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Research paper

Chronic stress modulates the relationship between acute stress-related cortical-limbic circuit functional connectivity and depression symptoms

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ABSTRACT

Background: Chronic stress impacts brain function and emotion regulation, increasing depression risk. How chronic stress shapes neural dynamics in response to acute stress remains unclear. This study investigates how chronic stress influences neural responses after acute stress, focusing on ventromedial prefrontal cortex (vmPFC)-amygdala and vmPFC-hippocampus functional connectivity (FC) and their relationship to depression symptoms.
Methods: Eighty-seven adults underwent resting-state fMRI at baseline, during acute stress, and during recovery. Participants were divided into High and Low chronic stress groups based on perceived stress over the past 4 weeks. Depression symptoms were measured with the Symptom Checklist-90. Linear mixed-effect model and repeated-measures ANOVA were used to analyse neural dynamics and interaction effects. Recovery-related changes in FC were calculated as differences between acute stress and recovery.
Results: Distinct neural dynamics patterns across stress phases emerged between groups. The Low group showed significant decreases in vmPFC-amygdala and vmPFC-hippocampus connectivity from acute stress to recovery, while the High group exhibited no changes. Chronic stress moderated the association between the recovery-related changes in vmPFC-amygdala connectivity and depression symptoms. In the High chronic stress group, greater decreases in FC from stress to recovery were associated with higher depression symptoms.
Conclusions: Chronic stress modulates neural dynamics during acute stress response and recovery, and their association with depression symptoms. Individuals with higher chronic stress exhibit blunted cortical-limbic circuit dynamics, potentially increasing depression vulnerability. Rapid disengagement of emotion regulation circuits may represent a maladaptive response supporting the allostatic load model. These findings clarify stress, brain, and depression relationships.

1. Introduction

As contemporary society continues to evolve at an ever-increasing pace, individuals are unavoidably exposed to increasing levels of stress in their daily lives (Liu et al., 2021). Such chronic stress exposure with maladaptation can have a profound impact on the brain, emotion, and mental health, often contributing to adverse outcomes such as impaired emotional regulation and increased risk for the onset and development of depression (Caspi et al., 2003; Orem et al., 2019). The human brain plays a central role in this stress exposure and adaptation by detecting stressors and top-down regulating behavioral and physiological responses (McEwen, 2017). However, prolonged exposure to chronic stress can overwhelm these regulatory capacities, leading to disruptions in neural processes critical for managing and recovering from stress (Franklin et al., 2012; Lupien et al., 2009). The mechanisms by which chronic stress modulates the brain's dynamic responses to acute stress challenges remain unclear. Uncovering the neural mechanisms underlying stress recovery is therefore essential for understanding stress adaptation and promoting resilience and mental health in the face of sustained stress.

Previous work has implied that the limbic-cortical circuit plays a crucial role in stress-related neural processes (Admon et al., 2013; Etkin et al., 2015; Veer et al., 2011). In particular, the functional interactions between the ventromedial prefrontal cortex (vmPFC), amygdala, and

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hippocampus are related to stress response and regulation (Hossein et al., 2023a; Van Marle et al., 2010). The vmPFC and amygdala are functionally connected in the regulation of emotion processing and stress response (Liu et al., 2020). Increased functional connectivity (FC) between the vmPFC and the amygdala was observed after stress compared with the neutral condition (Admon et al., 2009). Hippocampus, rich in receptors for stress-producing hormones, is highly susceptible to stress (Kim et al., 2015). The vmPFC regulates the effects of stress on the hippocampus through direct neural projections, with increased FC between the vmPFC and hippocampus observed under higher levels of daily stress (Ren et al., 2022). However, accumulating evidence suggests that chronic stress exposure may cause the neurons in vmPFC to develop debranching and shrinkage of dendrites that is associated with cognitive rigidity (McEwen et al., 2015) and impaired functional connectivity with amygdala and hippocampus, disrupting the formation of adaptive representations required for the execution of appropriate behavioral responses (Negrón-Oyarzo et al., 2016).

While extensive research has documented FC alterations associated with chronic stress (Franklin et al., 2012; Leone et al., 2025; Liu et al., 2020; Sabbah et al., 2026), there remains a significant gap in the understanding of how these changes affect real-time neural dynamics, particularly following acute stress exposure. Recent neuroimaging studies have begun to reveal the temporal dynamics of stress-induced FC changes across distinct phases of the stress response—from anticipation through acute stress to recovery—and their clinical relevance (Kühnel et al., 2022; Zhang et al., 2020, 2022). Dynamic changes in stress-related limbic-cortical circuit FC, especially the connectivity between the vmPFC and the amygdala and hippocampus, are significant for stress adaptation and resilience development (Chang et al., 2023; Oken et al., 2015). Critically, individual differences in stress-induced FC dynamics have been linked to both concurrent and prospective affective outcomes. For instance, increased frontocortical activation during laboratory stress tasks predicts reduced stress reactivity in daily life (Hur et al., 2022), and stress-induced network reconfigurations can predict stress-related symptom development over extended follow-up periods (Zhang et al., 2020), highlighting the potential of FC dynamics as markers of vulnerability and resilience.

Although accumulating research provided valuable insights into stress-induced reconfigurations of large-scale networks, such as the salience, default mode, and frontoparietal networks (Tutunji et al., 2025; Zhang et al., 2020, 2022), understanding how stress impacts the limbic-cortical circuit is particularly crucial for unraveling the neurobiological mechanisms linking stress to depression. This circuit integrates emotional and neuroendocrine processes that are directly implicated in the pathophysiology of mood disorders (Kung et al., 2023). Impaired recovery of limbic-cortical neural circuits has been involved in various psychopathologies, including depression, anxiety, and post-traumatic stress disorder (PTSD) (Chida and Hamer, 2008; Quaedflieg et al., 2015). However, most previous work has focused on healthy populations or anxiety-related disorders (Tutunji et al., 2025), and the relationship between stress-induced FC dynamics—particularly within the prefrontal-limbic circuit—and depression symptoms under different levels of chronic stress exposure remains poorly understood. Moreover, the relationship between neural recovery patterns and depression symptoms under varying levels of chronic stress exposure has yet to be systematically investigated.

