Reward sensitivity modulates the brain reward pathway in stress resilience via the inherent neuroendocrine system

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ABSTRACT

In the previous 10 years, researchers have suggested a critical role for the brain reward system in stress resilience. However, no study has provided an empirical link between activity in the mesostriatal reward regions during stress and the recovery of cortisol stress response. Moreover, although reward sensitivity as a trait has been demonstrated to promote stress resilience, it remains unclear whether it modulates the brain reward system in stress resilience and how this effect is achieved by the inherent neuroendocrine system. To investigate these uncertainties, 70 young adults were recruited to participate in a *ScanSTRESS* task, and their brain imaging data and saliva samples (for cortisol assay) were collected during the task. In addition, we assessed reward sensitivity, cortisol awakening response, and intrinsic functional connectivity of the brain in all the participants. We found that left putamen activation during stress exposure positively predicted cortisol recovery. In addition, reward sensitivity was positively linked with activation of the left putamen, and this relationship was serially mediated by the cortisol awakening response and right hippocampus-left inferior frontal gyrus intrinsic connectivity. These findings suggest that reward sensitivity modulates reward pathways in stress resilience through the interplay of the diurnal stress response system and network of the hippocampus-prefrontal circuitry. Summarily, the current study built a model to highlight the dynamic and multifaceted interaction between pertinent allostatic factors in the reward-resilience pathway and uncovered new insight into the resilience function of the mesostriatal reward system during stress.

1. Introduction

Stress is an omnipresent phenomenon that can trigger or exacerbate a wide array of psychiatric disorders (e.g., depression) and physical health conditions (e.g., cardiovascular disease) (Cohen et al., 2007; Hammen, 2005; McEwen, 2004). Cortisol, the terminal product of the hypothalamic-pituitary-adrenal (HPA) axis, acts on organ systems to redirect energy resources for meeting demand (Herman et al., 2016). However, timely termination of cortisol hypersecretion is important for protecting individuals from the damage caused by stress (Lupien et al., 2009; McEwen and Gianaros, 2011). Therefore, efficient cortisol recovery following exposure to stress has been suggested as an important index for measuring stress resilience (Feder et al., 2019; Walker et al., 2017).

Given the potential adverse effects of stress, researchers have been committed to exploring the protective effects of stress resilience.

Research done over the last 10 years suggests a critical role of the reward system in conferring stress resilience to relieve cortisol stress response (Dutcher and Creswell, 2018; Holz et al., 2020). Based on the findings of behaviour and neurology studies on reward-stress resilience effects, as well as the close chemical transmission between the reward and stress regions of the brain, activation of the mesostriatal reward regions in association with reward-related activities during stress has been speculated to have an essential contribution to the down-regulation of cortisol overreaction (Dutcher and Creswell, 2018; van Steenbergen et al., 2021; Franklin et al., 2012; Tabibnia, 2020). Indeed, the suppression of brain reward regions as commonly observed during stress has been strongly associated with the onset and development of psychiatric disorders (Bogdan et al., 2013; Knowland et al., 2017). Conversely, disinhibition or activation of the mesostriatal reward regions during stress may contribute to reward-related processing and positive experience (Jiang et al., 2014), which originate from motivated

behaviours and active coping with stress. This form of neural representation is considered to be an important mechanism of stress resilience, and behavioural pattern has been found to promote cortisol stress recovery (Tabibnia, 2020; Folkman and Moskowitz, 2000a, b). It follows that greater activation of the mesostriatal reward regions, which are suppressed during stressful exposure, may be a potential neurobiomarker of stress resilience. However, to date, no study has reported or provided direct physiological evidence for an empirical link between greater activation of the mesostriatal reward regions during stress and efficient cortisol recovery.

Reward sensitivity is often used to measure individuals' reward function, which refers to the tendency and reactivity of individuals to approach and respond to reward-related stimuli at multidimensional levels of psychology and physiology (Corral-Frías et al., 2016; Ethridge et al., 2020). Emerging human studies suggest that higher reward sensitivity supports healthy adaptation under stressful circumstances; for example, higher reward sensitivity was found to modulate positive emotions, subjective stress feeling, and risk of psychopathology following stress (Corral-Frías et al., 2016; Tashjian et al., 2018; Vidal-Ribas et al., 2019). Moreover, increased positive emotions after stress result from reward-seeking behaviour even in stressful conditions (Corral-Frías et al., 2016). Considering the characteristics of highly reward-sensitive people, we inferred that they may pursue positive feedback as a kind of self-reward during stressful tasks, and this may be represented as stronger activation of reward-related brain regions during stress. In addition, previous studies have found that individuals with high reward sensitivity have efficient dopamine transmission, which is related to active coping with stress (Bowirrat and Oscar-Berman, 2005; Reuter et al., 2006). Summarily, these behavioural and neurobiological bases could rebound the neural reward system under stress (van Steenbergen et al., 2021; Cabib and Puglisi-Allegra, 2012). Therefore, we hypothesized that individuals with high reward sensitivity may show more activation of brain reward regions during stress.

Furthermore, a longitudinal study reported that children's reward sensitivity could predict their subjective stress levels after 3 years, which means that the effect of reward sensitivity on stress resilience can be regarded as a relatively stable ability or trait (Vidal-Ribas et al., 2019). This, then, informs the question of how individuals' reward sensitivity modulates the neural representation associated with stress resilience. The question about long-term neurobiological pathways linking the reward system with stress resilience is also one of the crucial issues in the field of stress. Recent reviews suggest that stress resilience is a complex and dynamic process that relies on the interaction of protective factors at multiple phenotypic levels, including the stress response system and neural circuitry function (Feder et al., 2019; Gan et al., 2022). When considering the effect of the neurobiological pathway of the reward system in fostering stress resilience, we need to explore the roles and interplay of the diurnal stress response system and stress regulation-related intrinsic connectivity in the brain, which was conceptualized as the function of the inherent neuroendocrine system.

Specifically, in the stress response system, diurnal cortisol secretion exhibits changes and surges within 30–45 min of awakening from night sleep, and this is known as the cortisol awakening response (CAR) (Pruessner et al., 1997). A study found that CAR was lower in healthy adults with high reward sensitivity, as a critical reference point within the healthy cortisol rhythm response (Monteleone et al., 2014). CAR may serve an adaptive function in the short term by mobilizing the body's resources to help the individual cope with perceived daily demands (Adam et al., 2006; Powell and Schlotz, 2012); however, persistent cortisol level elevation, which is always caused by allostatic load, is detrimental to the plasticity and function of the brain in the long term and linked to increased risk of stress-related psychiatric disorders (Adam et al., 2010; Vrshek-Schallhorn et al., 2013). Therefore, the total output of the CAR over a long period is regarded as an important index of the ability of the stress response system to regulate daily stressors (Klimes-Dougan et al., 2018), and the lower CAR of people with high

reward sensitivity reflects their efficient HPA axis and fewer expectations of strain. Furthermore, the better diurnal cortisol regulation in such people could contribute to plasticity of the neural networks involved in stress resilience.

