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Neural habituation during acute stress signals a blunted endocrine response and poor resilience

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Original Article

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Abstract

Background. A blunted hypothalamic–pituitary–adrenal (HPA) axis response to acute stress is associated with psychiatric symptoms. Although the prefrontal cortex and limbic areas are important regulators of the HPA axis, whether the neural habituation of these regions during stress signals both blunted HPA axis responses and psychiatric symptoms remains unclear. In this study, neural habituation during acute stress and its associations with the stress cortisol response, resilience, and depression were evaluated.

Methods. Seventy-seven participants (17–22 years old, 37 women) were recruited for a ScanSTRESS brain imaging study, and the activation changes between the first and last stress blocks were used as the neural habituation index. Meanwhile, participants' salivary cortisol during test was collected. Individual-level resilience and depression were measured using questionnaires. Correlation and moderation analyses were conducted to investigate the association between neural habituation and endocrine data and mental symptoms. Validated analyses were conducted using a Montreal Image Stress Test dataset in another independent sample (48 participants; 17–22 years old, 24 women).

Results. Neural habituation of the prefrontal cortex and limbic area was negatively correlated with cortisol responses in both datasets. In the ScanSTRESS paradigm, neural habituation was both positively correlated with depression and negatively correlated with resilience. Moreover, resilience moderated the relationship between neural habituation in the ventromedial prefrontal cortex and cortisol response.

Conclusions. This study suggested that neural habituation of the prefrontal cortex and limbic area could reflect motivation dysregulation during repeated failures and negative feedback, which might further lead to maladaptive mental states.

Introduction

A blunted stress response is a lower level of cardiovascular or endocrine response during acute stress (Howden et al., 2015; Jansen et al., 1998). Researchers found that this blunted response, especially to psychological stressors, is associated with various mental and behavioral disorders, such as a lower level of resilience and a higher level of depression (Adinoff, Junghanns, Kiefer, & Krishnan-Sarin, 2005; Carroll, Phillips, Hunt, & Der, 2007). Since the brain is the core regulator of the stress response (Dedovic, Duchesne, Andrews, Engert, & Pruessner, 2009; Kogler et al., 2015), understanding the blunted hypothalamic–pituitary–adrenal (HPA) axis reactivity at the neural level could not only provide insight into the mechanisms of the maladaptive stress response and its relationship with mental health but also offer potential treatment options (McCarty, 2016).

The HPA axis activation begins with the paraventricular nucleus of the hypothalamus releasing the corticotropin-releasing hormone (CRH) and ends with the adrenal cortex producing glucocorticoid hormones (mainly cortisol in humans) into blood (Koning, Buurstede, Van Weert, & Meijer, 2019; López, Akil, & Watson, 1999). Glucocorticoid hormones act on the body via mineralocorticoid receptors (MRs) and glucocorticoid receptors (GRs) (Kim, Han, & Iremonger, 2019), which regulate various stress processes, such as threat detection, emotion regulation, and cognitive control (Carroll, Ginty, Whittaker, Lovallo, & de Rooij, 2017; Pruessner et al., 2008). It has been found that a repeated psychological stressor would lead to a decreased cortisol response (Cyr & Romero, 2009), and further influence the risk of various mental and behavioral disorders (Peters & McEwen, 2015).

Both MRs and GRs are widely distributed in the brain, particularly in the prefrontal cortex and limbic area (e.g. hippocampus, amygdala) (Kim, Pellman, & Kim, 2015). Animal studies have demonstrated that cell loss in the hippocampus can affect HPA axis function (Bratt et al., 2001), while human studies have found that higher hippocampus and amygdala volume levels can predict a more robust HPA axis activity (Pagliaccio et al., 2014; Pruessner, Pruessner, Hellhammer, Bruce Pike, & Lupien, 2007). Functional neuroimaging studies have also shown that insufficient activity in the hippocampus, amygdala, and ventromedial prefrontal cortex (vmPFC) is negatively correlated with the endocrine stress response (Ginty, Gianaros, Derbyshire, Phillips, & Carroll, 2013; Lederbogen et al., 2011; Pruessner et al., 2008). Importantly, researchers found that the neural response to repeated stimuli will exhibit habituation patterns too. This neural habituation phenomenon was first discovered with sensory stimuli (Wilson, Babb, Halgren, Wang, & Crandall, 1984), then with emotional stimuli (Stevens et al., 2017). Recent evidence further documented neural habituation during acute stress. First, CRH neuronal activity robustly habituates to repeated presentations of the same stressors (Kim et al., 2019). Furthermore, a number of neuroimaging studies found that habituation in the prefrontal cortex and limbic system was more pronounced than that in other areas (Plichta et al., 2014; Sladky et al., 2012). Lastly, a study that used aversive images to induce stress found neural habituation in the hippocampus and insula (Sinha, Lacadie, Todd Constable, & Seo, 2016).

Notably, although previous studies have documented the critical role of the prefrontal cortex and limbic activity in ensuring a sufficient endocrine response, whether neural habituation during the task could affect the HPA axis response is still unclear. Given that habituation represents a reduced response to certain stimuli (Rankin et al., 2009), we hypothesized that neural habituation in these areas might interfere with the endocrine system and result in a blunted endocrine response. Further, depression and chronic stress are common mental disorders associated with a blunted endocrine response (Carroll et al., 2007; Ren et al., 2022). Therefore, we also hypothesized that neural habituation would positively correlate with depression and chronic stress.

Conversely, resilience refers to the ability to overcome adversity and stress to promote adaptive behaviors and positive health outcomes (Holz, Tost, & Meyer-Lindenberg, 2020; Rutter, 2006). The prefrontal cortex is the critical component in generating resilience coping (Maier & Watkins, 2010). Previous studies have documented that increased vmPFC activity during stress positively correlates with resilience (Sinha et al., 2016). Therefore, we hypothesized that neural decline in the prefrontal cortex caused by habituation would be negatively associated with resilience. Moreover, evidence also showed that the low emotional resilience group would exhibit a blunted endocrine stress response. In contrast, the high resilience group will not be related to the endocrine response (Krkovic, Clamor, & Lincoln, 2018), indicating that resilience may moderate the relationship between neural activity and endocrine stress response. This hypothesis would be also tested in this study.