The present study aims to address the aforementioned research gaps by examining how chronic stress influences neural dynamics after acute stress exposure, with a specific focus on the interaction between the functional connectivity of the vmPFC with the amygdala and the hippocampus and depression symptoms. We hypothesize that individuals with different levels of chronic stress will demonstrate distinct neural FC dynamics after acute stress exposure. Furthermore, we predict that chronic stress will affect the relationship between neural FC dynamics and depression symptoms. To test these hypotheses, we use adult resting-state fMRI data measured at three time points: baseline, immediately after acute stress induction, and after a period of rest from the stress task. Acute stress induction involves the Montreal Imaging Stress Task (MIST), with participants' emotion states being tracked using the Profile of Mood States (POMS) at each time point. Chronic stress levels are evaluated using the Perceived Stress Scale (PSS), while depression symptoms are measured using the depression subscale of the Symptom Checklist-90 (SCL-90). We specifically focus on the functional connectivity between vmPFC-Amygdala and vmPFC-Hippocampus circuits, examining their dynamic changes across different stress phases. To investigate the impact of chronic stress, we classified participants into high- and low-chronic-stress groups based on their PSS scores and compared their neural dynamics across different stress phases. Finally, we conduct moderation analyses to examine how chronic stress levels influence the relationship between recovery-related functional connectivity and depression symptoms, controlling for relevant demographic variables and emotional states.

2. Materials and methods

2.1. Participants

This study was approved by the Human Research Ethics Committee (HREC) at The University of Hong Kong (ethics number: EA1909038). Written informed consent was obtained from all participants before taking part in the study. We initially recruited 98 right-handed adults (49 females and 49 males) aged 25 to 37 years (M_{age} = 30.50 years, SD_{age} = 2.91 years) via print and social media advertisements. Eligibility required at least secondary-level education and absence of clinical psychopathology.

Exclusion criteria were applied to ensure a healthy, non-clinical sample. Participants were excluded if they met any of the following criteria: (1) a history of major physical or neurological illness; (2) current or lifetime diagnoses of major psychiatric conditions (including depressive disorders, anxiety disorders, schizophrenia, or addiction), verified through the Structured Clinical Interview for DSM-5 Disorders, Clinician Version (SCID-CV); (3) any medication or treatment received within two weeks before the study; or (4) pregnancy or breastfeeding (for female participants). We also screened for lifetime traumatic event exposure through self-report. Any participant who self-reported symptoms meeting diagnostic criteria for post-traumatic stress disorder (PTSD) was excluded (Shao et al., 2023).

All participants who met the criteria above underwent three resting-state fMRI sessions. To ensure data quality, only participants who met the head motion criteria across all three sessions were included in the final analysis. Specifically, participants were required to have minimal head motion, defined as absolute head motion $\leq$2 mm translation and $\leq 2^{\circ}$ rotation, or a mean frame-wise displacement (FD) $\leq$ 0.2 mm (Chen et al., 2025; Jenkinson et al., 2002; Yan et al., 2013). After applying these criteria, 87 participants (43 females and 44 males; M_{age} = 30.50 years, SD_{age} = 2.95 years) were retained for the final analyses.

2.2. Study procedure

Eligible participants were invited to join the study, which was conducted consistently between 3:00 and 6:00 p.m. to control for time-of-day effects on stress reactivity and FC. Upon arrival at the laboratory, participants completed questionnaire assessments, including the Perceived Stress Scale (PSS), Connor-Davidson Resilience Scale (CD-RISC), Symptom Checklist-90 (SCL-90), and the first Profile of Mood States (POMS; baseline) to measure their baseline emotional states. They then underwent the first 10-minute resting-state fMRI scan. Immediately after this, participants completed the laboratory stress task, MIST, for acute stress induction, followed by the second 10-minute resting-state fMRI scan. Upon completion, they filled out the second POMS (acute stress) and self-reported stress level questionnaires to assess their emotional states and stress levels right after the acute stress induction.

Following a 50-minute rest period, participants completed the third 10-minute resting-state fMRI scan. Upon finishing this last scan, they completed the third POMS (recovery) to evaluate their emotional states after the recovery phase. This procedure allowed us to examine the immediate impact of acute stress on participants' emotional states and brain function, as well as their recovery after the stressor was removed.

2.3. Questionnaire assessment

2.3.1. Chronic stress assessment

The Perceived Stress Scale (PSS) is used to assess long-term stress in this study. It is a well-validated self-report questionnaire that quantifies participants' perceived stress over the past month (Cohen et al., 1983). This scale consists of 10 items, each rated on a Likert scale ranging from 0 to 4. The items comprise both positive and negative descriptions, such as "In the last month, how often have you felt nervous and stressed?" or "In the last month, how often have you felt confident about your ability to handle your personal problems?" The overall score ranges from 0 to 40, with higher scores indicating greater chronic stress.

2.3.2. Resilience assessment

The Chinese version of The Connor-Davidson Resilience Scale (CD-RISC) assesses resilience. The scale has demonstrated reliability and validity, with a reliability coefficient of 0.91 (Yu and Zhang, 2007). This scale consists of 10 items, each rated on a Likert scale ranging from 0 to 4. The total scores range from 0 to 40, with higher scores indicating greater resilience.

2.3.3. Depression symptoms assessment

The Symptom Checklist-90 (SCL-90) measures psychological symptoms experienced over the past week. The 10 different dimensions of psychological symptoms measured include depression, anxiety, somatization, obsessive-compulsive, interpersonal sensitivity, hostility, phobic anxiety, paranoid ideation, psychoticism, and additional concerns. This scale is well-validated in both identifying individuals with mental disorders and measuring subclinical psychological symptoms in nonclinical populations. The SCL-depression subscale is used as an index of depression symptoms among the participants in this study.

2.3.4. Emotion states assessment

The Profile of Mood States (POMS) assesses five transient negative emotion states (tension, anger, fatigue, confusion, and depression) and two positive emotion states (vigor and esteem). All items are rated on a Likert scale ranging from 0 to 4. Studies have confirmed the reliability and validity of both dimensions, with a mean internal consistency across the subscales of 0.942 (Cheung and Lam, 2005; Shao et al., 2023) and subscale reliabilities ranging from 0.62 to 0.82 (Pang et al., 2023).