In the neuroscience model of building resilience, in addition to mesostriatal reward function during stress (which is associated with up-regulating the positive), the down-regulating effect of the limbic-prefrontal circuitry on the negative is also indispensable to stress recovery (Ulrich-Lai and Herman, 2009; Tabibnia, 2020). In the limbic-prefrontal circuitry, the synergistic and separate regulation of stress response by the hippocampus (HIP) and prefrontal cortex is crucial for stress resilience, and these areas are particularly vulnerable to the neuromodulatory effects of excessive cortisol secretion (e.g., Metz et al., 2019; Pagliaccio, 2015; Labad, 2019; Ulrich-Lai and Herman, 2009). Thus, better functioning of the diurnal stress response system and HIP-prefrontal cortex could set a stress regulation-related tonic tone in individuals with high reward sensitivity, and disinhibition of reward-related brain regions during stress may benefit from this antagonistic coupling of stress load and reward function (Montoya et al., 2016; Porcelli et al., 2012). Therefore, in this study, we aimed to verify the effect of CAR on intrinsic connectivity of the HIP and prefrontal cortex, and explore the specific brain region in this circuitry that works with CAR to shape the neurobiological pathway that links reward sensitivity to neural representation in stress resilience.

In the current study, there were three research questions concerning the role and pathway of the reward system in stress resilience. They are as follows: Can activation of the mesostriatal reward regions during stress predict the recovery of cortisol levels? Can neural representation be modulated by reward sensitivity? How is this relationship further mediated by an individual's inherent neuroendocrine system? Based on the theories and inferences discussed earlier, we built a tonic-phasic neuroendocrine model for the reward-resilience effect (Fig. 1). In this model, reward sensitivity (as a trait) and the neuroendocrine system responsible for stress regulation (including the HPA axis and HIP-prefrontal circuitry) constitute the background and underlying structure of the reward-resilience effect. These entities set a tonic tone to support organisms to cope actively with sudden and new stressors, and the process is specifically characterized by activation of the mesostriatal reward regions during stress. Based on this model, we hypothesized that reward sensitivity can modulate the activation of brain reward regions during acute stress, and that the regulation is serially mediated by the diurnal HPA axis function and intrinsic connectivity of the HIP-prefrontal circuitry. To test these hypotheses, we conducted a study that combined reward sensitivity, the mean value of the incremental area under the curve (AUC_G) (Pruessner et al., 2003) for CAR (recorded for 3 days in a week), resting-state intrinsic functional connectivity, and brain activation during psychosocial stress tasks. The experiment was conducted among young adults, using blood-oxygen-level-dependent functional magnetic resonance imaging (fMRI), as well as cortisol levels. Correlation and chain mediation analyses were implemented to determine the possible associations between the variables.

2. Materials and methods

2.1. Participants

Eighty young adults were recruited from a local university via advertisements. Some participants were excluded due to missing behavioural data (two participants), univariate outliers (one participant), failure to collect saliva sample at the right time (one participant), excessive head movement in any run (>2.5 mm, three participants) during task-dependent fMRI scan, excessive head movement during resting-state fMRI scan (one repeated participant), and withdrawal due to physical discomfort (three participants). Therefore, the final sample comprised 70 participants (31 females and 39 males; age range = 18–26 years; mean age = 20.06 ± 1.92 years).
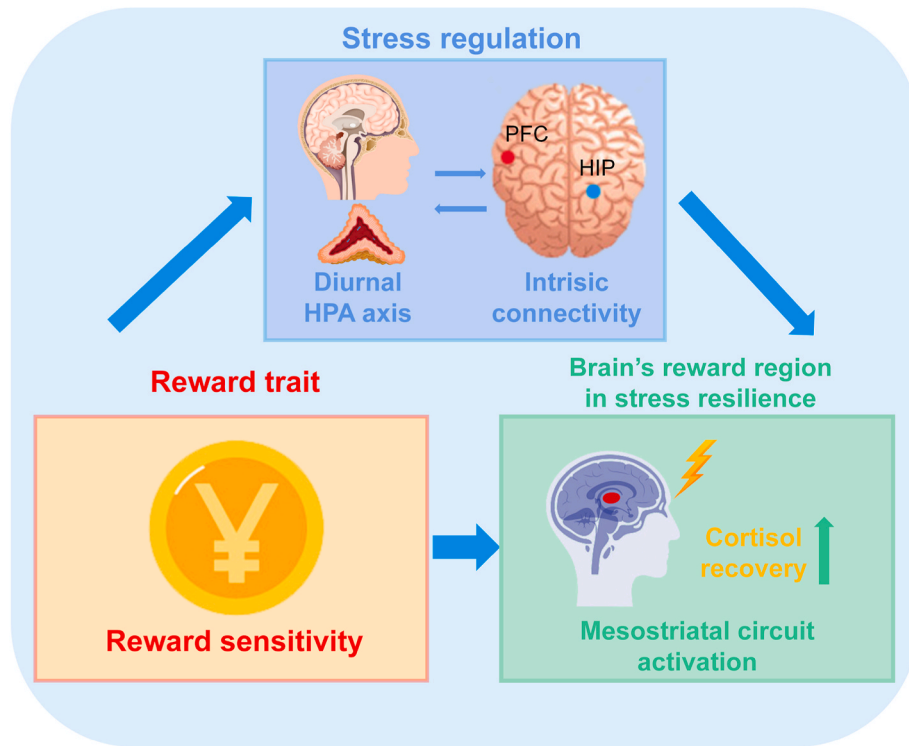
Fig. 1. The tonic-phasic neuroendocrine model of the reward system in stress resilience.