An adapted version of the ScanSTRESS paradigm (Lederbogen et al., 2011), which adopts uncontrollability and social evaluative threat to induce acute stress (Lederbogen et al., 2011), was used to induce stress. During this paradigm, stress contexts were induced four times, and both whole-brain-wise and region-of-interest (ROI)-wise analyses were conducted to explore neural habituation during stress induction. Furthermore, we used the amplitude difference between the first and last stimulation blocks to estimate the individual level of neural habituation (Plichta et al., 2014). Subjective and endocrine stress reactivities were also measured repeatedly throughout the experiment, and the levels of depression and resilience were also collected. The relationships between neural habituation, cortisol response, depression, and resilience were also estimated. Finally, we used the Montreal Image Stress Test (MIST) to validate the neural habituation hypothesis (Dedovic et al., 2005) and its relationship with a blunted endocrine response. In this dataset, chronic stress was used to validate the relationship between neural habituation and mental health.

Materials and methods

Participants

Seventy-seven participants were recruited online for the ScanSTRESS study (mean age, 19.10 years; range 17–22; 37 women). All participants were healthy college students. Exclusion criteria were head injury, a history of alcoholism, or drug abuse. Female participants were tested during their luteal phase (around 10 days before menstruation) and did not use oral contraceptives leading up to the experiment (Roche, King, Cohoon, & Lovallo, 2013; Sharma et al., 2020).

ScanSTRESS paradigm and experimental procedure

There were two conditions in this paradigm: a stressful 'performance phase' and a control 'relaxation phase' (Nowak et al., 2020). Under stressful conditions, social evaluative threat and uncontrollability were used to induce acute stress (Fig. 1a). These two components were removed in the control condition (Fig. 1b). There were two runs in this paradigm; each run contained four blocks, two of which were stressful (each block contained a serial subtraction task and a mental rotation task) and the other was relaxed (each block contained a figure matching and a number matching task, Fig. 1c). To mediate the effect of the cortisol rhythm on the experimental results, participants were required to arrive at the laboratory in the mid-afternoon, between 12:00 and 15:00 hours. Subjective stress reports and salivary cortisol data were collected repeatedly from the scanner five times throughout the experiment (Fig. 1d).

Data acquisition

Salivary cortisol data acquisition and analyses

Saliva samples were collected using a sampling device (Salivette, Sarstedt, Germany), and all saliva samples were stored at −20 °C until analysis. Cortisol concentrations were analyzed using an enzyme-linked immunosorbent assay kit (IBL-Hamburg, Hamburg, Germany). The sensitivity of the cortisol assay was 0.005 μg/dL. Following the previously reported methods of calculation (Calvi et al., 2017), the interassay coefficient of variation for the cortisol assay was 11.92%, which is acceptable (below 15%).

Subjective reports

Participants self-reported their feelings of stress on a 7-point Likert scale ranging from 1 (not at all) to 7 (total). Self-reported measurements were collected five times along with salivary cortisol collection.

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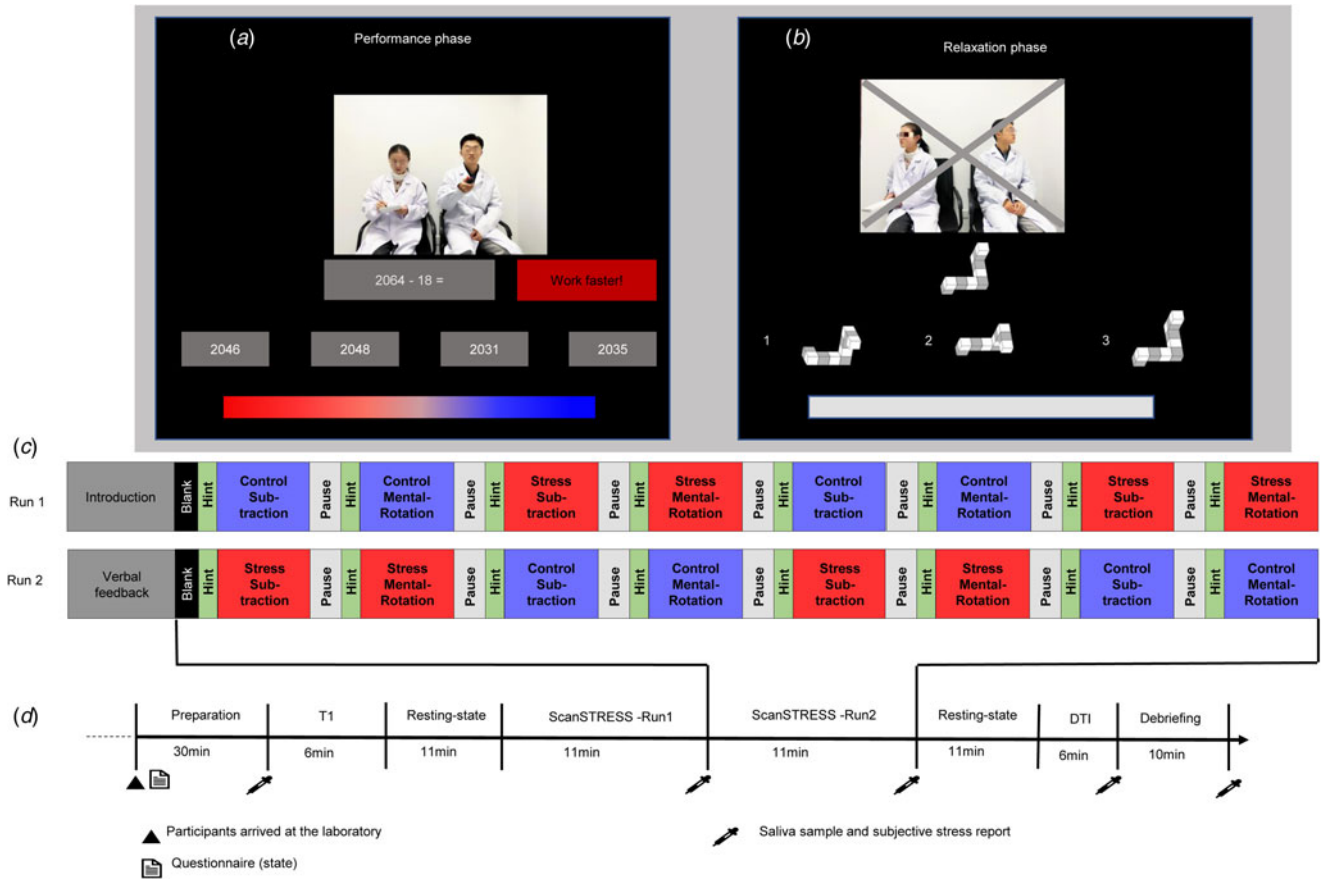

