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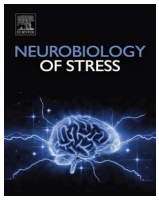

Stress-induced cortisol response predicts empathy for pain: The role of task-based connectivity between the insula and sensorimotor cortex during acute stress

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ABSTRACT

Empathy for pain is a key driver of prosocial behavior and is influenced by acute psychosocial stress. However, the role of task-based brain connectivity during acute stress have been neglected. Hence, we aimed to explore the relationship between the magnitude of cortisol response to acute stress and empathy for pain, as well as the neural connectivity mechanisms involved. In this study, 80 healthy participants (37 women and 43 men) were exposed to the acute psychosocial stress paradigm (ScanSTRESS) and were scanned by functional magnetic resonance imaging. Saliva samples were collected to measure the magnitude of cortisol stress response. Subsequently, the participants took part in a pain-video task to assess their empathy for pain. Six participants were excluded because of physical discomfort or excessive head movement in all runs during the task-dependent fMRI scan. Therefore, 33 women and 41 men were included in data analysis. We found that empathy for pain was negatively correlated with the magnitude of cortisol stress response (r = -0.268, p = 0.018) and that the task-based connectivity between the salience network and sensorimotor network, including its sub-network and sub-region, was negatively correlated with the magnitude of cortisol stress response, and positively correlated with empathy for pain. Furthermore, task-based connectivity between the insula and the paracentral lobule mediates the effect of the stress-induced cortisol response on empathy for pain (indirect effect = -0.0152, 95% CI = [-0.036, -0.001], p = 0.036). Our research suggests that empathy is not only correlated with stress-induced glucocorticoids but also tied to the stress-induced reduced communication between basic and higher brain regions.

1. Introduction

Acute stress is ubiquitous in modern society and is known to significantly influence human perception, emotional cognition, and social behavior (Hermans et al., 2014; Starcke and Brand, 2012). Researchers have taken a keen interest in the implications of acute stress on social functioning. Among these, empathy for pain has gradually become a focus, perhaps because it plays an important role in individual survival and social interactions. On the one hand, effective perception of others' pain helps individuals avoid threats and realize self-protection, which is of great significance for self-protection and survival (Frith and Frith, 2006). On the other hand, empathy for pain enables humans to feel the pain of others, thus promoting their prosocial behaviors, and improving better interpersonal relationships (Christov-Moore and Iacoboni, 2016; Decety et al., 2016; Spinrad and Gal, 2018).

Several previous studies have reported the effects of acute stress on empathy (Wingenfeld et al., 2018; Wolf et al., 2015) and empathy for pain (Buruck et al., 2014; Gonzalez-Liencres et al., 2016; Tomova et al., 2017). A recent study has investigated the relationship between stress-induced glucocorticoids and empathy (Nitschke et al., 2022). However, cortisol negatively regulates brain activity through negative feedback of glucocorticoids (Joëls et al., 2008; Karst et al., 2004), and the brain is a crucial organ influencing empathy for pain (Decety, 2011). Therefore, it is interesting to further investigate the role of brain activity during stress, which plays a key role in the relationship between stress-induced cortisol response and empathy for pain, from a

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neuroendocrine perspective.

The hypothalamic-pituitary-adrenal (HPA) axis is a neuroendocrine stress response system (Chrousos, 2009). During the acute stress response, the HPA axis enables the body to cope with environmental challenges by releasing its end product, cortisol, which releases stored energy (McEwen and Gianaros, 2011). Therefore, the HPA axis reactivity to acute stress is frequently assessed by repeated sampling of salivary cortisol levels. Numerous studies have reported that high cortisol responses are linked to adverse psychological and behavioral problems, such as social withdrawal, anxiety, apathy, and aggressive behavior (Granger et al., 1994, 1996; McBurnett et al., 1991; Perry et al., 2022; Schechter et al., 2012; Steeger et al., 2017). These adverse psychological and behavioral problems are usually accompanied by reduced empathy for pain because impaired empathy for pain is an important hallmark of these maladaptive mental and behavioral problems (Findlay et al., 2006; Repetti et al., 2022; Serbic et al., 2020; Zoratto et al., 2018). For example, previous studies have found a negative correlation between stress intensity and empathy through subjective reporting, which could provide evidence for our inference to a certain extent (Chlap and Brown, 2022; Keumhee and Kwon, 2017; Skogevall et al., 2022). In summary, we hypothesized that the magnitude of cortisol stress response to acute stress would be negatively correlated with empathy for pain (Hypothesis 1).

Previous studies have shown that empathy for pain depends on a neural representation system mapping the mental states of others to the same brain regions that represent the same states of the self (Decety, 2011; Keysers and Gazzola, 2009). Specifically, empathy for pain includes two dimensions, as well as pain experience (Bufalari et al., 2007; Bufalari and Ionta, 2013). One is the affective motivation dimension, representing emotional experiences, such as unpleasant emotions (Pasquini et al., 2020; Shi et al., 2020); its representative brain regions are the anterior insula (INS) and anterior cingulate gyrus (ACC). These areas work together to help people perceive and understand other people's pain sensations (Botvinick et al., 2005; Jankowiak-Siuda and Zajkowski, 2013; Singer et al., 2006). The second is the perceptual dimension related to the physical somatosensory properties of the painful stimuli (Decety et al., 2008; Levy et al., 2019; Singer and Frith, 2005); its representative brain region is the sensorimotor cortex, including the primary and secondary somatosensory cortices (Aziz-Zadeh et al., 2012; Betti and Aglioti, 2016; Riecansky and Lamm, 2019). The two dimensions are coordinated rather than independent (Betti et al., 2009; Schurz et al., 2021). The abovementioned regions belong to salience network (Pruessner et al., 2003) and sensorimotor networks (SMN). Previous studies have found that the salience network (SN) is responsible for selecting and coordinating information on both internal and external receptors (Morrison et al., 2007; Saarela et al., 2007), and may be associated with a proper motion response (e.g., escape or helping behavior) when it contacts the motor cortex (Betti and Aglioti, 2016). Interestingly, some evidence suggests that both the SN and SMN are affected by acute stress. For example, a neuroimaging study found that the task-based connectivity of both the SMN and SN was reduced in individuals who experienced acute stress (Zhang et al., 2015). Another study found reduced task-based connectivity between the SN (especially the INS) and other networks during acute stress; reduced connectivity in low-level perceptual networks, including the SMN, is associated with attentional bias and adverse emotional perception after experiencing acute stress (Shang et al., 2014). Based on the above findings, we hypothesized an interesting assumption that the task-based connectivity between the SN and SMN might be reduced during acute stress, which further is related to reduced empathy for pain (Hypothesis 2).