We ascertained participants' eligibility, current health status, and health behaviours using their self-reports. Exclusion criteria were acute or chronic psychiatric or somatic diseases, psychotropic or glucocorticoid medication intake, alcohol/drug abuse, and enrolment in other fMRI studies. All the women were tested during the luteal phase of their menstrual cycle (determined by oral reports). Participants were asked not to smoke on the day of their appointment and not to engage in strenuous exercise, consume alcohol or caffeine, eat, or brush their teeth
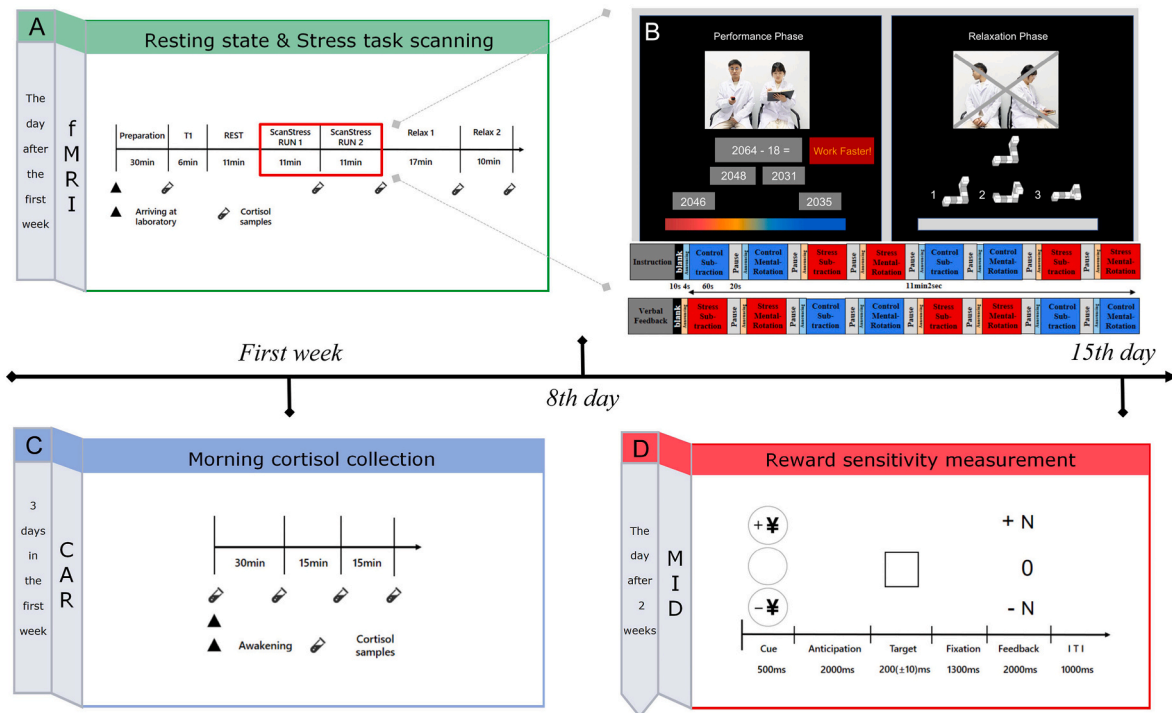

Fig. 2. The experimental procedure and paradigms. (A) Process of fMRI scanning. **(B)** Subtraction and figure-matching tasks are presented separately in the performance and relaxation phases of the stress paradigm. The design of the ScanSTRESS paradigm has two runs, which are preceded by an instruction phase. **(C)** The time points of morning cortisol collection. **(D)** Process of MID task.
fMRI: functional magnetic resonance imaging; MID: monetary incentive delay.

within 1 h before the session. All participants provided written informed consent to participate. All protocols were approved by the local institutional review board and complied with the standards of the Declaration of Helsinki.

2.2. Measurements

2.2.1. Psychosocial stress task

Neural psychosocial stress processing was studied using the *ScanSTRESS* paradigm, a recent tool for stress induction in the MRI environment (Streit et al., 2014) (Fig. 2A & 2B). In the stress condition, participants performed tasks that challenged serial subtraction and mental rotation abilities under time pressure. For psychosocial stress induction, two investigators in laboratory coats gave disapproving feedback when the participants answered wrongly or slowly on the live video stream. In the control condition, participants performed figure- and number-matching tasks without time pressure or feedback. Details of the tasks are presented in Supplemental Material.

2.2.2. Cortisol awakening response

Participants were instructed to collect saliva at the time of awakening, then after 30, 45, and 60 min (Fig. 2C). They collected the sample by placing a cotton bud into their mouths, chewing on it for 3 min, and spitting it back into the sampler. They were instructed not to have breakfast or brush their teeth within 30 min before a sample was collected. Additionally, participants were reminded to refrain from touching the cotton buds with their hands or any other objects during the process to avoid contaminating the sample. The saliva was collected in a saliva collector (Salivette SARSTEDT, Germany). All samples were put in track caps (e.g., Medication Event Monitoring: MEM cap) that electronically monitored sampling time to ensure that the samples were collected on time. Samples were stored in a refrigerator at $-20\ ^\circ$C.

2.2.3. Reward sensitivity

Reward sensitivity was quantified in the participants by using a monetary incentive delay (MID) task and refined for behavioural research (Dillon et al., 2009; Knutson et al., 2000; Oumeziane et al., 2017). There were four blocks of 24 trials. Trials began with one of three visual cues (lasting 500 ms) that signalled potential outcomes: a black circle with the Chinese currency symbol ("¥") indicated a monetary contingency (i.e., "+¥" and "-¥" symbols respectively expressed reward and penalty; N = 64), and an empty circle indicated a no-incentive trial (i.e., no reward or penalty; N = 32). Following an inter-stimulus interval of 2,000 ms, a black box (with white background) was presented for a variable duration. Participants were instructed to press the left mouse button as quickly as possible to win money or avoid losing money. Following a second inter-stimulus interval of 1,300 ms, visual feedback (lasting 2,000 ms) showed delivery of "+N" (e.g., "+3", indicating the amount of money gained), "-N" (e.g., "-3", indicating the amount of money lost), or "0" (indicating no change). Monetary amounts of rewards and penalties ranged from ¥1 to ¥3. Reward trials ended with gain or no change, punishment trials ended with loss or no change, and no-incentive trials always ended in no change. An inter-trial interval of 1,000 ms separated the trials. The schematic of the MID task is shown in Fig. 2D.

Participants were told that the computer would automatically sum up the money they won finally, and they would be given this money at the end of the experiment. Before MID tasks, the participants completed a practice task (20 trials) to determine the initial presentation time of the target page (up and down from 200 ms) based on the participants' response time. The task enabled us to adjust the target presentation time so that participants maintained approximately 67% accuracy in all trials. After the second and fourth blocks, participants were asked to rate, on a scale of 1–5, their affective responses to cues and feedback for the arousal (1 = very low, 5 = very high) and valence (1 = very negative, 5 = very positive). Affective ratings of reward have been widely used as

indices to estimate the sensitivity of emotional response to reward (Dillon et al., 2009; Knutson et al., 2003; Martucci et al., 2018). These indices have reliable validity, as they are sensitive for monitoring changes in reward sensitivity that is related to chronic stress and depressive symptoms (Dillon et al., 2009; Pizzagalli et al., 2009).