Figure. 1. ScanSTRESS paradigm and an overview of the experimental procedure. (a) In the stressful 'performance phase', participants were asked to solve challenging cognitive tasks (serial subtraction and mental rotation) under time pressure; in addition, two juries (a man and a woman) is presented on the screen to increase the social evaluative threat. Time limits were adapted to the individual's performance resulting in frequent failure; if the participants could not answer the question in time or correctly, there would be negative feedback shown on the screen as 'work faster' or 'error' insistently. In the meantime, one of the juries would press a red button in his/her hand and another jury would record the participant's failure; this could also increase participants' feelings of social threat. (b) In the control 'relaxation phase', participants went through similar although much easier tasks (find the matched figure or number) with abundant time, and the negative feedback from the screen and the juries were removed. Furthermore, the juries were instructed to look away to remove the social evaluative threat. (c) The order for conditions is counter-balanced, in the first run, the stimuli were given in the 'control–stressful–control–stressful' order; in the second run, the stimuli were given in the 'stressful–control–stressful–control' order. (d) After arriving at the laboratory, the participants were asked to rest for 30 min before entering the MRI scanner. During the scanning, a T1 image was acquired first, followed by a resting-state image. Immediately, the ScanSTRESS paradigm was used to induce a stress response for 22 min. Then, there was another resting-state scan and structural scan; lastly, participants were debriefed for 10 min before they left the laboratory. During this period, participants provided five saliva samples. The experimenter paused the scan to collect the second, third, and fourth samples. Participants were temporarily removed from the scanner for saliva sampling, after which they returned and completed head localization again. The first and fifth samples were collected outside the MRI scanner.

Connor–Davidson Resilience scale

The Connor–Davidson Resilience scale (CD-RISC) was developed as a measure of 'bounce-back' and adaptability by the original authors (Vaishnavi, Connor, & Davidson, 2007), with a 5-point Likert scale ranging from 0 (not at all) to 4 (almost always).

Center for Epidemiologic Studies Depression scale

The Center for Epidemiologic Studies Depression Scale (CES-D) was designed to measure depression mood in general populations (Radloff, 1977). There are 20 items on the CES-D, including 4 negative and 16 positive items. Participants were required to estimate the frequency of symptoms in the last week on a 4-point Likert scale from 0 (rarely or none of the time) to 3 (most or all the time).

Functional magnetic resonance imaging (MRI) data acquisition

Functional and anatomical whole-brain images were acquired using a 3T Siemens Trio MRI scanner (Munich, Germany). A total of 331 volume functional images were acquired from each participant using a T2-weighted gradient echo-planar imaging sequence during the task [repetition time (TR), 2000 ms; echo time (TE), 30 ms; matrix, 64×64; spatial resolution, $3 \times 3 \times 3$ mm^3; field of view (FOV), 192×192 mm^2]. High-resolution T1-weighted three-dimensional (3D) fast-field echo sequences were obtained for anatomical reference (slices, 176; TR, 1900 ms; TE, 2.52 ms; slice thickness, 1 mm; FOV, 256 mm × 256 mm; voxel size, 1 mm × 1 mm × 1 mm).

Functional MRI data analysis

Preprocessing

Functional MRI data were processed with MATLAB (Natick, MA) using the DPABI toolbox (Yan, Wang, Zuo, & Zang, 2016). First, 3D images were transformed into four-dimensional images, which were then sliced time-corrected in milliseconds for each slice individually. Subsequently, all images were realigned to

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correct for the head motion for acquisition, co-registered with individual participants' T1-weighted images, spatially normalized to the Montreal Neurological Institute template using the Dartel segments, and smoothed using a 4-mm full-width at half-maximum Gaussian kernel.

Neural habituation analysis

Each run included two regressors (stressful and control conditions), and six movement parameters were included as additional covariates. To estimate the general effects of stress induction, contrast images of *stress v. control* over two sessions were analyzed using a one-sample *t* test (Henze et al., 2020). In addition, to test the neural habituation between blocks under different conditions, the interaction between *stress* and *block* was calculated using a 2×4 analysis of variance (ANOVA) with *stress* and *block* as within-subject variables.

To further calculate the level of brain changes over the entire stress induction period, we modeled each stress block separately and extracted a total of four brain response estimates per participant. Based on the whole-brain-wise ANOVA, ROIs were identified using masks from the automated anatomical labeling (AAL) template, and the selected ROIs were primarily located in the medial prefrontal cortex–limbic areas. Mean amplitude levels within each block were extracted using the selected ROI template as a mask, and the amplitude difference between the first and last stimulation blocks was measured to estimate neural habituation during stress induction (Blackford, Allen, Cowan, & Avery, 2013; Plichta et al., 2014).

Statistical analysis

All statistical analyses were performed using SPSS (version 22). As subjective and endocrine stress reactivities were measured repeatedly throughout the experiment, we calculated the areas under the curve with respect to ground (AUCg) and areas under the curve with respect to increases (AUCi) to reflect the level of the stress response, as recommended by previous researchers (Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003). Specifically, AUCg is an index of total subjective or cortisol response during stress, while AUCi is an index of subjective or cortisol response with respect to increase (online Supplementary Fig. S1). Participants were categorized as responders if an increase in the cortisol level was detected ($\geqslant$1 nmol/L) either immediately or 20 min after stress relative to baseline (Hamer, O'Donnell, Lahiri, & Steptoe, 2010), afterward, the neural habituation pattern differences between cortisol responders and non-responders were explored. A correlation analysis between neural habituation and cortisol response was tested to analyze the relationship between neural habituation and cortisol response. Furthermore, a correlation analysis between neural habituation, depression, and resilience was conducted. We also defined moderate models with neural habituation as the independent variable, stress reactivity as the dependent variable, and resilience as the moderating variable. All *p* values in statistical analysis were corrected using the false-discovery rate (FDR) approach.