Recent studies have subdivided networks into more precise subnetworks based on their intrinsic functional connections. Therefore, building upon our understanding of the SMN and SN networks, we aimed to further explore more specific brain regions that play a central role in the magnitude of cortisol stress response and empathy for pain, from large networks to small networks and small brain regions. This approach gradually helped us to explore and understand the neural mechanisms involved at three different brain scales. According to the sub-network proposed by Yeo et al. (2011), the SMN includes two sub-networks: the SMNa and SMNb. The SMNa mainly consists of the paracentral lobule (PCL), anterior central gyrus (PreCG), and posterior central gyrus (ProCG), and is related to the individual's somatosensory and motor functions (Spasojevic et al., 2013). The SMNb mainly comprises the temporal lobe and is related to auditory and long-term emotional memory (Dolan et al., 2000). The SMNa is more closely related to the perceptual dimension of empathy for pain and is more susceptible during acute stress. The SN could be divided into two sub-networks: the SNa and SNb. The SNa primarily comprises the INS, whereas the SNb primarily comprises the ACC. Both brain regions are closely related to the affective motivation dimension of empathy for pain; however, previous studies have reported a closer relationship between INS and acute stress (Carr et al., 2003; Schulze et al., 2013). Therefore, we can reasonably speculate that the reduced task-based connectivity between the SNa and SMNa is involved in the mechanisms by which a high acute cortisol stress response is related to reduced empathy for pain (Hypothesis 3).

The purpose of this study was to explore the relationship between the magnitude of cortisol stress response and empathy for pain and the role of task-based brain connectivity during acute stress. Here, the stress response was induced using the ScanSTRESS paradigm, which includes two stress-inducing conditions (the feeling of losing control and being threatened). Videos depicting other people's faces receiving painful stimuli were used to induce empathy for pain (Xu et al., 2009). Compared with pictures depicting other's hands or feet receiving painful stimuli, this material has more ecological validity (Gu and Han, 2007; Schmidt et al., 2020; Meng et al., 2024). Functional magnetic resonance imaging (fMRI) was used to obtain brain activity data during acute stress to explore whether task-based connectivity between the SN and the SMN, and even its sub-regions, was reduced during acute stress, which is further related to the reduced empathy for pain.

2. Materials and methods

2.1. Participants

The participant sample in prior studies utilizing the same experimental paradigm or exploring topics ranged from about 40 to 60 (Henze et al., 2020; Nowak et al., 2020; Sandner et al., 2020; Konzok et al., 2021; Streit et al., 2014). 80 healthy participants (37 women) aged 18–35 years were recruited for this study. Participants were excluded because of physical discomfort (three participants) and excessive head movement in all runs (>2.5 mm, three participants) during the task-dependent fMRI scan. Therefore, 33 women and 41 men between 18 and 26 years (mean: 20.08 ± 1.93 years) were included. The portion of acute stress dataset has been previously published for different research purposes (Hu et al., 2022; Liu et al., 2023; Ren et al., 2023).

Participants with acute or chronic mental or physical illnesses, consumption of psychotropic drugs or glucocorticoids, alcohol or drug abuse, or participation in other fMRI studies were excluded. All women were tested during the luteal phase of their menstrual cycle (as confirmed by oral reports). The participants were asked not to engage in strenuous exercise on the day of their appointment. All participants were asked not to brush their teeth, smoke, or consume any food other than water for at least 1 h before the test. Participants provided written informed consent and received a financial reward upon completion of the study. The study was approved by the Ethics Board of Southwest University (H22008).

2.2. Procedures

The experimental sessions started from 2:00 p.m. to 5:00 p.m. to

control for the cortisol circadian rhythm (O'Byrne et al., 2021). Fig. 1A illustrates the experimental procedure. First, participants were requested to practice the basic operation of the experiment and to fill out the questionnaires. Afterwards, they rested for 30 min in a quiet room (Henze et al., 2020). Subsequently, they were brought to the stress task laboratory and the first saliva sample (baseline) was collected before scanning the brain images during the ScanSTRESS task. Approximately 10 min after the stress treatment (the last saliva sample), the participants completed the empathy test.

2.3. Measurement

2.3.1. Neuroimaging stress paradigm

Acute stress response was induced using the ScanSTRESS paradigm, an adapted paradigm for neuroimaging stress induction in an fMRI environment. The task details can be found in published articles (Streit et al., 2014). Briefly, the procedure comprised a mental arithmetic challenge and a mental rotation task. In the stress condition, participants had to respond under time pressure and social evaluation threats. They were told that their behavior and answers would be recorded and analyzed by two psychologists (one woman and one man) in terms of professional attire. In the implementation of the ScanSTRESS protocol, the experimenters presented the participants with a live video feed with interactive feedback. In the control blocks, participants performed a less demanding task without time restrictions, an evaluation of their performance, or observation by the experimenters. The paradigm consisted of 16 epochs alternating with a stress and control block (Fig. 1B). They were told at the end of the experiment that negative feedback had nothing to do with their performance.