2.3. Experimental procedure

We measured and recorded the participants' CAR for 3 days in a week, performed brain scans during the resting state and *ScanSTRESS* tasks, and finally measured reward sensitivity 2 weeks after the acute stress tasks (Fig. 2A–D). The *ScanSTRESS* task was conducted between 1:30 p.m. and 5:00 p.m. to control for the circadian rhythm of cortisol. Participants rested for 30 min and filled out the questionnaires after arriving at the laboratory. Saliva collection for cortisol measurement was done at five time points: before participants entered the scanner, after the first run of the task (run1), after the second run of the task (run2), after a 17-min rest (relax1), and after a 10-min rest (relax2). To obtain saliva samples while a participant was in the scanner, a researcher handed a saliva tube to the participant at the end of each run. Participants put the tube in their mouths and chewed for about 2 min. Afterward, they expelled the tube and handed it back to the researcher, at which point they were ready for the next experimental task. Each sampling lasted about 5 min. To avoid interaction between stress and reward tasks, participants were asked to complete the MID task in the laboratory 2 weeks later to evaluate their reward sensitivity.

2.4. Image data acquisition and pre-processing

Functional and anatomical whole-brain images were acquired on a SIEMENS PRISMA 3 T scanner (Erlangen, Germany). We acquired 331 volume-functional images from each participant during the ScanSTRESS task, using a T2-weighted gradient echo-planar imaging sequence. Each participant also underwent one resting-state fMRI scan, during which we acquired 235 volume-functional images (repetition time = 2,000 ms; echo time = 30.0 ms; slice thickness = 2.00 mm; field of view = 224 × 224 mm^2; voxel size = 2.0 × 2.0 × 2.0 mm^3; and flip angle = 90°). Pre-processing of the fMRI data was done using Statistical Parametric Mapping software (SPM12, Welcome Trust Centre for Neuroimaging, University College London, UK). The first five resting-state data volumes were discarded to stabilize the magnetic resonance signal. The remaining images were corrected for slice acquisition timing, realigned for six head motion parameters correction, spatially normalized into the standard Montreal Neurological Institute (MNI) space in 2.0 × 2.0 × 2.0 mm^3 voxel sizes, and smoothed by convolving a 6-mm isotropic three-dimensional Gaussian kernel. Detailed procedures are provided in Supplemental Material.

2.5. Statistical analyses

2.5.1. Reward sensitivity

A recent review indicated that activity of the mesostriatal reward circuit mainly conveys positive valence associated with expected rewards (Gu et al., 2019); thus, we focused on the sensitivity of individuals' emotional response to reward cues in the valence dimension.

2.5.2. Cortisol awakening response and the stress task

The concentrations of cortisol in the saliva samples were analysed using enzyme-linked immunosorbent assay (IBL-Hamburg, Germany), according to the manufacturer's instructions. The sensitivity of the cortisol assay was 0.005 μg/dL, and the inter-assay coefficient of variation was 11.55%.

To measure the daily total CAR and relatively stable CAR in the long term (Tian et al., 2021), we calculated the average AUC$_G$ for CAR for 3 days in a week. During the stress tasks, we analysed data on the participants' cortisol responses to stress at each time point. The change rate

of cortisol stress response during the recovery period represented individual differences in stress resilience. The recovery period lasted 32 min (including 17-min relaxation and 5-min specimen collection); therefore, we took time required for change (ΔX). We then adopted the change in stress response over 32 min between time points 3 (after run2) and 5 (the end of recovery) as the difference in stress resilience indices (ΔY). The ratio of these two parameters is the cortisol decline slope (denoted as R; $R = \Delta Y/\Delta X$). The larger R is, the steeper the slope, and the faster the decline in individuals' stress response. We examined all variables for distributional properties and deleted univariate outliers.

One-way repeated-measures analysis of variance (ANOVA) was used to test whether there was a difference in AUC_G of CAR among the 3 days of sample collection. It was also used to test the main effect of acute stress induction, with measured time as a within-subject variable. All results of repeated-measures ANOVA were subjected to Greenhouse-Geisser correction. Post-hoc tests were performed using Bonferroni-adjusted t-tests. Analyses were conducted using IBM SPSS Statistics for Windows, version 20.0.

2.5.3. Analysis of activation of the mesostriatal reward regions

Neuroimaging data were processed and analysed using SPM12. First-level effects were estimated by creating a general linear model, which incorporated two conditions (stress and control) convolved with the canonical hemodynamic response function and six movement parameters as covariates of noninterest. A high-pass temporal filter with a cut-off period of 128 s was applied. Second-level analyses were conducted using random-effects models to investigate group effects. The resulting statistical map was set at a threshold of $P < .001$ at the voxel level and cluster-level $P < .01$ (FDR-corrected) for the whole-brain exploratory analyses.

To examine the role of activation of the mesostriatal reward system in stress resilience, we conducted a region-of-interest analysis. Based on previous studies, we speculated that the inhibited mesostriatal reward regions in the stress versus control contrast are responsible for the functions we are concerned about, so we only focused on them. The region of interest was defined using the peak MNI coordinates of the bilateral mesostriatal reward regions in the stress vs. control contrast based on the Automated Anatomical Labeling (AAL90) template. The REX toolbox extracted the mean contrast values in spheres with a 6-mm radius. Meanwhile, we conducted subsequent correlation and mediation analyses.

2.5.4. Intrinsic functional connectivity analysis

To explore the target regions of HIP intrinsic connectivity that are significantly correlated with CAR, resting-state data were analysed using seed-based intrinsic functional connectivity analysis, which was conducted separately for the left and right HIP seeds with the CONN toolbox version 19c (Whitfield-Gabrieli and Nieto-Castanon, 2012). Pre-processing of resting-state images was performed using the CONN FC toolbox. Detailed procedures are provided in Supplemental Material. Individual-level connectivity maps were inputted into a second-level multiple regression analysis, with CAR as the covariate of interest, and sex, age, and depression as nuisance variables. Significant clusters were determined at a height threshold of $P < .001$ at the voxel level and an extent threshold of $P_{FDR} < 0.05$ at the corrected whole-brain cluster level. Parameter estimates were extracted from significant clusters.

2.5.5. Mediation analysis and covariates

The mediation models and statistical tests were examined using PROCESS in SPSS, based on regression analysis. The significance of mediation models has been assessed with the bootstrap method (Baron and Kenny, 1986; Wen and Ye, 2014). Emerging research suggests that differences exist in sex, age, and depression level in response to acute psychosocial stress (Chida and Hamer, 2008; Foley and Kirschbaum, 2010; Kajantie and Phillips, 2006), and that these variables have a marked effect on reward sensitivity (Alloy et al., 2016; Schreuders et al.,

2018; Warthen et al., 2020). Therefore, we included sex, age, and depression as covariates in our analyses.