Validation analysis

The low stability between different stress paradigms has long been criticized (Cao et al., 2021). Therefore, we used an independent sample under the MIST paradigm to validate the results (48 participants; 17–22 years old, 24 women). Information about the MIST paradigm has been previously reported in another article (Ren et al., 2022). Similar to the ScanSTRESS paradigm, the MIST paradigm also uses social evaluative threat and uncontrollability to induce acute stress. During stress induction, salivary cortisol was collected seven times, and the daily stress inventory was used as an index of chronic stress to reflect mental health levels (online Supplementary I and Fig. S2). The analysis procedures were the same as those in ScanSTRESS.

Results

Study population

Three participants were excluded because of head motion execution (Zuo et al., 2014), and another two participants were excluded because of outliers (more than 3 standard deviations outside the mean) in the cortisol data (Gump et al., 2008). A total of 72 participants (32 women) were included in the final analysis.

Subjective, endocrine, and neural responses to stress

Regarding the behavioral and endocrine levels, time was determined to be a significant intra-subject variable in subjective stress self-reports ($F_{(4,\ 68)} = 42.33$, $p < 0.001$, $\eta_p^2 = 0.713$). The post-hoc analysis revealed that participants' subjective stress levels increased significantly after stress induction [$p_{time2-time1} < 0.001$, 95% confidence interval (CI) 0.955–1.539], attained the highest levels of subjective stress after stress induction ($p_{time3-time2} < 0.001$, 95% CI 0.275–0.780), and then decreased significantly after stress induction ($p_{time3-time4} < 0.001$, 95% CI 1.370–2.019). Time was also found to be a significant variable for salivary cortisol levels ($F_{(4,\ 68)} = 3.30$, $p = 0.016$, $\eta_p^2 = 0.162$). Post-hoc analysis revealed that participants' salivary cortisol levels increased significantly after stress induction ($p_{time2-time1} < 0.05$, 95% CI 0.007–0.066, $p_{time3-time1} < 0.05$, 95% CI 0.006–0.076), remained a high level after stress induction, and then decreased significantly ($p_{time4-time5} < 0.05$, 95% CI 0.015–0.056). The overall change in stress reactivity is shown in Fig. 2a.

The whole-brain analysis (two-tailed combined FDR-corrected $q < 0.05$; Fig. 2b) revealed similar activation and deactivation patterns seen in previous studies (Akdeniz et al., 2014; Sandner et al., 2020), indicating that acute stress-induced activation in the dorsal anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (dlPFC), and temporal areas and deactivation in the vmPFC, posterior cingulate cortex, and insula. Detailed information is provided in online Supplementary Table S1.

Behavioral correlations

Correlation analysis showed that depression was positively correlated with the total subjective stress feelings during stress (SSAUCg, $r = 0.27$, $p = 0.021$, 95% CI 0.043–0.492) and negatively correlated with cortisol secretion with respect to increase (CortiAUCi, $r = -0.23$, $p = 0.051$, 95% CI −0.467 to 0.044). There was no correlation between stress response and age and any of the other variables (online Supplementary Table S2).

Neural habituation during repeated stress induction

ANOVA at the whole-brain level (two-tailed combined FDR-corrected $q < 0.05$) revealed a significant interaction between

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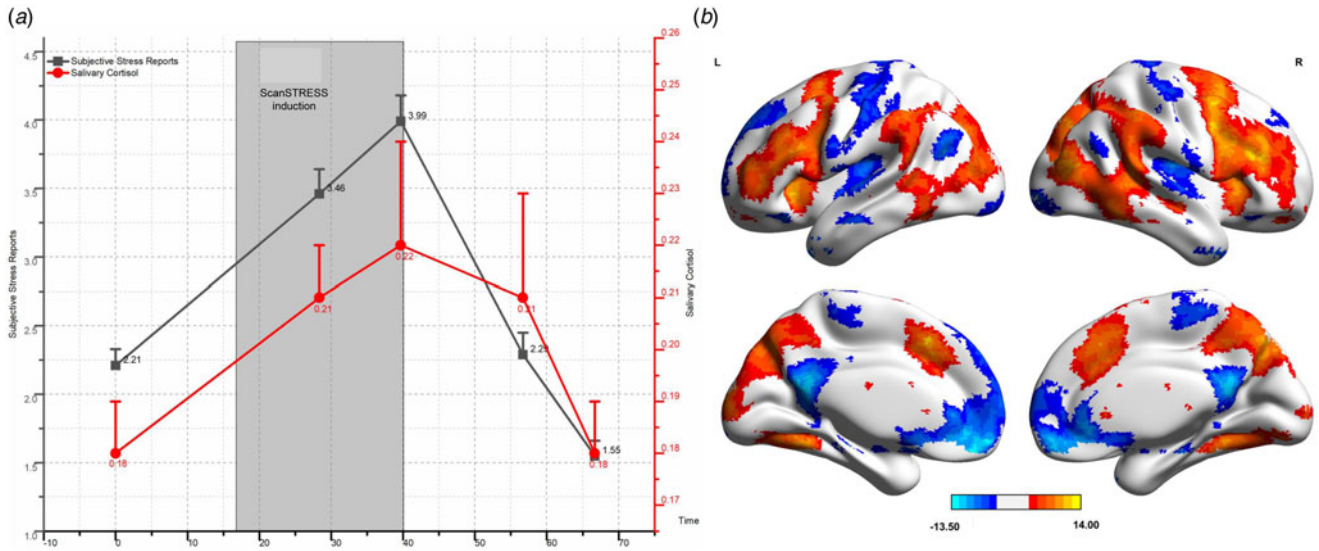

Figure. 2. Validation of stress induction in the ScanSTRESS paradigm. (a) Subjective stress report and salivary cortisol secretion during ScanSTRESS. (b) Neural response to stress induction in the ScanSTRESS paradigm (stress > control, FDR-corrected $p < 0.05$).

stress and *block* within the prefrontal and limbic areas, including the dlPFC, vmPFC, anterior cingulate cortex, insula, hippocampus, and amygdala (Fig. 3a). The detailed information is presented in online Supplementary Table S3. In addition, the activation value in each block was extracted using the *F* test map as a mask, and the neural activity declined significantly during the four stress blocks while remaining stable during the four control blocks (Fig. 3b). Group-level analysis revealed that compared to responders, non-responders showed a greater neural decline during stress induction (online Supplementary Fig. S3). Finally, activation changes between the first and last stress blocks were used as the neural habituation index.