Functional and anatomical whole-brain images were acquired using a 3T SIEMENS PRISMA scanner (Erlangen, Germany). In total, 331 volume-functional images were acquired from each subject using a T2-weighted gradient echo-planar imaging (EPI) sequence during the ScanSTRESS task (repetition time, 2000 ms; echo time, 30 ms; slice thickness, 2 mm; voxel size, $2 \times 2 \times 2$ mm^3; field of view, 224×224 mm^2; and flip angle, 90°). High-resolution T1-weighted 3D fast-field echo sequences were obtained for anatomical reference (192 slices, repetition time, 2530 ms; echo time, 2.98 ms; slice thickness, 1 mm; field of view, 256×256 mm^2; voxel size, $0.5 \times 0.5 \times 1$ mm^3; flip angle, 7°).

2.3.2. Saliva sampling and analysis

Saliva samples were collected using a Salivette sampling device with a white cap containing a cotton swab (Sarstedt AG & Co., Nümbrecht, Germany). All the saliva samples were frozen at −20 °C immediately after the experiment until analysis. Before the beginning of the experiment, the participants were instructed to use the Salivette sampling device, gently unscrew the cap of the Salivette sampling device and insert the cotton swab into their mouths. After fully chewing the cotton swab for approximately 60 s, they were asked to spit the cotton swab back into the saliva sampling device. Throughout the entire process, the participants were not allowed to touch the cotton swabs with their hands or other objects to avoid sample contamination. Saliva samples were collected at five different time points: immediately before the participants were placed in the scanner tube (T1), after the first run of the ScanSTRESS (T2), after the second run of the ScanSTRESS (T3), after a 17-min relaxation in the scanner tube (T4), and immediately after a 10-min relaxation out of the scanner tube (T5). The participants were asked to complete the empathy task in the laboratory after the last saliva sample collection to avoid the effects of the empathy task on the last salivary cortisol level. Each sampling lasted approximately 5 min.

Cortisol concentrations were determined using an enzyme-linked immunosorbent assay (ELISA; IBL, Hamburg, Germany) with the number RE52611. The one-way repeated-measures analysis of variance (ANOVA) was used to test the effect of the within-subject sampling time on stress induction with the within-subjects factor time (five repeated measures for cortisol). Analyses of the ANOVA were corrected using the Greenhouse-Geisser correction. Post-hoc tests were performed using Bonferroni-adjusted t-tests, following the ANOVA, to further examine whether the stress-induced cortisol response showed a significant increase compared to the baseline cortisol levels. Analyses were conducted using IBM SPSS Statistics for Windows, version 20.0. The area under the curve with respect to the ground (AUCg) was calculated to assess the

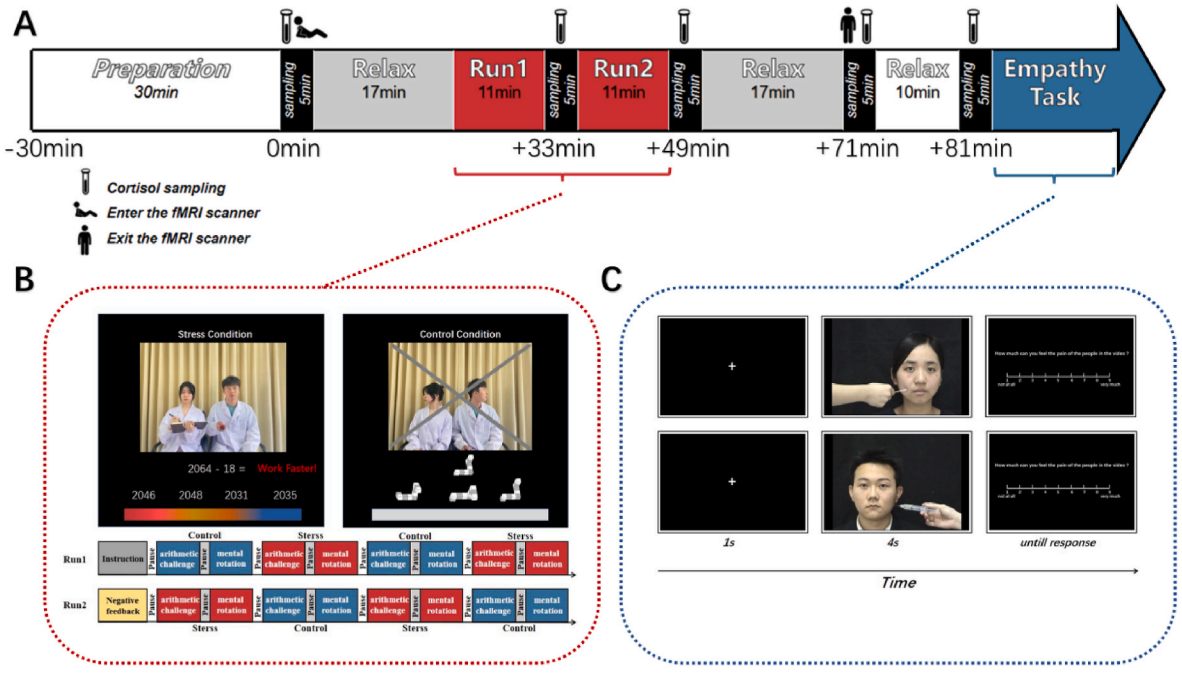

Fig. 1. Experimental procedures and materials. (A) The experimental procedure concludes the time of cortisol sampling. (B) Screenshot of the two different tasks. Mental rotation and subtraction tasks were presented in the performance phase of the stress paradigm and the design of the ScanSTRESS paradigm with two runs, preceded by an instruction phase and interrupted by critical verbal feedback given by one panel member to the participant. (C) Illustration of the empathy for pain paradigm with faces receiving painful and non-painful stimuli.

magnitude of cortisol response during acute stress (Pruessner et al., 2003). The sensitivity of the cortisol assay was 0.005 μg/dL, and the inter-assay coefficient was 8.55%.

