et al., 2011). As is well established, cognitive flexibility – one of the executive functions – is a critical indicator of creativity (Boot et al., 2017). Creative outputs result from two distinct cognitive processes, flexibility and persistence (Nijstad et al., 2010), according to the Dual Pathway to Creativity Model. We predicted that the stress-related HPA axis would therefore adjust the balance between flexibility and persistence to optimize behavior in a changing environment. By this means, stress-induced cortisol elevation enhances perseverative errors, impairs cognitive flexibility and leads to worse creative performance, in line with our results.

Accordingly, cortisol and negative emotions may indirectly influence each other via brain functions. Further studies can employ a cognitive neuroscientific approach to investigate the relationships between different types of negative emotions and cortisol during various types of creative task performance to develop a comprehensive account of the underlying brain mechanisms that are at play.

4.2. Stress-induced modulation of SAM activation on creativity

The present study also examined the role of SAM activation in how acute stress affects creativity performance. The activation of the dopaminergic system and central noradrenergic system are the markers of SAM activation (Allen et al., 2014; Bremner et al., 1996). The mediation of SAM activation was examined via two serial modulation models, with Model 2 focusing on DA and Model 3 on NE. In such a way, we investigated how stress impairs creativity by affecting SAM activation and cognitive flexibility.

As a reliable measure of assessing DA function, we found the EBR of participants significantly increased after acute stress induction, thereby implying increased DA release. The serial mediation model indicated that stress conditions enhanced EBR, which was related to decreased cognitive flexibility and ultimately resulted in worse creative performance. The enhancement in DA levels facilitates or impairs creativity and is influenced by the concurrent effects of the increased striatal and prefrontal DA (Boot et al., 2017). The striatal DA of the nigrostriatal pathway is associated with flexible processing, while prefrontal DA and the integrity of the mesocortical dopaminergic pathway are associated with persistent processing (Boot et al., 2017). According to a recent model, the fronto-striatal network biases towards flexibility when striatal DA exceeds prefrontal DA, and the fronto-striatal network biases towards persistence when prefrontal DA exceeds striatal DA (Dodds et al., 2008). When dopaminergic activity in either the PFC or striatum is too high or low, the balance between flexibility and stability is disturbed. This is indicated by the inverted U-shaped relationship between DA levels and flexibility in divergent thinking (Chermahini & Hommel, 2010). An excessive release of DA under stress is associated with attenuated striatal activity (Kellendonk et al., 2006), which leads to the enhancement of perseverative errors and a decrease in creativity, consistent with our findings.

As we expected, the ocular results showed that participants in the stress group had significantly higher pupil dilation during acute stress induction, reflecting higher NE levels. The results also indicated that the NE levels of the participants significantly increased after the MIST task. The serial mediation model showed that the stress condition was associated with higher pupil dilation, which reduced cognitive flexibility, leading to inferior creative performance. Previous evidence suggests that NE improves the transmission of dominant neural signals while inhibiting noise to enhance vigilance and alter cognitive processing under threatening conditions (Hermans et al., 2014). According to Adaptive Gain Theory, the activity of the LC neurons can be distinguished into two modes: phasic and tonic (Usher et al., 1999). The activity of the LC neurons shifts from tonic to phasic to optimize behavior in a changing environment, which is modulated by the NE level (Guedj et al., 2017; Usher et al., 1999). This account is also consistent with findings that the effects of stress on cognitive flexibility are adjusted by antagonists of β-adrenergic receptors (Alexander et al., 2007). Evidence has shown that only a narrow range of 1–3 Hz tonic firing of LC-NE neurons would facilitate phasic firing of the LC-NE neurons, leading to optimal performance (Howells et al., 2012). This is consistent with the inverted U-shaped curve relationship between stress and creativity. When the stress-induced tonic activity of LC neurons is too high, then an individual's attention span becomes narrow, which is detrimental to flexible switching and impairs creative thinking, otherwise the opposite is the case. By such means, stress-related NE elevation would impair cognitive flexibility, and thus reduce creativity, which is in line with our data.

4.3. Limitations and future directions

The limitations of the current research should also be addressed. First, the co-activation patterns of the HPA and SAM axis cannot be overlooked. Future research should examine SAM-HPA co-activation throughout both the reactivity and recovery phases of the stress response after acute stress exposure. Second, the difference in stress-induced arousal may also be affected by individual differences such as chronic stress level,

cortisol stress response pattern and creativity level (Heilman et al, 2003; Knauft et al., 2021). Individual differences exist the way that the effects of stress on creativity are modulated through different neurotransmitters and hormonal baselines (Chermahini & Hommel, 2012; Howells et al., 2012). Thus, further exploration is needed to incorporate individual differences in participants to better understand the regulating effect of individual baselines between stress-induced arousal and creativity. Third, although our sample size was limited, our statistical analysis yielded appropriate statistical power. Nonetheless, future studies might investigate the stress effect on creative processing by expanding the sample size.

5. Conclusion

The present findings indicate that acute stress may impair creativity via concomitant HPA and SAM activation that modulates cognitive flexibility. This was demonstrated by the enhanced level of cortisol, dopamine and norepinephrine as well as the decrease in cognitive flexibility under stress. Following these results, we conclude that stress-induced arousal may restrict flexible switching and divergent thinking, mediated by distinct neurocognitive mechanisms. To our knowledge, the current research is the first attempt to uncover the potential cognitive and neurophysiological mechanisms underlying creative processing under acute stress. Future research would benefit from integrating multimodal cross-cutting techniques to form a multi-level model of stress-influenced creativity at the "biochemical-cognitive-behavioral-brain" level and to construct a systematic and comprehensive explanatory framework.

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