To capture participants' overall negative emotion, the negative subscale score is calculated by summing the items measuring the five negative emotional states and subtracting the scores for the positive emotional states (Cella et al., 1987; Pang et al., 2023). A higher, positive score indicates a more pronounced experience of negative emotion. A score of 0 indicates a neutral emotional state, and a negative score indicates a positive emotional state. Participants completed the POMS at three time points in this study: before the first resting-state scan (baseline), immediately after the second resting-state scan (acute stress), and after the third resting-state scan (recovery). This allowed us to evaluate their current emotional states at baseline, immediately following acute stress, and after recovery.

2.4. Resting-state fMRI imaging data acquisition and preprocessing

Whole-brain images were acquired from a Siemens 3.0 T MRI scanner (MAGNETOM Prisma) with a 64-channel head coil. The three 10-minute resting-state fMRI sessions, acquired at different times, were acquired using a multiband gradient-echo echo-planar imaging pulse sequence. Each time of resting-state scanning consisted of 750 volumes and applied these parameters: slice thickness = 2 mm; repetition time (TR) = 800 ms; echo time (TE) = 30 ms; flip angle = 52°; voxel size = 2 × 2 × 2 mm^3, FOV = 208 × 208 × 144 mm^3. Additionally, high-resolution anatomical images were obtained for each participant using three-dimensional sagittal T1-weighted magnetisation-prepared rapid gradient-echo (MPRAGE) sequences. The scanning protocol comprised 320 slices (slice thickness = 0.8 mm), with parameters set at TR = 2.5 ms, TE = 2.2 ms, flip angle = 8°, voxel size = 0.8 × 0.8 × 0.8 mm^3, FOV = 166 × 240 × 256 mm^3.

Data preprocessing, including functional and anatomical data, was conducted using CONN's default settings and pipeline (Whitfield-Gabrieli and Nieto-Castanon, 2012). The functional data were realigned with susceptibility distortion correction interactions using the SPM realign & unwarp procedure (Andersson et al., 2001), followed by slice timing correction. Using ART, outlier scans were identified based on framewise displacement exceeding 0.9 mm or global BOLD signal changes above 5 standard deviations (Power et al., 2013). Both functional and anatomical data were then normalized to standard MNI space using SPM's unified segmentation and normalization algorithm, with resampling to 2 mm isotropic voxels using the IXI-549 tissue probability map template. Finally, functional data were spatially smoothed using an 8 mm full-width half-maximum (FWHM) Gaussian kernel (Andersson et al., 2025).

Following preprocessing, additional denoising steps were implemented. The functional data were regressed for confounding signals, including white matter and cerebrospinal fluid signals, head motion parameters and their first-order derivatives (Friston et al., 1996), and linear trends within each functional run. The images were then bandpass filtered (0.008 Hz to 0.09 Hz). Quality control criteria were applied to exclude participants with excessive head motion, defined as translation >2 mm, rotation >2°, or mean frame-wise displacement (FD) > 0.2 mm (Jenkinson et al., 2002; Yan et al., 2013). After these quality control measures, 87 participants were included for final analysis.

2.5. Regions of interest and functional connectivity analysis

Based on the literature on chronic and acute stress, we chose the core regions of the cortical-limbic circuit as our regions of interest (ROIs). They were, namely, the ventral medial prefrontal cortex (vmPFC), amygdala, and hippocampus. The vmPFC mask was based on previous literature (Shao et al., 2018), whereas the amygdala and hippocampus masks were defined using the automated anatomical labeling (AAL-90) template (Tzourio-Mazoyer et al., 2002).

We used the CONN toolbox to extract functional connectivity between the vmPFC and the amygdala and hippocampus (Whitfield-Gabrieli and Nieto-Castanon, 2012). Regional time series for these 3 ROIs were extracted from resting-state fMRI data at each phase for each participant by averaging the time series of all voxels within each node. Functional connectivity was calculated by correlating the mean time series of each ROI pair using Pearson's correlation. Subsequently, a Fisher's *r*-to-*z* transformation was applied to the correlation coefficients in each participant for further analysis.

2.6. Recovery-related changes in functional connectivity (ΔFC)

To represent the true recovery-related changes in functional connectivity (FC), we calculated a FC contrast (ΔFC) by subtracting FC values at the recovery phase from those at the acute stress phase. This was done for both vmPFC-amygdala and vmPFC-hippocampus connectivity. A larger ΔFC indicated a more pronounced shift in FC from the acute stress phase to the recovery phase, suggesting a more rapid recovery of the neural dynamics. We also explored an alternative index to represent recovery-related FC changes by subtracting FC values at the recovery phase from those at the baseline phase; the results are presented in the Supplementary Information (SI).

Recovery – related ΔFC = FC (Acute stress) – FC (Recovery)

2.7. Statistical analysis and mediation analysis

First, independent-samples *t*-tests were used to characterise group differences in resilience and depression symptoms. Then, partial Pearson correlation analyses were conducted to investigate the pair-wise relationship among chronic stress, resilience, and depression symptoms, with age and sex included as covariates. Next, a linear mixed-effects model (LMM) was applied to estimate the dynamic changes in emotion states and FC across phases, with age and sex of each subject included as covariates. Additionally, to examine the interaction effect between different phases and chronic stress on FC, we conducted separate 2 (Groups: High vs. Low chronic stress groups) × 3 (Stress phases: Baseline, Acute stress, and Recovery) Repeated Measures ANOVA analyses. Age, sex, POMS at the three phases, resilience, and depression symptoms were all included as covariates. Post hoc analyses were then used to examine further the simple effect of dynamic changes in FC within each stress group (High and Low chronic stress groups) across the different phases. The critical value for statistical significance testing was corrected for multiple comparisons using the Benjamini-Hochberg (BH) false discovery rate (FDR).

Next, to examine whether the grouping of chronic stress moderated the relationship between the true recovery-related changes in FC (ΔFC) of vmPFC-Amygdala as well as vmPFC-Hippocampus and depression symptoms, we conducted moderation analyses by using SPSS version 21 with the PROCESS macro (IBM Corp., Armonk, NY) (Hayes, 2013). In these moderation analyses, the recovery-related ΔFC was treated as the independent variable (X), the stress grouping as the moderator (W), and the score on depression symptoms as the dependent variable (Y). Additionally, we included age and sex as covariates to account for their potential effects on the relationships being studied. The significance of the interaction effect (X × W) was assessed using 5000 bootstrap samples, bias-corrected.