2.3.3. Empathy for pain paradigm

Empathy for pain was measured using the paradigm proposed by Xu et al. (2009). The stimuli consisted of 48 video clips, each played for 4 s, showing others with neutral expressions of the face being stimulated by painful (needle penetration) or non-painful (Q-tip touch) stimuli (Fig. 1C). These faces were acquired from 12 models (six women). Each participant watched 16 video clips (eight female and eight male faces, half with painful and half with non-painful simulations in random order). After each video clip, participants rated the degree of their empathy for pain ("How much can you feel the pain of the people in the video?") using a nine-point Likert-type scale (1 = not at all, 9 = very much) by pressing the button.

2.4. Data analyses

2.4.1. Behavioral data

2.4.1.1. Empathy for pain. A paired-sample *t*-test was used to investigate whether there were differences in the scores of all participants between the two types of stimulation (needle penetration and Q-tip touch). Participants' empathy for pain was calculated using the average score for the stimuli (pain stimuli minus non-pain stimuli).

2.4.1.2. Associations between the magnitude of cortisol stress response and empathy for pain. The relationship between the magnitude of cortisol stress response and empathy for pain was assessed using Pearson's correlation analysis. Two-tailed *p*-values less than 0.05 were considered statistically significant. In addition, nonparametric permutation tests (1000 times) were used to verify the results of the Spearman correlation analysis.

2.4.1.3. Further analyses on gender differences. Studies have found gender differences may exist in both stress response (Heck and Handa, 2019; Ordaz and Luna, 2012) and empathy (Han et al., 2008; Rochat, 2023). Therefore, we conducted further analyses to examine whether the results of this study might be influenced by gender effects. First, two-sample *t*-tests have used to assess gender differences in cortisol stress response and empathy for pain. Subsequently, we performed a partial correlation analysis, treating gender as a covariate, to explore whether the correlation between cortisol stress response and empathy for pain is influenced by gender. Finally, we conducted a moderation analysis to investigate whether gender might moderate the relationship between cortisol stress response and empathy for pain. In this analysis, AUCg of cortisol was treated as the independent variable, the scores of empathy for pain as the dependent variable, and gender as the moderating variable.

2.4.2. fMRI data

2.4.2.1. fMRI data preprocessing. Neuroimaging data were processed and analyzed using Statistical Parametric Mapping software (SPM12 version 7771, http://www.fil.ion.ucl.ac.uk/spm) and the DPABI toolbox (Yan et al., 2016). First, the three-dimensional dicom images of each participant were converted into a four-dimensional nifiti image. Subsequently, all images were realigned to correct for head motion and co-registered with the individual participants' T1-weighted images. After that, the Dartel procedure was used to segment the T1 images and normalize them to the Montreal Neurological Institute (MNI) space, with the resulting transformation parameters applied to the normalization of the BOLD images from the native space to the MNI space. A Gaussian kernel with a full width at half parameter (FWHM) of 4 mm was used in the smoothing procedure. In the subsequent analysis, data with head movements >2.5 mm in run 1 or run 2 were excluded. Denoising using signals extracted from white matter and cerebrospinal fluid (CSF) were used as confounded regressors based on the aCompCor algorithm (Muschelli et al., 2014) and a high-pass filter of 128 s was applied. The preprocessed data, including smoothed data from the DPABI toolbox, were imported into the CONN toolbox for further task-based connectivity analysis. In addition, a generalized linear model (GLM) was used to test the activation pattern of the stress conditions at the whole-brain level to confirm the success of the experiment. Specifically, the whole-brain analyses of activations used the contrast of stress > control, while deactivations used the contrast of control > stress. This part of the analysis is provided in the Supplementary Material.

2.4.2.2. Task-based connectivity analysis. Generalized Psychophysiological Interaction (gPPI (McLaren et al., 2012),) was carried out using CONN software (https://www.nitrc.org/projects/conn/) to examine task-based connectivity during acute stress (stress > control). Task-based connectivity analysis was performed using a region of interest (ROI)-to-ROI approach. The data used for the task-based connectivity analysis in the CONN toolbox had previously undergone preprocessing, including smoothing, using the DPABI toolbox. The results of interest were the task-based connectivity that was associated with the AUCg of cortisol and empathy for pain. To explore the task-based brain connectivity related to cortisol and empathy for pain, cortisol and empathy data were imported into the fMRI mode in CONN, and a generalized linear model was used to test the linear association. Subsequently, significant brain connectivity data that correlated with cortisol and empathy for pain were extracted from the CONN and corrected for multiple comparisons. Finally, based on the Pearson correlation, we generated scatter plots of brain connectivity and empathy for pain and cortisol levels. Three levels of analysis were used to progressively locate the precise task-based brain connectivity. First, at the network level, task-based connectivity between the SMN and SN was analyzed using the seven-network template developed by Yeo et al. (2011). At the sub-network level, task-based connectivity between the sub-networks of the SMN (SMNa, SMNb) and SN (SNa, SNb) was analyzed using the 17-network template developed by Yeo et al. (2011). Finally, the same task-based connectivity analysis at the brain region level was performed using the Anatomical Automatic Labeling (AAL) template to further localize the neural substrates. The AAL template, developed by the MNI, delineates brain regions based on human anatomy. It encompasses 90 cerebral regions and 26 cerebellar regions and is widely utilized in neuroscience research (Tzourio-Mazoyer et al., 2002). To identify the most critical task-based connectivity, networks with significant results at the network level were included in the analysis at the sub-network level, and the main brain templates of sub-networks with significant results were included in the analysis at the brain level.