Correlation between neural habituation, endocrine stress response, and mental health

Twenty-two ROIs located in the prefrontal cortex and limbic areas were selected from the AAL template, and the *F* map derived from the ANOVA was also defined as an ROI. Correlation results showed that neural habituation at the whole-brain level as well as the ROI level was accompanied by a blunted total cortisol secretion during stress (CortiAUCg). Besides, CortiAUCi is negatively correlated with ROI which is located in the dlPFC and vmPFC. Lastly, neural habituation of some ROIs located in the prefrontal cortex was negatively correlated with resilience, and neural habituation of ROIs located in the limbic area was positively correlated with depression (Fig. 4).

Moderation analysis

With neural habituation (whole-brain level and 22 ROIs) as the independent variable, cortisol response (CortiAUCg and CortiAUCi) as the dependent variable, and resilience as the moderate variable, results showed that the level of resilience tend to moderate the relationship between the dlPFC and vmPFC neural habituation and blunted stress response (online Supplementary Table S4). Only one model with vmPFC [right middle frontal gyrus (MFG), orbital part (orb)] habituation as the independent variable could survive the FDR correction, indicating that CortiAUCi was significantly lower in the high vmPFC habituation group among participants with low resilience ($B = -3.458$, $p < 0.001$), but not among those with high resilience ($B = 1.960$, $p = 0.054$) (FDR-corrected $q < 0.05$; online Supplementary Fig. S4).

Validation analysis

Stress induction in MIST paradigm resulted in similar subjective stress feeling and endocrine increases (online Supplementary Fig. S5) as well as neural activation (online Supplementary Fig. S6). Participants' subjective chronic stress levels were negatively correlated with acute endocrine stress responses. Compared to cortisol responders, non-responders showed more profound neural habituation (online Supplementary Fig. S7). Furthermore, when the same ROI was selected, neural habituation at the whole-brain level and ROI level could signal blunted cortisol response (FDR-corrected $q < 0.05$; Fig. 5). Neural habituation in the right insula was positively correlated with subjective chronic stress level ($p = 0.039$, uncorrected). Notably, this result did not survive FDR correction, and it was reported solely for the purpose of completeness, and should be interpreted with caution. Neither depression nor resilience was measured in the MIST paradigm.

Discussion

To our knowledge, this is the first study to explore the neural mechanism of the acute HPA axis response from a neural habituation perspective. Our results showed that neural responses in the limbic area and prefrontal cortex, such as the dlPFC, vmPFC, hippocampus, and amygdala, showed decreased activity during repeated stress induction. The level of neural habituation in these areas could signal a blunted endocrine-stress response. Moreover, the level of neural habituation was negatively correlated with the resilience level but positively correlated with the depression level, highlighting the maladaptive role of the blunted stress response. Furthermore, the level of resilience could moderate the

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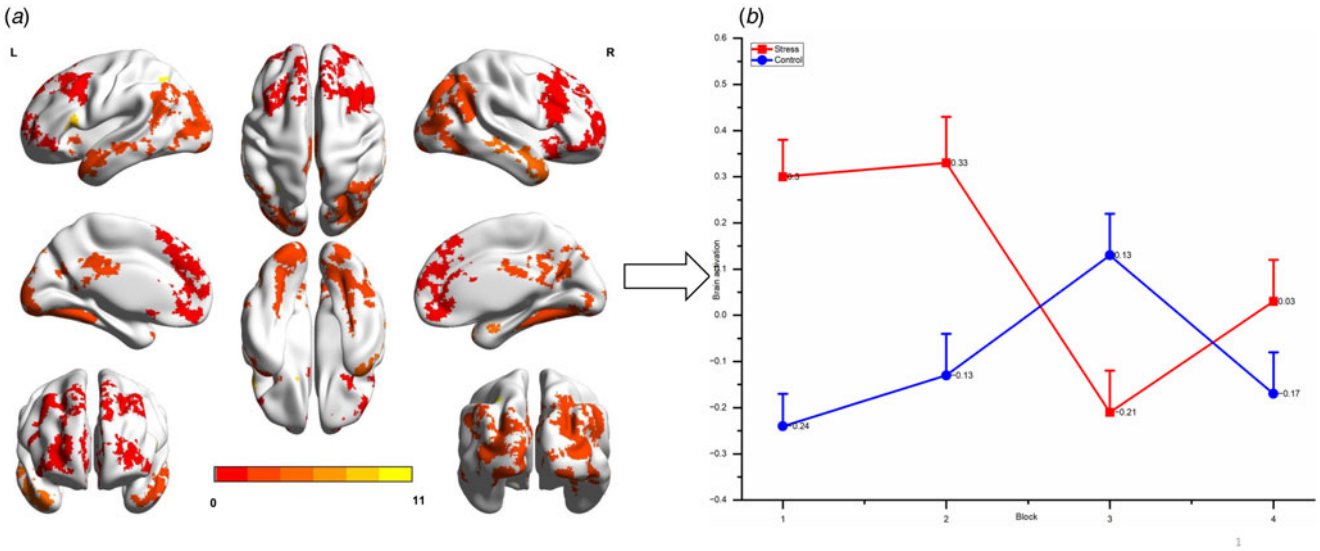

Figure. 3. Neural habituation between stressful conditions in the ScanSTRESS paradigm (FDR-corrected $p < 0.05$). (a) The interaction between *block* and *stress*. (b) Neural habituation during four blocks in the areas investigated.

relationship between neural habituation and blunted stress, which underlies the mechanism by which resilience can generate protective effects on stressful events. Notably, the same neural habituation tendency and relationship to blunted stress response are also found in the MIST paradigm, which suggests that the neural habituation level is also positively correlated with the chronic stress level (which is negatively correlated with the endocrine response). Overall, our study provides a novel perspective for considering the neural mechanism of the blunted stress response, offers a potential bridge between psychiatric disorders and blunted stress responses, and reveals how resilience could help the organism fight against the maladaptive response.