3. Result

3.1. Descriptive data

Descriptive data of reward sensitivity, CAR AUC_G, and acute cortisol secretion are presented in the Supplemental Material (Table S1). CAR at each time point and the average for the 3 days are shown in Fig. 3A, and the descriptive data are presented in the Supplemental Material (Table S2). One-way ANOVA showed no significant difference in the AUC_G of CAR among the 3 days ($F_{(2, 122)} = 1.255$, $P = .289$, $\eta^2 = 0.020$), even after controlling for sex, age, and depression. Cortisol levels at all time points during acute stress are shown in Fig. 3B. For acute stress responses, one-way ANOVA with time point as a within-subject variable showed that time had a significant main effect on acute stress responses, even after controlling for sex, age, and depression: stress induction resulted in robust increases in salivary cortisol level ($F_{(4, 264)} = 3.774$, $P = .020$, $\eta^2 = 0.058$). Post-hoc analysis showed that the cortisol levels of the participants after run1 ($M_{run1} = 0.22$, standard deviation [s.d.] = 0.12) and run2 ($M_{run2} = 0.23$, s.d. = 0.16) were both higher than baseline levels ($M_{baseline} = 0.17$, s.d. = 0.10), and cortisol levels after relax1 ($M_{relax1} = 0.22$, s.d. = 0.14) were higher than the levels at the end of recovery ($M_{relax2} = 0.19$, s.d. = 0.13) (all $P < .05$).

3.2. Mesostriatal reward regions in stress resilience

The main brain regions that were activated under stress > control conditions are shown in Fig. 4A and B and partly labelled. All significantly activated brain regions are presented in the Supplemental Material (Tables S3A and S3B).

Compared with control conditions, stress induction only engaged and mainly inhibited the bilateral putamen ($P_{FDR} < .01$, whole-brain corrected). After controlling for sex, age, and depression, correlation analyses indicated significantly positive association between left putamen deactivation estimates in the stress > control contrast and cortisol decline rate (left MNI coordinates: x = −27, y = 0, z = 0; $r = 0.31$; $P = .010$; right MNI coordinates: x = 24, y = 12, z = −9; $r = 0.23$; $P = .060$) (Fig. 4C). Correlation analyses also indicated significantly positive association between reward sensitivity and left putamen deactivation estimates in the stress > control contrast ($r = 0.24$; $P = .048$) after controlling for sex, age, and depression (Fig. 4D). However, reward sensitivity was not significantly related to right putamen deactivation estimates ($r = 0.04$; $P = .746$).

In addition, the average accuracy of each block in the serial subtraction task was positively correlated with left putamen activation during stress ($r = 0.25$; $P = .035$), and it was also marginally positively correlated with reward sensitivity ($r = 0.22$; $P = .064$). Complete results are shown in Supplemental Material (Table S4).

3.3. Chain mediation analysis of the relationship between reward sensitivity and putamen activation estimate via CAR and HIP-IFG intrinsic connectivity

Before validating the chain mediation model, we investigated how CAR modulates the intrinsic functional connectivity of the HIP. Whole-brain multiple regression analyses were conducted separately for the left and right HIP intrinsic connectivity targets, with CAR as the covariate of interest while controlling for other covariates. These analyses revealed significant clusters in the inferior frontal gyrus (IFG): intrinsic connectivity of the right HIP and left IFG (MNI coordinates: x = −42, y = 14, z = 22) negatively correlated with CAR ($P_{FDR} = .006$) (Fig. 5A and B; Table S5 in the Supplemental Material), but it positively correlated with left putamen activation during psychosocial stress ($r = 0.30$, $P = .015$). The analysis was controlled for sex, age, and depression (Fig. 5C).
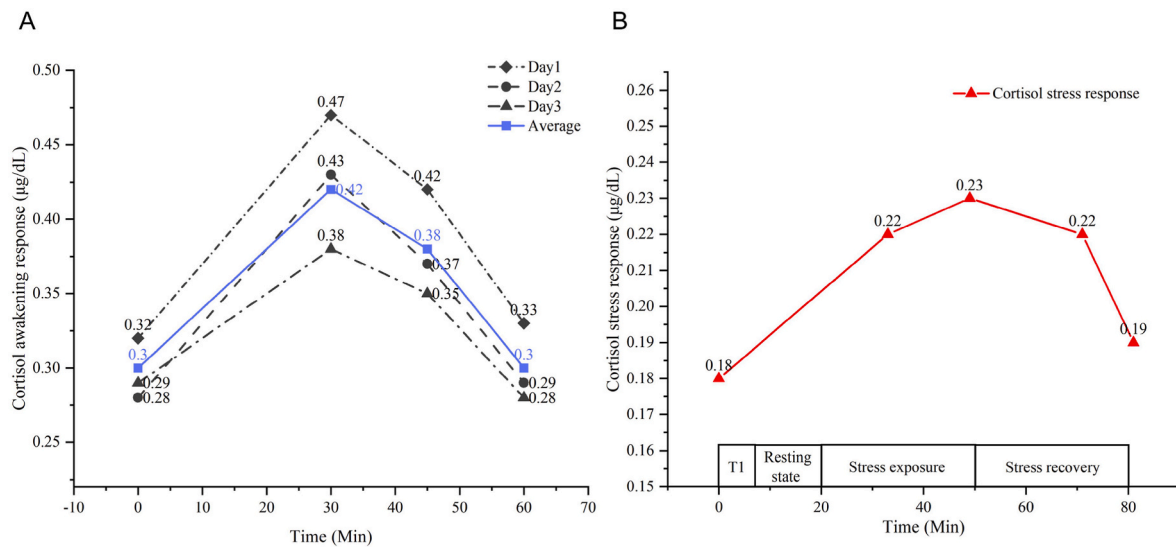
Fig. 3. **The dynamic change in cortisol levels. (A)** Separate and average cortisol levels for the 3 days at four time points in the morning. **(B)** Cortisol levels during acute stress at all time points.
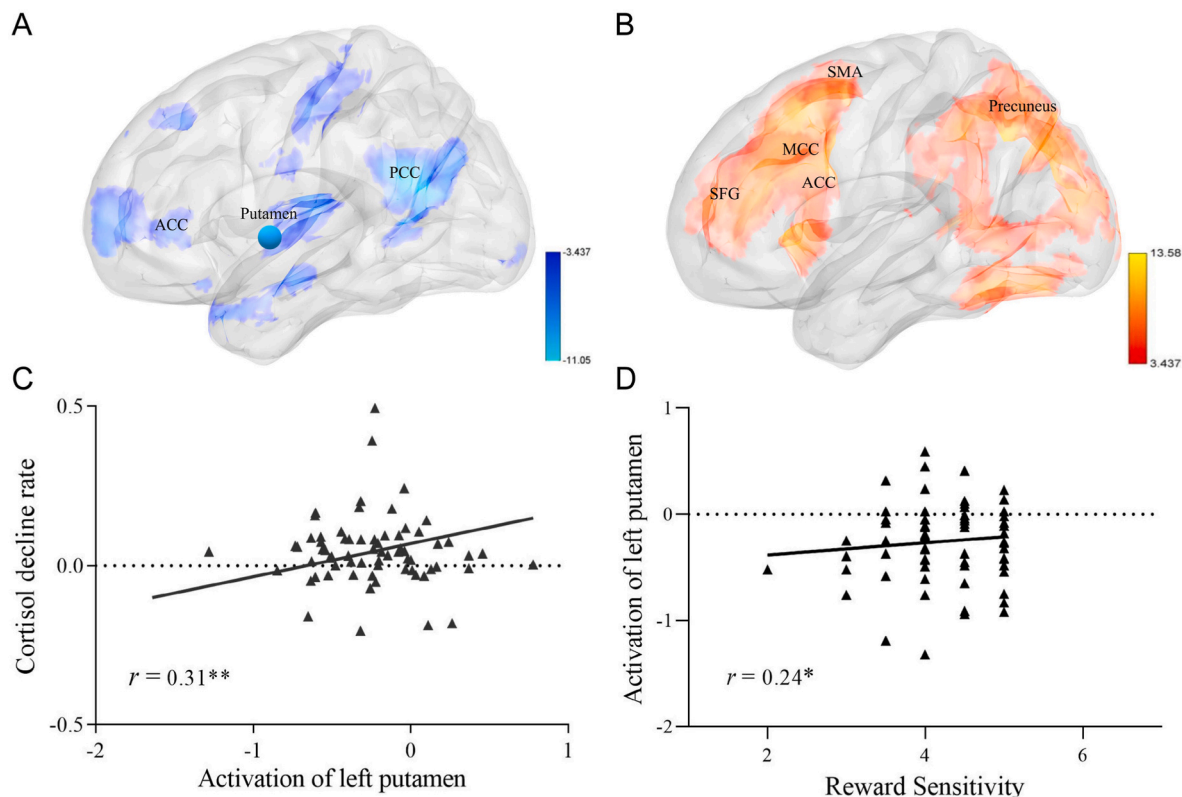