2.4.3. Mediation analyses

To verify whether the magnitude of cortisol stress response decreased empathy for pain through task functional network connectivity during acute stress, a mediation analysis was carried out using the R statistical software (version 4.1.2) and the mediation package (version 4.5.0) using the bootstrapping approach (Hayes and Scharkow, 2013). In our study, the analysis of three levels (network vs. subnetwork vs. brain region level) was progressively carried out, with a gradual narrowing of the brain scope and more accurate localization of brain regions. Using this approach, we aimed to find the task-based connectivity in brain regions that mediate the relationship between the magnitude of cortisol stress response and empathy for pain. Therefore, only the task-based connectivity of the final brain regions was included in the mediation model analysis. Specifically, the task-based connectivity of the ROIs was treated as the mediator variable, empathy for pain as the dependent variable, and the AUCg of cortisol as the independent

variable. The significance of the mediating effect was assessed using a bootstrapping method with 5000 iterations and a 95% confidence interval.

3. Results

3.1. Behavioral results

3.1.1. Stress and pain paradigm manipulation check

The cortisol levels at all time points during the acute stress period are shown in Fig. 2A. Stress induction resulted in a robust increase in salivary cortisol levels (F (4,304) = 4.574, $p < 0.001$, $\eta_p^2 = 0.057$). The post-hoc analysis showed that the cortisol levels of participants increased significantly after stress induction ($p_{time2\text{-}time1} < 0.001$, $p_{time3\text{-}time1} < 0.001$). For empathy for pain, the paired-sample t-test revealed that the scores of all participants were noticeably higher for the needle video clips than for the Q-tip touch ($T = 24.693$, $df = 76$, $p < 0.001$) (Fig. 2B).

3.1.2. Correlation between magnitude of cortisol stress response and empathy for pain

Correlation analysis between cortisol and empathy for pain revealed that the AUCg of cortisol was negatively correlated with empathy for pain ($r = -0.268$, $p = 0.018$; Fig. 2C). In addition, non-parametric permutation tests (1000 times) were used to verify the results of Spearman's correlation analysis ($r = -0.202$, $p = 0.047$).

3.1.3. Gender differences check

The two-sample t-tests results show that there were no significant differences in AUCg of cortisol ($T = -1.206$, $p = 0.232$, $df = 75$) or the scores of empathy for pain ($T = -1.031$, $p = 0.305$, $df = 75$) between the male and female groups. The partial correlation analysis revealed that, after controlling for gender, the AUCg of cortisol was still negatively correlated with the scores of empathy for pain ($r = -0.291$, $p = 0.011$, $df = 74$). In addition, the results of the moderation analysis did not indicate a significant moderation effect ($\beta = -0.300$, $p = 0.498$, 95% CI = [-1.180,0.564]). Overall, the results of this study indicated no gender differences.

3.2. fMRI results

3.2.1. Task-based network connectivity based on the brain network level

All seven-network templates were included in the analysis. Compared to the control condition, only the task-based connectivity between the SMN and SN (Fig. 3A) under stress conditions was significantly negatively correlated with the AUCg of cortisol ($T = -3.000$, p-FDR = 0.022; Fig. 3B) and was significantly positively correlated with empathy for pain ($T = 2.910$, p-FDR = 0.029; Fig. 3C).

3.2.2. Task-based network connectivity based on the brain sub-network level

The SMNa, SMNb, SNa, and SNb were included in the analysis (Fig. 3D). Compared to the control condition, only the task-based connectivity between the SMNa and SNa under stress conditions was significantly negatively correlated with the AUCg of cortisol ($T = -2.490$, p-FDR = 0.045; Fig. 3E) and was significantly positively correlated with empathy for pain ($T = 2.990$, p-FDR = 0.011; Fig. 3F).

3.2.3. Task-based network connectivity based on the brain region level

According to Yeo et al. (2011), the main brain regions of the SMNa are the preCG, proCG, and PCL, while the main brain region of the SNa is the INS. The left and right brain regions of the INS, preCG, proCG, and PCL were included in the analysis. No task-based connectivity showed a significant correlation with the AUCg of cortisol and empathy for pain simultaneously with FDR correction. Compared with the control condition, only the task-based connectivity between the right paracentral lobule (PCL.R) and the left insula (INS.L) under stress conditions was significantly negatively correlated with the AUCg of cortisol ($T = -2.700$, p-FDR = 0.039; Fig. 4A), and was significantly positively correlated with empathy for pain ($T = 2.550$, p-UNC = 0.013; Fig. 4B).

3.3. Mediation models

To test whether the relationship between the AUCg of cortisol and empathy for pain could be explained by the task-based connectivity between the PCL.R and INS.L during stress, mediation analyses were performed. As illustrated in Fig. 4C, the task-based connectivity of the INS.L and PCL.R mediated the link between the AUCg of cortisol and empathy for pain (indirect effect = -0.015, 95% CI = [-0.036, -0.001], p = 0.036).

4. Discussion

The current study charts a possible relationship between the magnitude of cortisol stress response, task-based brain connectivity caused by acute stress (stress > control), and the reduction of empathy for pain. Specifically, a high magnitude of cortisol response to acute stress was associated with reduced empathy for pain, and this decrease was associated with diminished task-based connectivity between the SN and SMN during acute stress. Furthermore, reduced task-based connectivity between the INS in the SN and the PCL in the SMN mediates the effect of the magnitude of the acute cortisol stress response on empathy for pain.