Perhaps the most profound and convincing theory for a blunted stress response is the motivational dysregulation theory, which considers blunted psychological stress reactivity as a marker of central motivational dysregulation (Carroll, David Batty, Mortensen, Deary, & Phillips, 2011; Carroll, Lovallo, & Phillips, 2009). A review found that all the factors associated with a blunted stress response, such as addiction (Paris, Franco, Sodano, Frye, & Wulfert, 2010), depression (Phillips, Hunt, Der, & Carroll, 2011), and anxiety (Bibbey, Ginty, Brindle, Phillips, & Carroll, 2016), share a complaint of motivation dysregulation (Carroll et al., 2017). In the laboratory stress test, motivational tasks (e.g. public speaking or cognitive tasks) are important components of stress induction (Shields, 2017), by manipulating participants' performance on a high error level, giving negative feedback after each wrong answer, inducing feelings of uncontrollability, and threatening the social self (Noack, Nolte, Nieratschker, Habel, & Derntl, 2019), which could affect motivation level, and further lead to a significant psychological and endocrine stress response (Foley & Kirschbaum, 2010). Empirical research from animal and human studies has shown that acute stress can disrupt motivation functions related to reward (Bai, Belin, Zheng, Liu, & Zhang, 2017; Hollon, Burgeno, & Phillips, 2015). More recently, a study also found that a threatening stimulus during acute stress can lead to motivational disengagement, and the level of motivation decline could signal blunted cardiovascular reactivity (Hase, aan het Rot, de Miranda Azevedo, & Freeman, 2020).

At the neural level, the limbic system and prefrontal cortex, such as the cingulate gyrus and amygdala, are key regions that support motivation (Ginty et al., 2013; Phillips, Ginty, & Hughes, 2013). The dlPFC is vital for purchasing goals and interplays with motivation circuits, such as the ACC and vmPFC, to construct a network for goal regulation (Lee & Reeve, 2020; Spielberg et al., 2012). The hippocampus and amygdala are also essential areas for generating motivation (Cardinal, Parkinson, Hall, & Everitt, 2002; Jarrard, 1973), and their activation could ensure a sufficient cortisol response (Khalili-Mahani, Dedovic, Engert, Pruessner, & Pruessner, 2010). Previous studies have suggested that deactivation in these areas during acute stress could signal a blunted stress response (Carroll et al., 2017; Phillips et al., 2013). In the current study, rather than deactivation, the activity decline in the prefrontal cortex and hippocampus was accompanied by the blunted endocrine stress response. This may reflect a reduced effort and motivation in answering the questions correctly. Taken together, we suggested that neural habituation during acute stress could reflect a motivation disengagement during repeated failures and negative feedback.

In line with our hypothesis, the results showed that mental health (depression and chronic stress) related to blunted stress was positively correlated with neural habituation levels. We validated these results using two paradigms, respectively. In the ScanSTRESS study, we found greater right hippocampus and amygdala habituation in people with a higher level of depression, whereas in the MIST study, we found greater right insula habituation in people with a higher level of chronic stress. Depression and chronic disorders are associated with prefrontal and limbic system dysregulation (Dwivedi et al., 2015; Ren et al., 2022; Xu et al., 2021; Yang et al., 2013). For example, the depression level could alter the prefrontal cortex and limbic system function both at rest and during a task (Mujica-Parodi, Cha, & Gao, 2017; Pannekoek et al., 2013), especially in reward-related tasks (Gold, Morey, & McCarthy, 2015; Hu, 2018). In addition, chronic stress can disrupt the brain functions responsible for motivation (Evans & Stecker, 2004; Harmon, Greenwald, McFarland, Beckwith, & Cromwell, 2009). In the current study, we infer that neural habituation could reflect motivation dysregulation,