3. Results

3.1. Demographics and chronic stress groups

We used the median PSS score as the cutoff to divide participants into High and Low chronic stress groups in this study. This cutoff was chosen because it exceeded the estimated population mean range of 13.0 to 16.1, as determined by studies involving 1143 to 2387 participants (Berlowitz et al., 2020). The High chronic stress group included 49 participants (M_{age} = 30.5 years, SD_{age} = 3.07 years; Female/Male ratio = 23/26), with scores above the median PSS score of 17. The Low chronic stress group consisted of 38 participants (M_{age} = 30.5 years, SD_{age} = 2.83 years; Female/Male ratio = 20/18). To ensure there were no significant differences in age or sex between the two groups, we conducted independent samples *t*-tests ($t_{(85)} \leq 0.52$, $p \geq 0.60$, Cohen's $d \leq 0.11$). The results revealed that the High and Low chronic stress groups were matched on age and sex composition. Table 1 lists the demographics of our overall sample.

Table 1
Participants' demographics in high and low chronic stress groups.

	Participants in total	High chronic stress group	Low chronic stress group
Total number	87	49	38
Age in years (M_{age} ± SD_{age})	30.5 ± 2.95	30.5 ± 3.07	30.5 ± 2.83
Sex	43 F/44 M	23 F/26 M	20 F/18 M
PSS (median ± S·D.)	17 ± 5.56	20 ± 3.87	14 ± 3.25

PSS: The Perceived Stress Scale, M: Male, F: Female, S.D.: Standard deviation.

3.2. Dynamics of emotion states during acute stress between different chronic stress groups

First, to examine the impact of acute stress induction, we investigated the dynamics of emotion states by comparing the POMS scores at three time points: baseline, acute stress, and after recovery. A linear mixed effects model was conducted, controlling for age and sex as covariates. The analysis revealed a significant time effect on the POMS ($F_{(2,\ 170)} = 59.25$, $p < 0.001$). Post-hoc tests further showed that the POMS was significantly higher after the acute stress task induction than at baseline (t(170) = −10.01, p < 0.001) and during recovery ($t_{(170)} = 8.71$, $p < 0.001$). There was no significant difference in the POMS between the baseline and recovery phases ($t_{(170)} = -1.31$, $p = 0.39$), indicating a return to baseline emotion state after recovery (Fig. 1A).

To further characterise group differences in POMS across phases, we compared POMS scores between the High chronic stress and Low chronic stress groups using separate independent-samples *t*-tests. After FDR correction, we observed that POMS at each phase was significantly higher in the High chronic stress group than the Low chronic stress group ($t_{(85)} \geq 2.31$, $p \leq 0.023$, $p_{(FDR)} \leq 0.025$, Cohen's $d \geq 0.499$; Fig. 1B). These results demonstrated the successful induction of acute stress, as evidenced by the significant dynamic changes in participants' self-reported emotion states. The acute stress task did induce a transient increase in negative emotion that returned to baseline levels after a period of recovery. Specifically, while the acute stress task induced a similar pattern of mood change in both groups, participants in the High chronic stress group consistently reported higher negative emotion states across all phases.

3.3. Dynamics of stress-related FC during acute stress between different chronic stress groups

Next, we investigated the neural dynamics of acute stress-related FC during different phases. Separate LMM analyses were conducted, controlling for age and sex as covariates. After FDR correction, we observed that both the FC of vmPFC-Amygdala ($F_{(2,\ 172)} = 6.12$, $p = 0.003$, $p_{(FDR)} = 0.008$) and that of vmPFC-Hippocampus ($F_{(2,\ 172)} = 15.03$, $p < 0.001$, $p_{(FDR)} < 0.001$) exhibited significant dynamical changes across phases (see Fig. 2). Post hoc analysis revealed that the FC of vmPFC-Amygdala and that of vmPFC-Hippocampus at acute stress were significantly higher than both baseline ($t_{(172)} \leq -2.5$, $p \leq 0.035$) and recovery ($t_{(172)} \geq 3.37$, $p \leq 0.003$). There was no significant difference in each FC between baseline and recovery ($t_{(172)} \leq 1.91$, $p \geq 0.14$).

To further examine potential interaction effects between chronic stress grouping (High vs. Low Chronic stress) and stress phase (baseline, acute stress and recovery) on FC, we conducted two repeated-measures ANOVA, with age, sex, resilience, depression symptoms, and emotion states at each phase included as covariates. The results revealed that, after FDR correction, there were significant interaction effects on FC of vmPFC-Amygdala ($F_{(2,\ 156)} = 3.49$, $p = 0.033$, $p_{(FDR)} = 0.033$, partial $\eta^2 = 0.043$) and that of vmPFC-Hippocampus ($F_{(2,\ 156)} = 4.06$, $p = 0.019$, $p_{(FDR)} = 0.038$, partial $\eta^2 = 0.049$).

Post-hoc analysis revealed distinct patterns of acute stress-related neural dynamics between the two chronic stress groups. For FC of vmPFC-Amygdala (see Fig. 3A), we did not observe any neural dynamics among the three stress phases within the High chronic stress group ($t_{(78)} \leq 1.41$, $p \geq 0.103$). To further verify this null effect, we conducted a Bayesian ANCOVA analysis in the High chronic stress group. The analysis generated a Bayes factor for the main effect of Time ($BF_{incl} = 0.498$). This result provided anecdotal evidence for the null hypothesis. On the other hand, within the Low chronic stress group, we observed a significant difference in FC of vmPFC-Amygdala between acute stress and recovery phases ($t_{(78)} = 2.73$, $p = 0.028$). But not between baseline and acute stress or recovery phases ($t_{(78)} \leq 2.73$, $p \geq 0.081$).