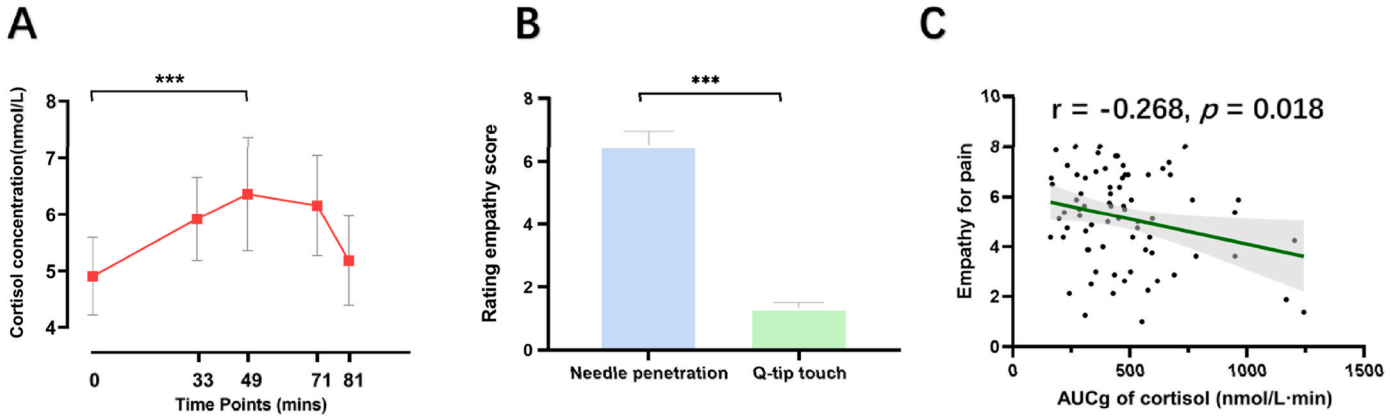

Fig. 2. The results of behavioral data. (A) Salivary cortisol secretion during ScanSTRESS at all time points. The numbers in the figure represent the exact sampling times. (B) Evaluation scores for different painful stimuli. (C) The correlation between the area under the curve with respect to the ground (AUCg) of cortisol and empathy for pain. *$p < 0.05$. **$p < 0.01$. ***$p < 0.001$.

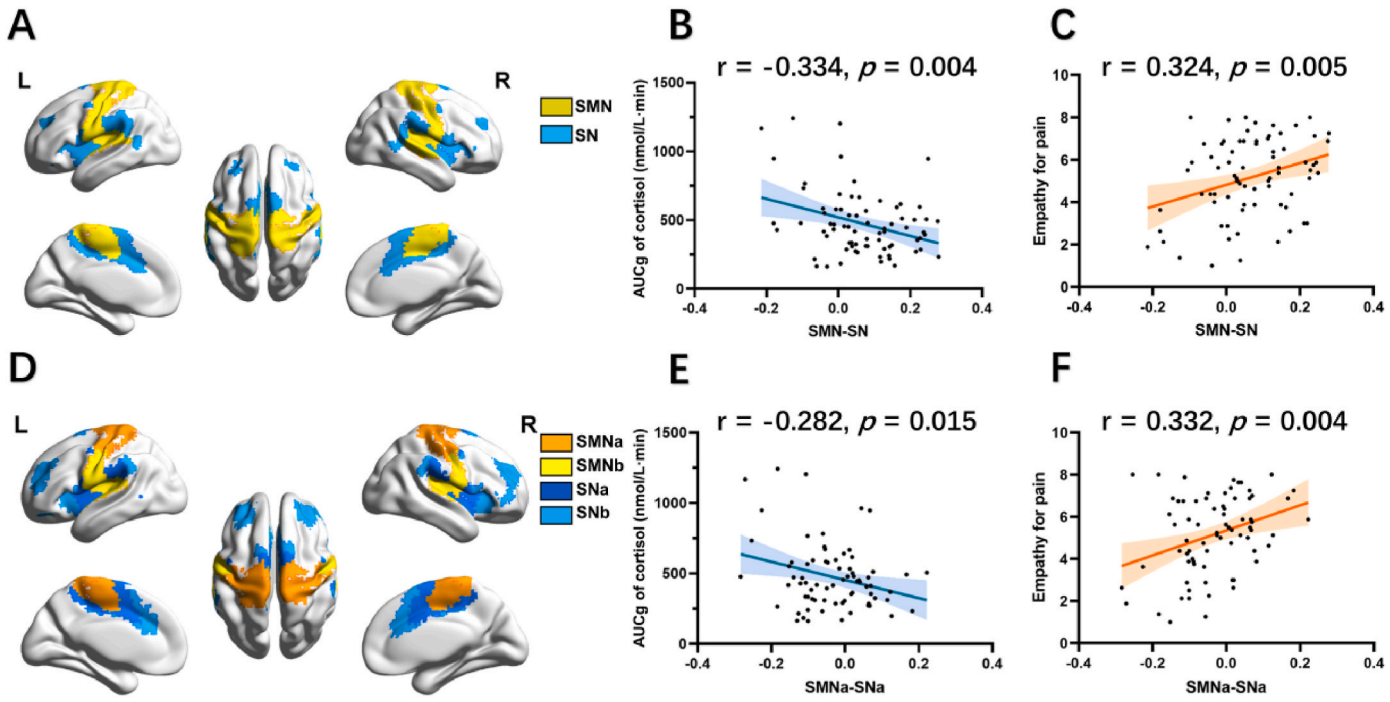

Fig. 3. The results of brain network and behavior data. (A) A representative brain structural map of the sensorimotor networks (SMN) and salience network (Pruessner et al., 2003) according to seven-network templates of Yeo et al. (2011). (B) The relationship between task-based connectivity of the SMN–SN and the magnitude of cortisol stress response. (C) The relationship between task-based connectivity of SMN–SN and empathy for pain. (D) A representative brain structural map of the SMNa, SMNb, SNa, and SNb according to 17-network templates of Yeo et al. (E) The relationship between task-based connectivity of SMNa–SNa and the magnitude of cortisol stress response. (F) The relationship between task-based connectivity of SMNa–SNa and empathy for pain.