Fig. 4. **Activation of the left putamen predicts cortisol recovery. (A)** The brain map shows significantly decreased activity (shown in blue-cyan) during stress, relative to neutral conditions, in the putamen, ACC, and PCC ($P_{FDR} < .01$, whole-brain corrected). **(B)** The brain map shows the main areas of significantly increased activity (shown in yellow-red) during stress, relative to neutral conditions, in the SFG, ACC, MCC, SMA, and precuneus ($P_{FDR} < .01$, whole-brain corrected). **(C)** The deactivation estimate of the left putamen in the stress > control contrast positively correlated with cortisol decline slope ($r = 0.31$, $P = .010$) after controlling for sex, age, and depression. *$P \leq .05$. **(D)** Reward sensitivity positively correlated with the deactivation estimate of the left putamen in stress > control contrast ($r = 0.24$, $P = .048$) after controlling for sex, age, and depression. *$P \leq .05$.

SFG: superior frontal gyrus; ACC: anterior cingulate gyrus; PCC: posterior cingulate gyrus; MCC: middle cingulate gyrus; SMA: supplementary motor area. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Furthermore, to investigate the role of CAR and intrinsic functional connectivity in the pathway from reward sensitivity to putamen activation during acute stress, we conducted mediation analyses while controlling for the covariates. The result revealed a chain mediating pathway, with higher reward sensitivity initially linked to lower CAR, which then related to stronger intrinsic connectivity of the right HIP and left IFG, and further led to greater putamen activation during psychosocial stress (effect = 0.020, standard error = 0.015, 95% confidence
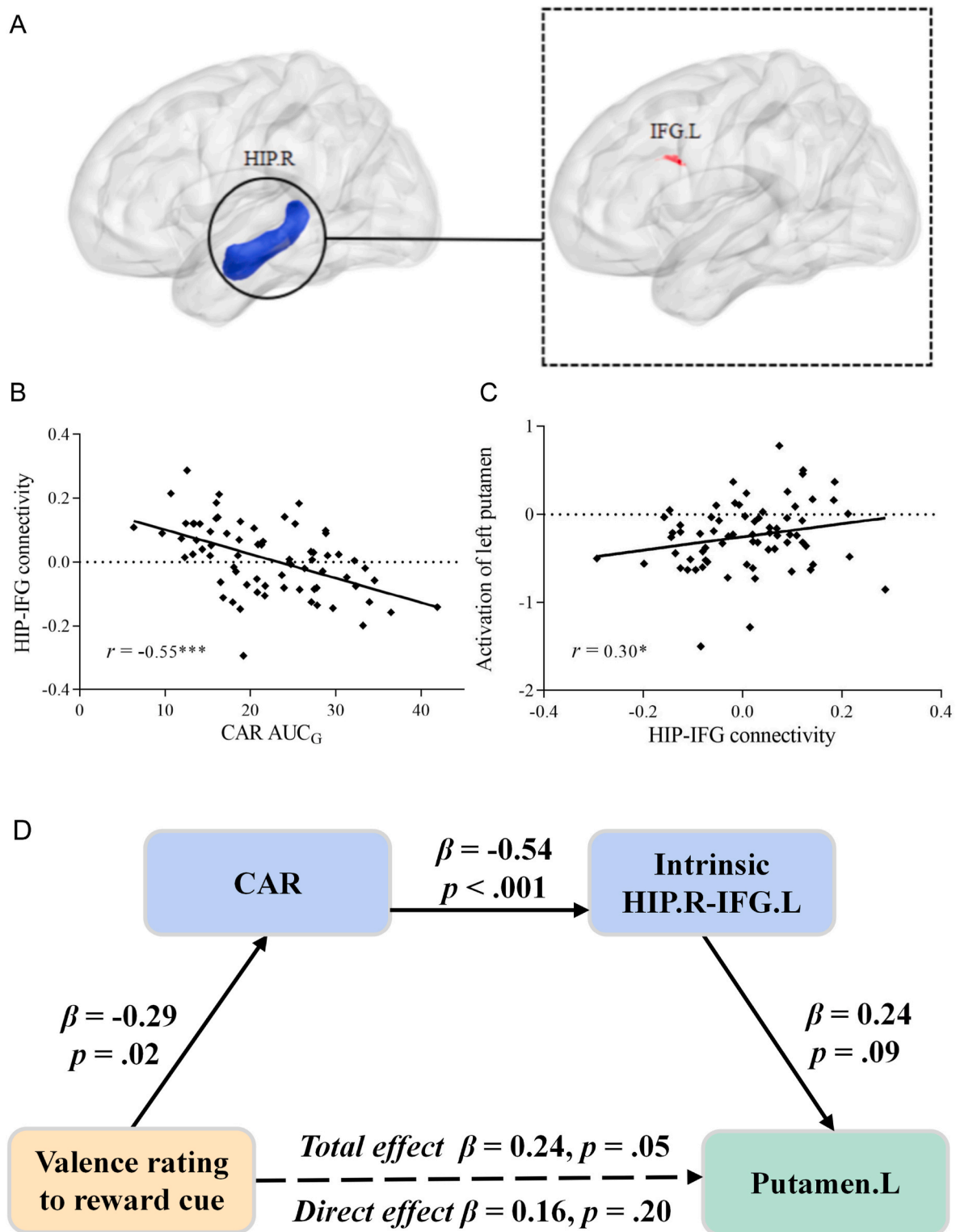
Fig. 5. Reward sensitivity affects intrinsic connectivity of the HIP.R-IFG.L through CAR. (A) A representative brain map showing the intrinsic connectivity of the right HIP and left IFG, which was significantly related to CAR. **(B)** CAR negatively correlated with intrinsic connectivity of the right HIP and left IFG ($r = -0.55$, $P_{FDR} = .006$). **(C)** The intrinsic connectivity of the right HIP and left IFG positively correlated with deactivation estimate of the left putamen in the stress > control contrast ($r = 0.30$, $P = .015$). **(D)** The chain mediation model demonstrated a mediatory role of CAR and intrinsic connectivity of the right HIP and left IFG on the association between reward sensitivity and putamen activation during the stress task.