For the FC of vmPFC-Hippocampus (see Fig. 3B), similar patterns were observed in the High chronic stress group, in which no significant

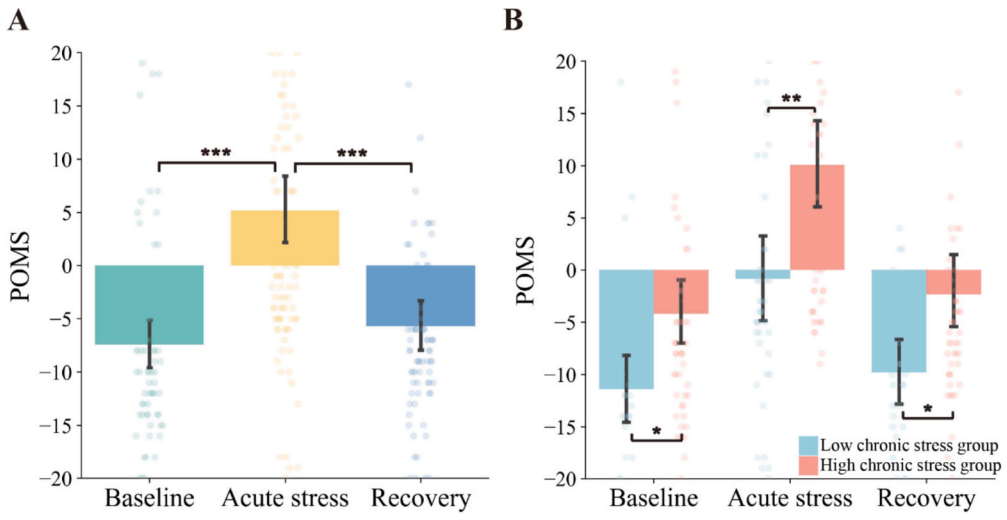

Fig. 1. Emotion state dynamics were measured using the Profile of Mood States (POMS) before and after the acute stress task. (A) A linear mixed effect model revealed a significant time effect on POMS: $F_{(2,\ 170)} = 59.25$, $p < 0.001$. Post hoc analysis revealed that POMS after acute stress was significantly higher than both baseline ($t_{(170)} = -10.01$, $p < 0.001$) and after recovery ($t_{(170)} = 8.71$, $p < 0.001$). There was no difference between the POMS at baseline and after recovery ($t_{(170)} = -1.31$, $p = 0.39$). (B) POMS in the High chronic stress group were significantly higher than in the Low chronic stress group at each stress phase ($t_{(85)} \geq 2.31$, $p \leq 0.023$, $p_{(FDR)} \leq 0.025$, Cohen's $d \geq 0.499$).

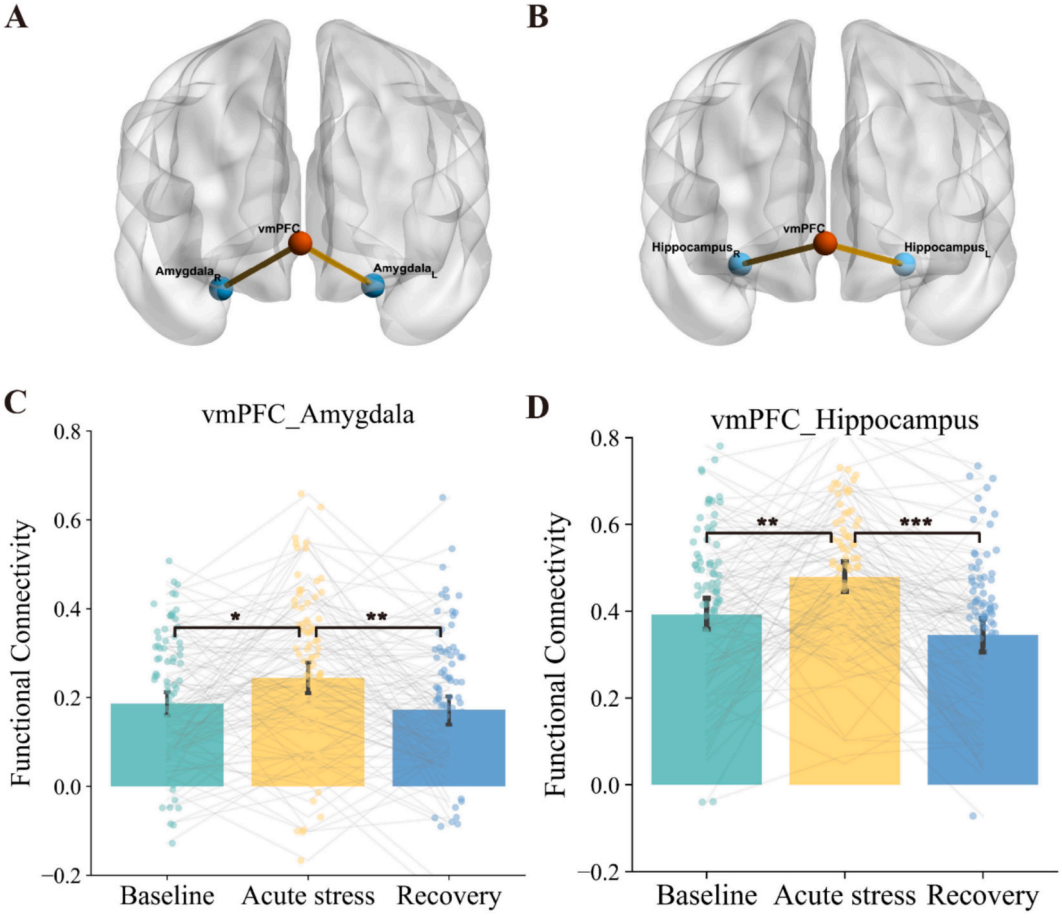

Fig. 2. The dynamics of functional connectivity (FC) among different acute stress phases. (A)(B) illustration of the vmPFC-Amygdala and vmPFC-Hippocampus connectivity. (C) Linear mixed effect model analysis revealed a significant main effect of phase on FC of vmPFC-Amygdala ($F_{(2,\ 172)} = 6.12$, $p = 0.003$, $p_{(FDR)} = 0.008$). Specifically, FC at the acute stress phase was significantly higher than both baseline ($t_{(172)} = -2.5$, $p = 0.035$) and recovery ($t_{(172)} = 3.37$, $p = 0.003$) phases. (B) A similar pattern was observed for vmPFC-Hippocampus connectivity ($F_{(2,\ 172)} = 15.03$, $p < 0.001$, $p_{(FDR)} < 0.001$); FC at acute stress was significantly higher than both baseline ($t_{(172)} = -3.5$, $p = 0.002$) and recovery ($t_{(172)} = 5.41$, $p < 0.001$) phases.