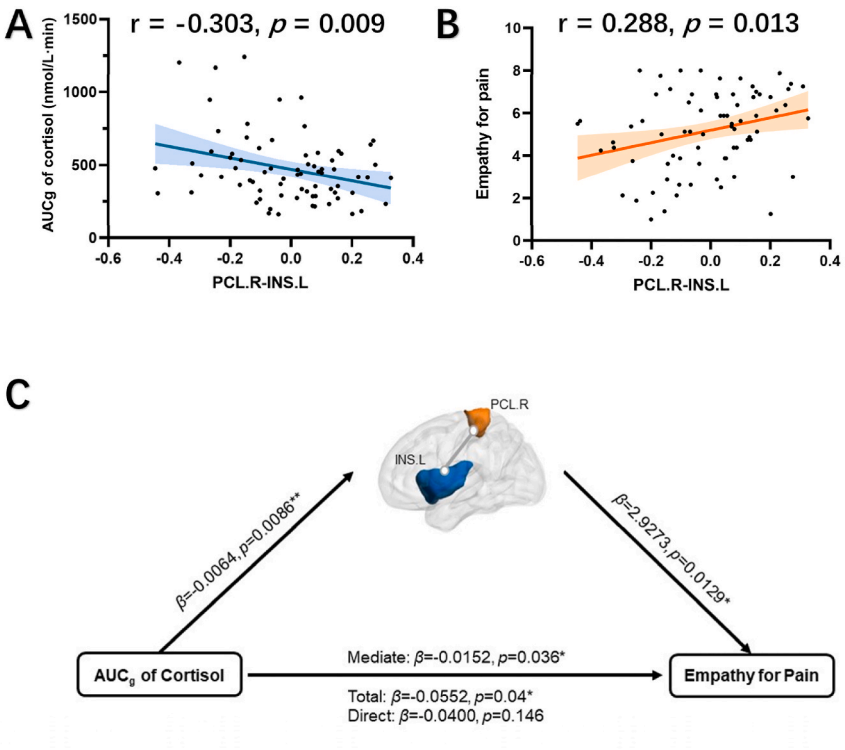

Fig. 4. The results of brain region and behavior data. (A) The relationship between task-based connectivity of the right paracentral lobule (PCL.R)–left insula (INS.L) and the magnitude of cortisol stress response. (B) The relationship between task-based connectivity of PCL.R–INS.L and empathy for pain. (C) The task-based connectivity of the INS.L and PCL.R mediates the influence of the magnitude of cortisol stress response on empathy for pain. Standardized regression coefficients are presented in the path diagram. *$p < 0.05$. **$p < 0.01$. ***$p < 0.001$.

4.1. Acute stress-induced cortisol response predicts empathy for pain

Our study found that individuals with a high magnitude of cortisol response to acute stress exhibited lower empathy for pain. This result is consistent with the well-known "fight or flight" stress response theory, which was proposed by Walter Cannon in 1932. Both fight and flight responses can adjust the body to an optimal state of preparedness to deal with threats and protect oneself (Lusk and Science, 1932). According to this theory, when an individual is faced with an acute stressor, the body secretes a large number of stress hormones and produces attacking or escaping behaviors, both of which involve decreased empathy towards the pain of others (Carlo et al., 2012; Jiang et al., 2021). Previous studies have found that individuals with high baseline cortisol concentrations or high cortisol awakening responses (CAR) in a resting state are more capable of empathy because they are physically prepared to cope with challenges, including noticing and caring for others' needs (Engert et al., 2014; Johnson et al., 2014). When individuals are faced with acute stress sources, a high cortisol stress response means mobilizing resources to deal with threats and challenges. Over time, the activity of the HPA axis is disrupted and the individual's physiological response to empathy is impaired. As a result, individuals do not have sufficient energy or resources to focus on others' pain, so their empathy for pain is reduced (Gu and Han, 2007; Hiraoka and Nomura, 2017).

Notably, our findings appear to be inconsistent with the much recent research, which reported a positive correlation between stress-induced cortisol response and empathic accuracy for men (Nitschke et al., 2022). Two reasons may account for the inconsistency: One is the different types of empathy. Empathic accuracy belongs to cognitive empathy. However, in our study, feeling the pain of someone who is suffering belongs to emotional empathy. These results imply that different components of empathy may have different correlations with stress-induced cortisol response. The other one is the different time intervals between the stress and empathy tasks. Nitschke and colleagues set the empathy task 5 min after the stress task, followed by saliva sample collection. In our study, the induction material of the empathy task was the video showing someone's face receiving a painful needle prick, which is a threatening stimulus for participants and may be an additional stressor, inducing the participants' stress response. To avoid the impact of painful material on ScanSTRESS-induced cortisol secretion, we conducted the empathy task immediately after saliva sampling was completed. Even though the stressor has dissipated, its impact on individuals can persist. These opposite results may indicate that stress-induced cortisol may have differential effects on empathy, even other social functions, at different time points following stress induction.

4.2. The role of task-based brain connectivity during stress on empathy for pain

Our results suggest that the magnitude of cortisol stress response was associated with reduced interaction between the SN and SMN, which further reduced empathy for pain. Many studies have consistently demonstrated the importance of the SN in social cognition, which is to filter information and regulate other networks. The SMN is a basic network that plays an important role in the perceptual localization of stimuli. Previous studies have found that individual cognition and emotion are affected when task-based connectivity between the SN and SMN is abnormal (Bulbul et al., 2022; De Micco et al., 2021; Fan et al., 2022; Javaheripour et al., 2021). This may be because the interaction between the SMN and SN helps individuals maintain their attention on somatic stimuli, generating corresponding emotional experiences. When the connection is too strong, the individual is too sensitive to physical information and thus has a stronger emotional experience, and vice versa. In the current study, when individuals were affected by an acute stressor, a higher magnitude of cortisol stress response and weaker task-based connectivity between SN and SMN may lead to insensitivity to the painful stimuli of others, making it difficult to empathize with the pain of others. Importantly, our results of task-based brain connectivity not only support the view that empathy for pain involves two pathways, the affective (Pasquini et al., 2020; Shi et al., 2020) and perceptual pathway (Decety et al., 2008; Levy et al., 2019; Singer and Frith, 2005) but also further validates that these two pathways are coordinated rather than independent (Betti et al., 2009; Schurz et al., 2021).