HIP: hippocampus; IFG: inferior frontal gyrus; CAR: cortisol awakening response.

interval = [0.001, 0.059]) (Fig. 5D; Table S6 in the Supplemental Material). These results indicate that higher reward sensitivity is related to greater left putamen activation during psychosocial stress through the CAR and intrinsic connectivity of the right HIP and left IFG.

4. Discussion

The current study aimed to investigate whether activation of the reward system of the brain is linked to cortisol recovery after acute stress exposure and how this neural representation is modulated by reward sensitivity. We found that greater activation of the left putamen during stress was positively correlated with cortisol decline rate in the recovery period. Moreover, when coping with stress, higher reward sensitivity was associated with greater putamen activation through the CAR and intrinsic connectivity of the right HIP and left IFG. Our findings provide initial human neuroimaging evidence of the potentially important contribution of the mesostriatal reward system to cortisol stress recovery. They also underscore the neuromodulatory effect of diurnal cortisol regulation on the HIP-IFG circuitry, which acts as the crucial mediator of the neurobiological pathway from reward sensitivity to stress resilience.

4.1. Brain reward system in cortisol stress recovery

Our results showed that activation of the left putamen during stress tasks could predict the decline rate of cortisol level, and it was also positively correlated with the individual's accuracy in serial subtraction tasks. Studies conducted in humans and primates have indicated that putamen neurons encode reward value and direction of actions, which guide the process leading from action-value mapping to goal-directed behaviours (Hori et al., 2009; Liu et al., 2011; Tobler et al., 2006). In the psychosocial stress paradigm, consistent failure with accompanying negative feedback can inhibit the individual's expectation and motivation to complete a task, and it is characterized by deactivation of the putamen (Mattfeld et al., 2011). However, obtaining rewards and escaping punishments are the natural impetus for human behaviour. The ability to derive self-reward from avoiding failure and answering correctly is gradually acquired during task processing, and it is characterized by disinhibition of the putamen under acute stress. In this study, since task difficulty was adjusted adaptively through the program, better task performance indicated that the participants could still strive for positive feedback and benefit from the task even when they experienced frequent negative evaluation. The phenomenon 'gaining positive from stress' was thought to be a crucial psychological mechanism for building stress resilience and also reported to predict adaptive hormonal responses to laboratory stressors (Folkman and Moskowitz, 2000b). Specifically, the cumulative self-rewarding experience may create a dynamic promotion effect, accompanied by a spiral of positive emotions such as inspiration, which in turn facilitates positive reappraisal by expanding cognitive perspective, such as transforming the stressor from a threat into a challenge (Catalino and Fredrickson, 2011). Over time, the bolstering positive affect helps the individual to build psychological resources for supporting continued adaptive coping (Folkman and Moskowitz, 2000a). Conversely, demotivation and negative mood in the face of denial and failure may induce dysregulated cortisol secretion in response to psychosocial stress, resulting in increased risk of mental illnesses (Hammen, 2005). Therefore, pursuing and obtaining reward experience from stress tasks may be the psychological mechanism underlying the effect of disinhibition of the putamen on stress resilience.

Underlying behavioural performance, pharmacological studies highlight the role of dopamine in fostering stress resistance. Coping with stress increases dopamine excitability in the mesostriatal circuit (Douma and de Kloet, 2019), and some researchers have theorized that the dopamine release leads to stress adaptation. Such adaptation serves as a critical feedback mechanism to prevent exaggerated stress responses and is associated with active coping with stressful events (Cabib and Puglisi-Allegra, 2012; Sullivan, 2004; Sullivan and Dufresne, 2006). In

the present study, dopamine may have been released during individuals' motivational behaviours in pursuit of positive feedback and reward experiences, which were accompanied by putamen activation (Schultz, 1998). Thus, we speculated that dopaminergic function in the putamen might also be a potential neurophysiological mechanism for its contribution to cortisol recovery. In addition to the functional and neurochemical mechanism, there is considerable anatomical link among the brain regions that subserve reward processing and stress responses (Dutcher and Creswell, 2018): for example, limbic reward system structures (including the putamen) project to the hypothalamus, which is responsible for regulating physiological stress response (Ulrich-Lai and Herman, 2009; Haber and Knutson, 2010; Heimer et al., 1991). Thus, the relationship between putamen activation and efficient cortisol recovery may benefit from the neuroanatomy of the brain's reward and stress system.

4.2. Reward sensitivity modulates activation of the brain reward regions during stress via the inherent neuroendocrine system

The current study found that reward sensitivity can predict left putamen activation during stress, and both reward sensitivity and left putamen activation were positively correlated with individuals' performance in the serial subtraction task. The nature of people with high reward sensitivity encourages them to positively anticipate and seek reward, even under stress. This serves as a kind of stress-resilient coping mechanism (Corral-Frías et al., 2016; Folkman and Moskowitz, 2000a; Hu and Yang, 2021; Hu et al., 2021). This state of focusing on challenging tasks and obtaining pleasure during active performance is similar to the 'flow', which depends on individual differences in the dopaminergic neurotransmission that is mainly derived from the putamen (De Manzano et al., 2013). This dopamine function was found to be strong in people with high reward sensitivity (Bowirrat and Oscar-Berman, 2005); therefore, these dopaminergic and personality advantages could promote positive seeking during stress in people with high reward sensitivity.