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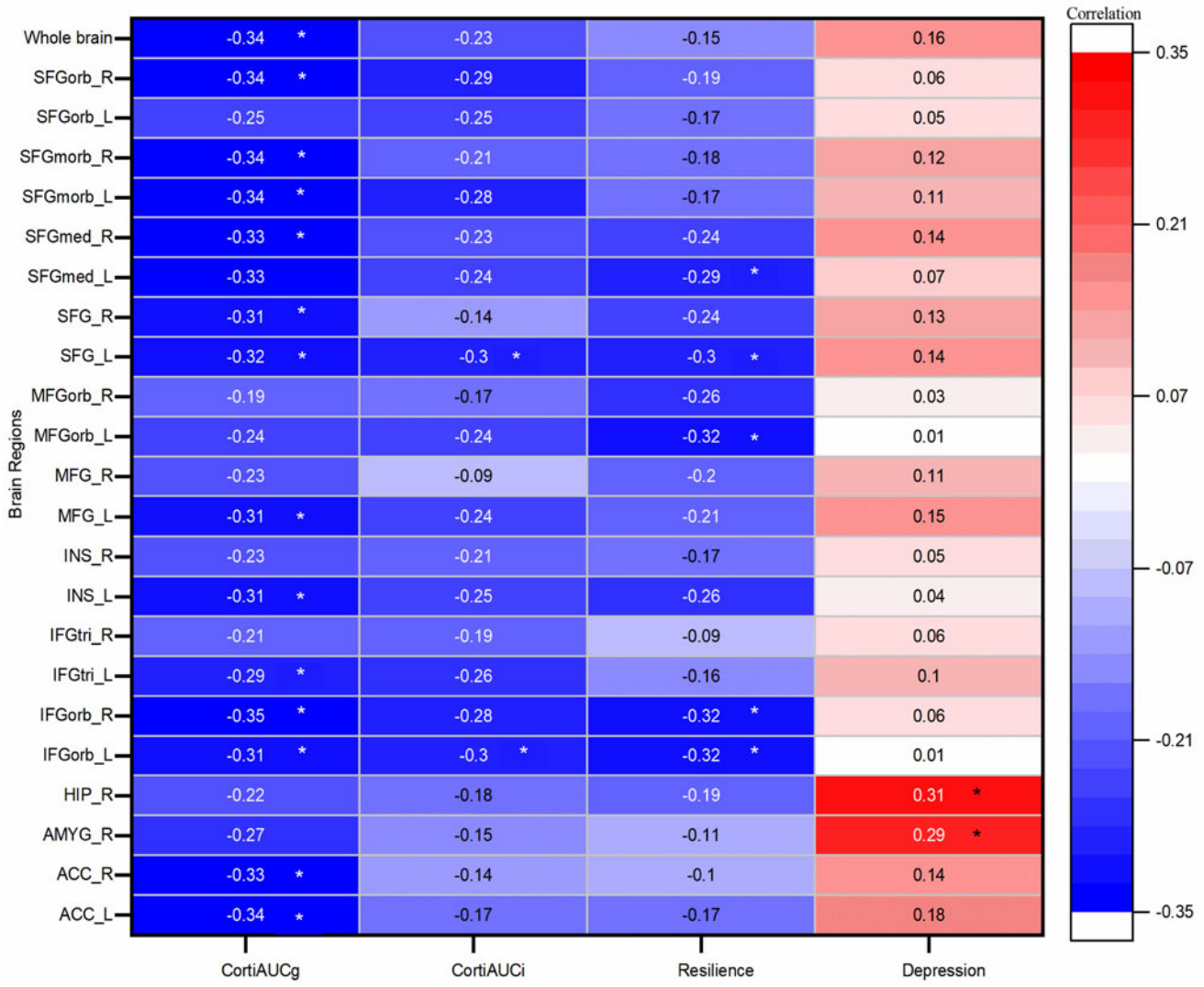

Figure. 4. Correlation between neural habituation (first block–last block) and stress reactivity as well as behavioral data in the ScanSTRESS paradigm. Neural habituation on the whole-brain level as well as regions of interest located in the dorsolateral prefrontal cortex (dlPFC) [including superior frontal gyrus (SFG) and middle frontal gyrus (MFG)], ventromedial prefrontal cortex (vmPFC) [including the inferior frontal gyrus (IFG), SFG, orbital part (orb), SFGmorb, SFG medial part (med), IFGorb, and anterior cingulate cortex (ACC)], and limbic area (insula) are accompanied by a blunted CortiAUCg, and neural habituation in the left dlPFC (SFG) and left vmPFC (IFGorb) are negatively correlated with CortiAUCi. Besides, neural habituation in the right amygdala and right hippocampus is positively correlated with the level of depression level. Lastly, the neural habituation in left dlPFC (mainly the SFG) and vmPFC (including the left SFGmed, left MFGorb, and both IFGorbs) is negatively correlated with the level of resilience. CortiAUCg and CortiAUCi indicate the areas under the curve with respect to ground and areas under the curve with respect to increases for salivary cortisol, respectively. * indicates FDR-corrected $q < 0.05$.

which suggests that neural habituation might serve as a general neural mechanism to explain the relationships between these psychiatric disorders and a blunted stress response.

Interestingly, the results showed that neural habituation in the prefrontal cortex is negatively correlated with resilience. Resilience can help individuals regulate negative emotions and generate adaptive coping behaviors during acute stress (Min, Yu, Lee, & Chae, 2013; Tugade & Fredrickson, 2007). Animal and human studies have identified that resilience can affect reward circuits and protect motivation functions (Der-Avakian, Mazei-Robison, Kesby, Nestler, & Markou, 2014; Vythilingam et al., 2009). Besides, since motivation and resilience are highly synergistic, some researchers have reported that motivation maintenance ability could be considered a direct indicator of resilience (Martin, 2002; Resnick, 2011). The prefrontal cortex, especially the vmPFC, is a key component of stress resilience (Holz et al., 2020; Sinha et al., 2016). A negative correlation between prefrontal habituation and resilience may underlie the protective mechanism of resilience, thus maintaining a relatively high motivation level despite uncontrollable, unpredictable, and threatening situations. Furthermore, the results also showed that resilience moderated the relationship between the vmPFC (right MFG, orb) habituation and endocrine stress response. Specifically, vmPFC habituation and a blunted endocrine response only existed in the low resilience group; interestingly, the high resilience group showed increased rather than decreased activity during acute stress. This phenomenon validates the positive correlation between an increase in vmPFC activity and resilience in previous research (Sinha et al., 2016), which means resilience could reduce vmPFC habituation, even regulate vmPFC activity to increase adversity and provide a sufficient stress response.