Furthermore, we found that a high magnitude of cortisol stress response was associated with reduced interaction between the INS in the SN and the PCL in the SMN during acute stress, which further reduced empathy for pain. PCL contains the primary motor cortex and the supplementary motor area, and it plays an important role on motor control and some cognitive functions, such as bodily sensory processing and spatial awareness. INS plays a key role on a wide range of functions, including the integration of sensory information, the processing and experience of emotional stimuli, and the regulation of the autonomic nervous system. The interaction between the PCL and INS helps individuals maintain their attention to somatic stimuli and generate corresponding emotional experiences. In the current study, when individuals were affected by acute stress, a higher magnitude of cortisol stress response and weaker task-based connectivity between the PCL and INS may lead to insensitivity to stimuli and impaired emotional experience, making it difficult to percept painful stimuli and empathize with the pain of others. Notably, previous meta-analyses have found that the INS is the brain region most susceptible to social or physiological acute stress (Berretz et al., 2021; Zhu et al., 2020), meanwhile a typically observed brain region in terms of empathy (Carr et al., 2003; Schulze et al., 2013). The involvement of the PCL may be related to the experimental materials used for empathy. To be specific, in our study, the empathy material described a physically painful stimulus that could be mirrored by the participants themselves, and required the involvement of the PCL for the perceptual localization and mapping to itself (Jauniaux et al., 2019). For other empathy materials that do not involve physical mirror perception, such as others' verbal painful expressions and emotionally painful faces, the PCL may not be involved (Aziz-Zadeh et al., 2012; Ding et al., 2020); therefore, reduced task-based connectivity between the INS and PCL during acute stress may not be able to reduce empathy for pain (Aziz-Zadeh et al., 2012; Ding et al., 2020).

4.3. The method from network to sub-network to sub-region

Our approach was to anchor the most interesting brain functional network connectivity (SN–SMN) by summarizing previous studies. After confirming the correlation between functional network connectivity and the magnitude of cortisol stress response and empathy for pain, we continued the same analysis focusing on their subnetworks and subregions. Thus, sub-network task-based connectivity (SNa–SMNa) and sub-region task-based connectivity (INS–PCL) during stress, which are closely related to the magnitude of cortisol stress response and empathy for pain, were successively obtained. Eventually, task-based connectivity between the INS.L in the SN and the PCL.R in the SMN was found to mediate the effect of the magnitude of acute cortisol stress response on empathy for pain. The study of the task-based connectivity between the main brain regions involved in the SMNa and SNa is an exploratory analysis, as we are currently unable to directly identify specific brain areas through the existing literature. We hope to conduct brain region-level analyses using data-driven methods to obtain interesting results. As brain area templates that completely matched the sub-network templates were not provided, we chose to use the AAL template widely used in the research area of brain neural activity to improve the generalizability of our study results. Thus, the results were progressive and stable. In our view, in the initial phase of a research field with a less theoretical basis, this method with the logic from large to small is timely and effective, which can help us explore and understand the neural mechanism by combining macro and micro perspectives.

4.4. Limitations

Firstly, an individual's task-based brain connectivity during stress is just like a brain state. Therefore, researchers may doubt whether the brain state could sustainably influence empathy for pain. Future studies may benefit from also directly measuring brain activity during empathy tasks. Secondly, there are two types of empathy for pain: physiological and social (Fan et al., 2010). In our study, empathy was associated with physiological pain. Although evidence suggests that some neural regions involved in processing physiological pain experiences overlap with those involved in processing social pain experiences (Eisenberger and Naomi, 2012; Kross et al., 2011), other studies have indicated that the neural mechanisms underlying empathy for physiological pain and social pain may be distinct (Masten et al., 2011; Meyer et al., 2013). Therefore, the findings of this study may not apply to empathy for social pain.

5. Conclusion

In sum, our study makes a unique contribution to social cognitive neuroscience and has important implications in real life. To the best of our knowledge, this is the first study to explore how endocrine and neural activity during acute stress contribute to empathy for pain, providing evidence for the importance of the SN in stress and empathy and notion that basic brain regions are also critical for complex social cognition. Additionally, due to the close relationship between empathy for pain and prosocial behavior, empathy for pain is considered an important driving factor of prosocial behavior (Decety et al., 2016). Meanwhile, there is a novel idea that the flexibility of the HPA axis can predict prosocial behavior (Miller, 2018). Therefore, our study lays the foundation for future studies exploring the relationships between prosocial behavior, empathy, the HPA axis, and brain connectivity.

5.1. Data availability statement

The data is available upon reasonable request from the corresponding author.

5.2. Code availability

Not applicable.

CRediT authorship contribution statement

Zihan Tang: Writing – review & editing, Writing – original draft, Project administration, Investigation, Formal analysis, Conceptualization. **Yadong Liu:** Investigation, Formal analysis. **Xiaolin Zhao:** Project administration, Investigation. **Weiyu Hu:** Investigation. **Mengning Zhang:** Investigation. **Yipeng Ren:** Investigation, Formal analysis. **Zhenni Wei:** Investigation. **Juan Yang:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Consent to participate

Participants provided written informed consent and received a financial reward upon completion of the study.

Compliance with ethical standards

All procedures performed in the study involving human participants were in accordance with the ethical standards and were approved by the Ethics Board of Southwest University (H22008).

Consent for publication

This manuscript has not been published or presented elsewhere and is not under consideration by another journal.

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Declaration of Competing interest

Declarations of interest: none.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ynstr.2024.100682.

Data availability

Data will be made available on request.

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