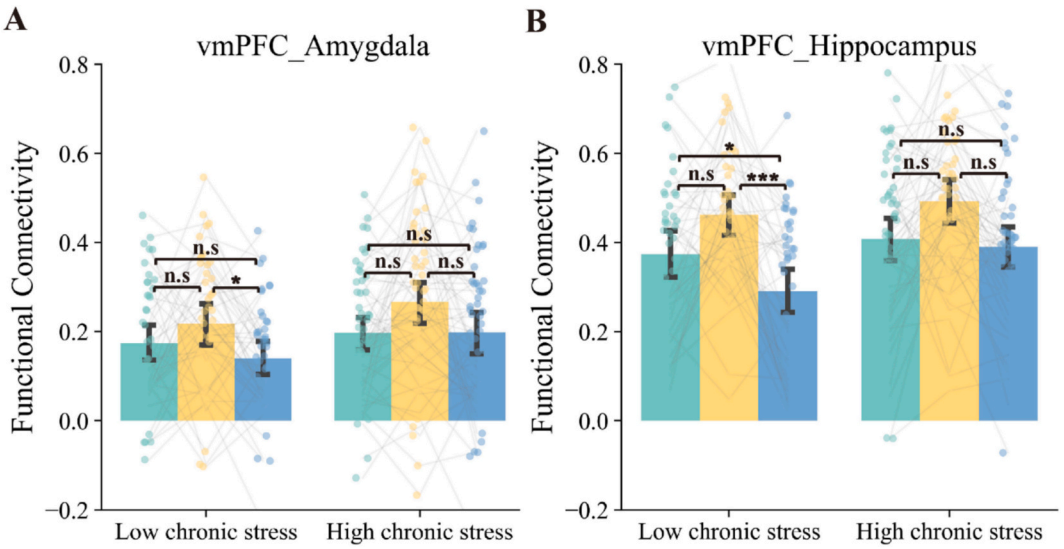

Fig. 3. The group differences in functional connectivity across stress phases. (A) Repeated measures ANOVA analysis revealed significant interaction effects between chronic stress grouping (High vs. Low Chronic stress) and stress phase (baseline, acute stress, and recovery) on FC of vmPFC-Amygdala ($F_{(2,\ 156)} = 3.49$, $p = 0.033$, $p_{(FDR)} = 0.033$). While there were no neural dynamics among the three stress phases within the High chronic stress group ($t_{(78)} \leq 1.41$, $p \geq 0.103$), the difference in FC of vmPFC-Amygdala between acute stress and recovery phases was significant in the Low chronic stress group ($t_{(78)} = 2.73$, $p = 0.028$). The difference in FC between vmPFC and Amygdala at baseline and during acute stress or recovery did not reach significance in the Low chronic stress group ($t_{(78)} \leq 2.73$, $p \geq 0.081$). (B) The interaction effect was also significant for FC of vmPFC-Hippocampus connectivity ($F_{(2,\ 156)} = 4.06$, $p = 0.019$, $p_{(FDR)} = 0.038$). Specifically, in the Low chronic stress group, the difference in FC at the recovery phase was significantly lower than both baseline ($t_{(78)} = 3.09$, $p = 0.03$) and acute stress ($t_{(78)} = 5.50$, $p < 0.001$) phases. The Low chronic stress group did not show significant differences in FC between the vmPFC and the Amygdala at baseline or during acute stress. In the High chronic stress group, there were no significant dynamics of this FC across baseline, acute stress, and recovery phases ($t_{(78)} \geq -2.86$, $p \geq 0.058$).

neural dynamics among the three stress phases were observed ($t_{(78)} \leq 2.61$, $p \geq 0.058$). However, Bayesian ANCOVA analysis did not support this null hypothesis ($BF_{incl} = 2.02$). This suggests that the High chronic stress group also exhibits neural dynamics, an effect that was not captured by the traditional repeated-measures ANOVA. Additionally, in the Low chronic stress group, we observed that FC at the recovery phase was significantly lower than both baseline ($t_{(78)} = 3.09$, $p = 0.03$) and the acute stress phase ($t(78) = 5.50$, $p < 0.001$). There was no significant difference in FC of vmPFC-Hippocampus between baseline and acute stress phases ($t_{(78)} = -1.34$, $p = 0.76$). Specifically, individuals with higher levels of chronic stress did not demonstrate neural dynamics across different phases of acute stress, including after a period of rest for recovery. In contrast, individuals with lower levels of chronic stress showed significant brain recovery.

Taken together, these findings indicate that the two chronic stress groups exhibited distinct patterns of neural dynamics in response to acute stress. For individuals with high chronic stress, both traditional and Bayesian analyses generally support the absence of substantial neural dynamics across stress phases, particularly for the vmPFC-Amygdala connectivity. However, for vmPFC-Hippocampus connectivity, Bayesian analysis provided moderate evidence for a Time effect that was not detected by traditional ANOVA, indicating the possibility of neural changes in the High chronic stress group. On the other hand, the low chronic stress group exhibited pronounced neural recovery, particularly in the vmPFC-Hippocampus circuit, for which both analytical approaches provided strong evidence of connectivity changes. Overall, these findings highlight blunted neural dynamics in individuals with higher levels of chronic stress and more robust phase-related changes in those with lower levels of chronic stress.

3.4. The moderation effect of chronic stress on the association between recovery-related FC and depression symptoms

Additionally, we conducted a moderation analysis to understand the moderating effect of chronic stress in the relationship between recovery-related FC and depression symptoms. Results demonstrated that chronic stress grouping significantly moderated the association between recovery-related vmPFC-Amygdala connectivity changes and depression symptoms ($F_{(1,\ 78)} = 6.08$, bootstrapped 95 % CI = [3.56, 33.05], $p = 0.016$; see Fig. 4A and Fig. 4C), after controlling for age, sex, and POMS at each phase. Follow-up simple slope analyses revealed a distinct pattern: individuals in the High chronic stress group showed a significant positive association between vmPFC-Amygdala connectivity and depression symptoms ($\beta = 9.36$, $p = 0.041$, 95 % CI [0.36, 18.24]). However, for individuals in the Low chronic stress group, this relationship was not significant ($\beta = -9.03$, $p = 0.124$, 95 % CI [−20.54, 2.53]). Chronic stress grouping did not significantly moderate the relationship between vmPFC-Hippocampus connectivity and depression symptoms (bootstrapped $p > 0.100$; see Fig. 4B and Fig. 4D).