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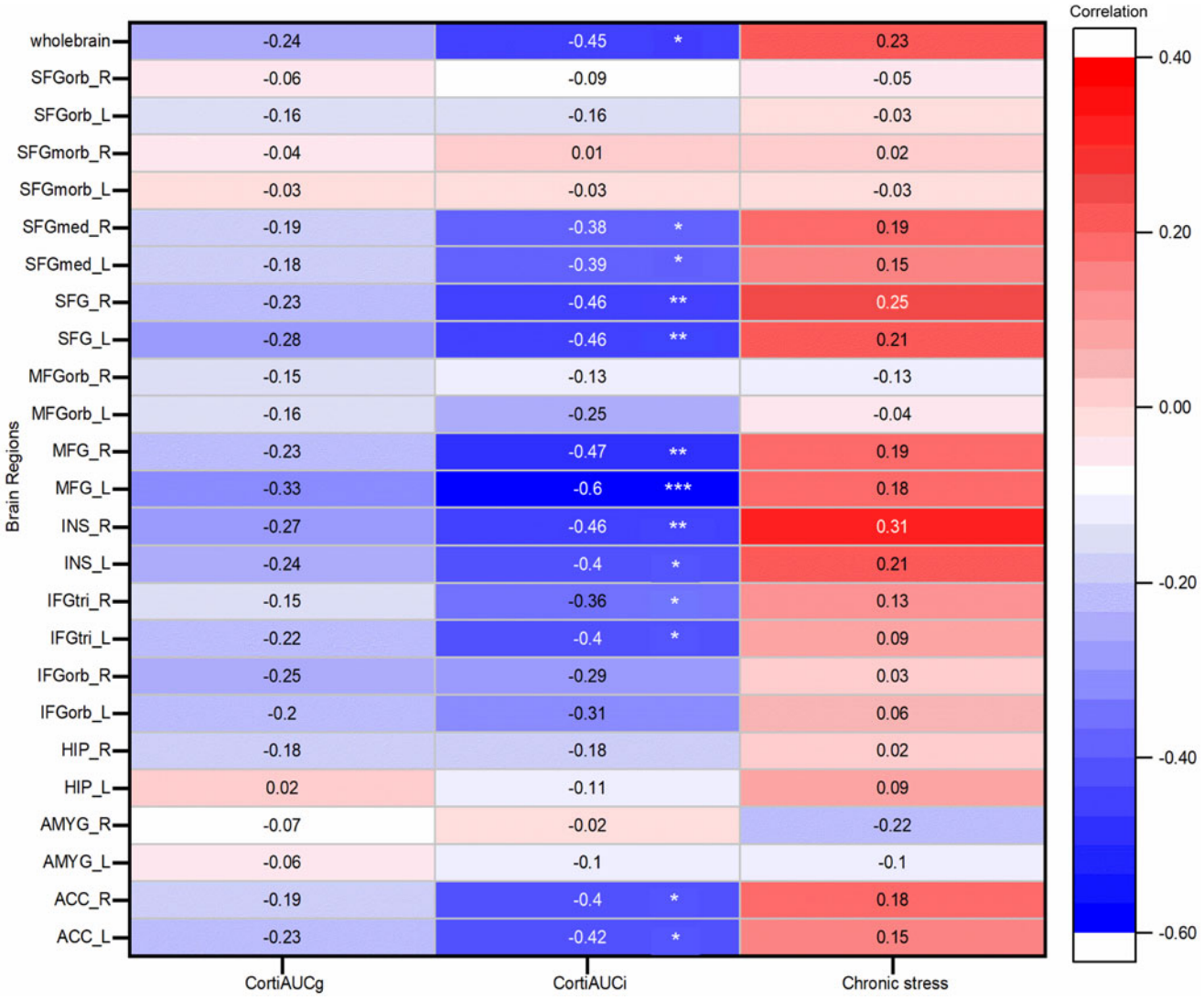

Figure. 5. Correlation analysis between neural habituation and stress reactivity in the MIST. ROIs were selected based on the ScanSTRESS results. Neural habituation on the whole-brain level, as well as regions of interest located in the dorsolateral prefrontal cortex (dlPFC) [including superior frontal gyrus (SFG) and middle frontal gyrus (MFG)], ventromedial prefrontal cortex (vmPFC) [including the superior frontal gyrus (SFG) medial part (med), inferior frontal gyrus (IFG) triangular part (tri), and anterior cingulate cortex (ACC)], and limbic area (Insula), are accompanied by blunted CortiAUCi. Besides, neural habituation in the right insula is positively correlated with the level of chronic stress ($p = 0.039$, uncorrected). CortiAUCg and CortiAUCi indicate the areas under the curve with respect to ground and areas under the curve with respect to increases for salivary cortisol, respectively. * indicates FDR-corrected $q < 0.05$, ** indicates FDR-corrected $q < 0.01$, *** indicates FDR-corrected $q < 0.001$.

In general, our research used a neural habituation perspective in consideration of the neural activity and motivation function during stress conditions, which not only provided solid evidence for the motivational dysregulation theory but also holds great methodological importance. Importantly, the current study recommended employing neural habituation rather than mean amplitude to measure neural activity during stress due to the following reasons. First, since the results showed significant neural activation differences across different sessions and blocks, using the mean amplitude to measure the neural activity during stress may decrease the sensitivity in detecting individual differences (Plichta et al., 2014). Second, the difficulty of building stable connections between neural systems and other systems, such as endocrine and psychological systems, has been reported in previous research (Henze et al., 2020). This inconsistency hinders researchers from unveiling interactions between different systems. Our results suggest that neural habituation could build stable relationships with the endocrine system. They indicate that neural habituation could serve as a potential neural marker that bridges the stress response at the neural, endocrine, physiological, and psychological levels. Third, the inconsistent results between different stress paradigms is another obstacle in the stress area (Berretz, Packheiser, Kumsta, Wolf, & Ocklenburg, 2021; Noack et al., 2019), and low general ability makes it impossible to compare results between different paradigms. Our results showed consistency across different paradigms, offering an indicator of horizontal contrast between different paradigms. Lastly, when dividing participants into cortisol responders and non-responders, there is a huge difference in neural habituation between responders and non-responders. Besides, the non-responder group contains more males than females. Former research has reported stronger endocrine response during stress in female participants (Van

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Paridon, Timmis, Nevison, & Bristow, 2017; Weekes et al., 2008), our study may underlie a neural mechanism to explain this gender difference.

This study has some limitations. First, the whole-brain level significant change between different sessions in the ScanSTRESS paradigm was not replicated in the MIST paradigms, potentially due to differences in task duration and difficulty. Future research should investigate these factors' influence on neural habituation during stress. Second, neural activity increased during control blocks, which may be due to participants gaining a sense of control and coping experience from high accuracy during the control task. Further research is needed to identify the psychological components of control blocks. Finally, the study did not measure resilience in the MIST paradigm, which may limit the generalizability of moderate results. Additionally, measuring hair cortisol levels could provide more insight into the relationship between neural habituation and the endocrine stress system in chronic stress.

Conclusions

These findings offer a general neural mechanism for the blunted endocrine stress response and the relationship between mental disorders and the blunted stress response, as well as how protective factors such as resilience could protect against this maladaptive process.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291723001666

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