More importantly, we combined endocrine and neuroimaging data and found that the 3-day average CAR during a week and intrinsic connectivity of the right HIP and left IFG serially mediated the indirect associations between reward sensitivity and putamen activation during stress. At first, consistent with existing reports, reward sensitivity was negatively associated with CAR in healthy adults (Monteleone et al., 2014). The lower CAR in individuals with high reward sensitivity suggests that they may have effective diurnal cortisol regulation and lower anticipated or perceived stress, and these effects may benefit from trait and state positive affects, which are accompanied by high reward sensitivity (Miller et al., 2016; Polk et al., 2005; Smyth et al., 1998; Steptoe et al., 2007). In the present study, CAR is thought to rapidly recruit energy for the anticipated workload, cognitive demands, and stress of the upcoming day based on prospective memory representations theory (Fries et al., 2009; Kunz-Ebrecht et al., 2004; Schlotz et al., 2004). Individuals report more positive to reward cue if they have more positive and optimistic anticipation of future rewards, which were found to mitigate the cortisol surge at the beginning of the day by reducing worry (Nicolson et al., 2020).

Furthermore, our study initially found that CAR can modify the intrinsic HIP-IFG connectivity based on the neuroregulatory effects of sustained cortisol secretion on the plasticity of the HIP and prefrontal cortex (Kremen et al., 2010; Labad, 2019). Neuroendocrinological studies have suggested that CAR may support readiness by decreasing subcortical activation and increasing cortical activation (Clow et al., 2010). The neuroendocrine mechanism lies in the rapid non-genomic and slow genomic actions of glucocorticoids on the limbic-frontal networks, especially the HIP and prefrontal cortex that are rich in related receptors (de Kloet et al., 2019; McEwen et al., 2015). However, sustained high CAR induced by chronic stress could impair executive control and stress regulation by triggering structural and functional changes

in the HIP and prefrontal cortex, and thus form a susceptibility factor for stress-related diseases (Arnsten, 2009; Brown et al., 2005; de Kloet et al., 2014; Izquierdo et al., 2006; Pechtel and Pizzagalli, 2011). For example, one empirical research found that greater CAR was related to impairment of executive function and increased stress perception, and this relationship was found in individuals who had high early-life stress and generally demonstrated deficits in reward sensitivity (Butler et al., 2017; LoPilato et al., 2020; Novick et al., 2018). Thus, it is plausible that efficient functioning of the HPA axis in people with high reward sensitivity could protect the HIP-prefrontal circuitry from the neurotoxic effects of excessive cortisol secretion. In that way, the stronger HIP-IFG intrinsic connectivity in such people may mean better synergistic regulation effect on the HPA axis activity, which in turn creates a virtuous circle and sets a better stress regulation-related tonic tone in individuals with high reward sensitivity. Conversely, people with anhedonia have disrupted prefrontal regulation of cortisol rhythmic responses due to impaired reward function, leading to mental illness (Putnam et al., 2010).

Furthermore, the association of stress regulation-related tonic tone with phasic change in putamen activation during stress may be due to the antagonistic coupling of daily life stress and reward function (Montoya et al., 2016; Porcelli et al., 2012). In fact, stress does not always decrease brain reward function. Stress-induced increases in catecholamine (including dopamine and norepinephrine) release are accompanied by increases in striatal-dependent behaviours like reward seeking (Kalivas and Duffy, 1995; Lemos et al., 2012; Shaham and Stewart, 1995; Weinshenker and Schroeder, 2007). However, when stressors become chronic or unbearable, reward dysfunction and anhedonic behaviours emerge (Ironside et al., 2018). On the one hand, as a result of continuous stress exposure, overproduction of circulating glucocorticoids, due to impaired negative feedback function that recruited the HIP and prefrontal cortex, has a direct down-regulation effect on the reward circuitry of the brain (Kinner et al., 2016; Mizoguchi et al., 2003; Montoya et al., 2014). On the other hand, the allostatic load accumulated from daily life stress can lead to deficiencies in dopamine secretion and dysregulation of the central motivational system if individuals do not adapt to it well (Beauchaine et al., 2011). It is difficult for psychological resources that have been depleted by repeated stress exposure to support positive coping and reward-seeking behaviour during stress (Nolen-Hoeksema et al., 1994; Rizvi et al., 2021; Schönfeld et al., 2016). Therefore, the present study highlights that more efficient regulation of daily life stress and better development of the inherent neuroendocrine system in individuals with high reward sensitivity promote the resilient role of the brain reward system when facing a new stressor.

The chain mediation analysis supported our tonic-phasic neuroendocrine model for the reward system in stress resilience, which builds a new reward-resilience framework. In this model, both the HIP and IFG belong to the limbic-prefrontal circuitry, which links with the processing and regulating of psychogenic and systemic stimuli from stressors (Ulrich-Lai and Herman, 2009). The vulnerability of this circuitry to excessive cortisol secretion and impaired plasticity caused by prolonged stress exposure have been identified as antecedents of stress-related cognitive impairment and psychopathology (Birn et al., 2014; Jay et al., 2004; Sotres-Bayon et al., 2012; Labad, 2019; Lupien et al., 2009). From a positive psychology perspective, this model suggests that reduced CAR (implying efficient diurnal cortisol regulation) in individuals with high reward sensitivity is linked with enhanced HIP-IFG intrinsic connectivity, which predicts greater activation of the brain reward regions during stress.

4.3. Limitations and future directions

The findings of this study must be considered in the light of some limitations. First, the physicochemical mechanisms underlying the effect of brain reward pathways on stress resilience were not sufficiently investigated in this study, and studies seeking to identify the neuronal

components and dopaminergic system with positron emission tomography are needed to verify the inferences we made. In addition, to extend the clinical implications of the current findings, subsequent studies may focus on people with dysfunction in the striatal dopaminergic system, such as those with depression or schizophrenia (Vaessen et al., 2015). Finally, in this study, we used only the efficiency of cortisol recovery as a measure of stress resilience; however, there are many other components and measurements of stress resilience (Walker et al., 2017). For a thorough understanding of the underpinnings of adaptive allostasis and stress resilience, it would be more informative to test multiple dimensions of stress resilience and add some calibrations of stress-related health status.

5. Conclusion

The results of the present study support the important contribution of the mesostriatal reward system to the recovery of cortisol stress response. Furthermore, we found an interplay between the diurnal stress response system and HIP-IFG intrinsic connectivity in shaping the tonic pathway from reward sensitivity to putamen activation during coping with stress. These findings have advanced our understanding of the mechanism and framework underlying the role of the brain reward system in stress resilience, and they have important implications for how stress resilience can be fostered from a long-term, multi-dimensional interactive perspective.

CRediT authorship contribution statement

Weiyu Hu: Conceptualization, Methodology, Formal analysis, Resources, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Xiaolin Zhao:** Investigation. **Yadong Liu:** Investigation, Methodology, Data curation. **Yipeng Ren:** Investigation. **Zhenni Wei:** Investigation. **Zihan Tang:** Investigation. **Yun Tian:** Methodology. **Yadong Sun:** Methodology. **Juan Yang:** Conceptualization, Resources, Writing – review & editing, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare no conflict of interest.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ynstr.2022.100485.

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