3.5. Group differences in resilience and depression symptoms

We conducted two independent-samples *t*-tests to examine group differences in resilience and depression symptoms. The results demonstrated significant differences between High and Low chronic stress groups in both resilience ($t_{(85)} = -5.03$, $p < 0.001$, Cohen's $d = -1.09$) and depression symptoms ($t_{(85)} = 3.58$, $p < 0.001$, Cohen's $d = 0.77$). While resilience in the High chronic stress group was significantly lower than in the Low chronic stress group, depression symptoms were significantly higher in the High chronic stress group. Partial correlation analyses, controlling for age and sex, revealed that resilience was negatively correlated with chronic stress ($r = -0.61$, $p < 0.001$, $p_{(FDR)} < 0.001$). In contrast, depression symptoms was positively correlated ($r = 0.58$, $p < 0.001$, $p_{(FDR)} < 0.001$) with chronic stress ($r = 0.58$, $p < 0.001$, $p_{(FDR)} < 0.001$; Fig. S1). The results revealed that individuals with high chronic stress exhibited significantly reduced resilience and higher depression symptoms compared to those with low chronic stress.

4. Discussion

In this study, we investigated how chronic stress is associated with dynamic changes in human brain functional connectivity (FC) across

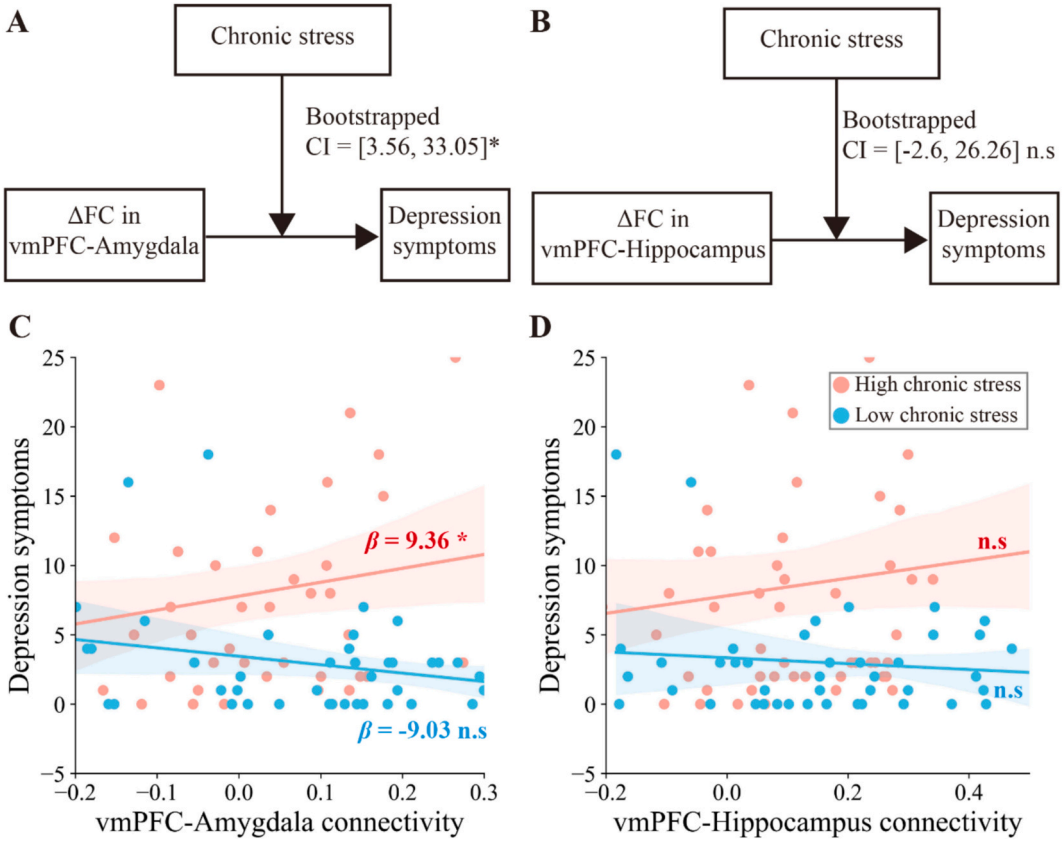

Fig. 4. The moderating effect of the chronic stress group on the association between recovery-related functional connectivity changes and depression symptoms. (A) (C) A moderation model analysis revealed that chronic stress grouping significantly moderated the association between recovery-related vmPFC-Amygdala connectivity changes and depression symptoms ($F_{(1,\ 89)} = 6.08$, bootstrapped CI = [3.56, 33.05], $p = 0.016$), after controlling for age, sex, and POMS at each phase. Individuals in the High chronic stress group showed a significant positive association between recovery-related FC changes and depression symptoms (β = 9.36, p = 0.041, 95 % CI [0.36, 18.24]). In contrast, individuals in the Low chronic stress group did not show any significant association between recovery-related FC changes and depression symptoms. (B) (D) Chronic stress grouping did not significantly moderate the relationship between recovery-related vmPFC-Hippocampus connectivity changes and depression symptoms (bootstrapped $p > 0.1$).

different acute stress phases. Behaviorally, our acute stress induction paradigm robustly altered participants' emotional states, with individuals reporting higher chronic stress consistently experiencing stronger negative emotions than those with lower chronic stress at each phase. At the neural level, we observed that FC between vmPFC and both the amygdala and hippocampus generally increased during the acute stress phase and decreased during recovery. However, further analyses revealed distinct patterns of FC dynamics between the High and Low chronic stress groups. Specifically, individuals with low chronic stress exhibited pronounced phase-related changes in both vmPFC-amygdala and vmPFC-hippocampus FC. In contrast, individuals with high chronic stress showed limited stress-related changes in FC, with Bayesian analyses providing additional support for the lack of neural dynamics in vmPFC-amygdala connectivity and moderate evidence for subtle changes in vmPFC-hippocampus connectivity. Furthermore, we observed a moderating effect of chronic stress grouping on the association between recovery-related changes in vmPFC-Amygdala FC (ΔFC) and depression symptoms, in which ΔFC was positively associated with depression symptoms among those with high chronic stress but not those with low chronic stress. As expected, individuals with high chronic stress also reported higher levels of depression symptoms compared to those with low chronic stress. Together, these findings highlighted heterogeneity in acute stress-related neural dynamics as a function of chronic stress exposure, suggesting a modulating role of chronic stress in the association of FC and depression symptoms.

4.1. Individuals with higher chronic stress demonstrated stronger negative emotions

Our findings regarding dynamic changes in emotion states across different phases (i.e., an increase in negative emotions from baseline to acute stress, followed by a decrease during the recovery phase) support the effectiveness of the laboratory acute stress induction paradigm in eliciting the stress arousal (Zeng et al., 2024). Additionally, the observation that individuals with higher chronic stress consistently experienced stronger negative emotions across the acute stress phases is consistent with previous research, which has reported associations between chronic stress exposure and persistent alterations in emotional processing, as well as greater negative emotion bias (Braund et al., 2019; McEwen et al., 2015). This enhanced negative emotion may reflect compromised stress adaptation mechanisms, as chronic stress has been shown to reduce the flexibility of emotional regulation systems (Kim et al., 2013; Russo et al., 2012). Such emotional dysregulation patterns have been associated with increased vulnerability to depression, particularly among individuals experiencing prolonged stress exposure (Berking et al., 2014).

4.2. Chronic stress blunted the neural dynamics in the face of acute stress

The increase in both the vmPFC-Amygdala and vmPFC-Hippocampus connectivity strength from baseline to acute stress phase reflects the brain's immediate response to acute stressor exposure. This enhanced connectivity following acute stress exposure is consistent with

previous findings (Goldfarb et al., 2020; Van Dijk et al., 2012), which suggest that increased coupling between vmPFC and both the amygdala and hippocampus right may represent engagement of emotion processing and regulation systems to support adaptive behaviors (Van Dijk et al., 2012). Moreover, the subsequent decrease in connectivity strength from the acute stress phase to the recovery phase may indicate a return of the neural system toward homeostasis following the dissipation of the acute stressor. The neural dynamic patterns observed across baseline, acute stress, and recovery phases in this study are consistent with previous research, which has highlighted the importance of dynamic prefrontal-limbic connectivity for emotion regulation, stress adaptation, and resilient coping (Hermans et al., 2014; Sinha et al., 2016).

However, these neural dynamics appear to show distinct patterns by different levels of chronic stress exposure. The observed decrease in both vmPFC-Amygdala connectivity and vmPFC-Hippocampus connectivity over recovery phase among individuals with low chronic stress may suggest more efficient neural recovery and dynamic neural connectivity after acute stress (Chang et al., 2023; Heller and Bagot, 2020; Sinha et al., 2016). This ability of returning to baseline connectivity level is consistent with prior reports of well-functioning stress response and adaptation mechanisms in more resilient individuals (Franklin et al., 2012). In contrast, the absence of such cross-phase neural dynamics among individuals with high chronic stress suggests that acute stress response and recovery adaption may be attenuated in the context of prolonged stress exposure. This pattern aligns with existing evidence of blunted acute stress response in individuals experiencing high daily stress (Ren et al., 2022), and may be related to dysfunction of the cortical-limbic circuit under high chronic stress (Arnsten, 2015). Such blunted connectivity patterns could represent a maladaptive response that is associated with increased vulnerability to stress-related disorders.

4.3. Chronic stress moderated the association between vmPFC-amygdala connectivity with depression symptoms

Our findings also reveal that the association between vmPFC-amygdala recovery FC and depression symptoms may differ depending on levels of chronic stress exposure. Specifically, Individuals with higher chronic stress reported more severe depression symptoms and showed greater decreases in recovery-related ΔFC in vmPFC-Amygdala following the dissipation of the acute stressor, In comparison, this relationship was not observed among those with lower chronic stress. From a compensatory mechanism perspective, this apparently "better" recovery (i.e., larger ΔFC over recovery from acute stress exposure) among individuals with higher chronic stress may represent an over-compensation response, in which rapid disengagement of emotion regulation circuits could reflect a premature withdrawal of necessary regulation resources (Etkin et al., 2015; Etkin and Schatzberg, 2011). Moreover, the amygdala has been consistently implicated in the pathophysiology of depression, particularly in its interactions with prefrontal regions during stress processing. Recent evidence suggests that attenuated connectivity between the basolateral amygdala and prefrontal cortex is a distinguishing feature of individuals with major depressive disorder, and that acute stress may induce similar connectivity patterns even in healthy individuals exposed to high levels of perceived stress (Hossein et al., 2023b).

Together with the current observation of blunted dynamics across the acute stress phases among those with higher chronic stress, our findings on recovery functional connectivity align with the allostatic load model (Juster et al., 2010). According to this framework, prolonged and repeated stress exposure may lead to compensatory neural adaptations that help maintain short-term functioning. Still, over time, such adaptations could increase vulnerability to neural dysfunction and psychopathology, including depression (Gold et al., 2015). While our results may support this perspective, future longitudinal and mechanistic studies will be necessary to clarify these associations. Furthermore, our null findings on such moderation effect for vmPFC-hippocampus connectivity suggest a circuit-specific vulnerability to chronic stress, with the emotion regulation circuit (vmPFC-amygdala) showing particular sensitivity to stress-induced dysfunction (Hermans et al., 2014; Sinha et al., 2016). These findings highlight the importance of examining neural recovery following acute stress and its potential variations among individuals with different levels of chronic stress burden. Such work sheds light on the mechanisms underlying the trajectory of stress-related psychopathology such as depression and the development of targeted interventions.

5. Limitation

There are several limitations to be considered in the current study. First, while our stress assessment methods provide valuable insights, our use of self-report measures on chronic stress exposure can be subject to recall bias and individual differences in stress perception. Second, despite our control for various confounding factors, the cross-sectional nature of our study prevents us from drawing causal conclusions about the relationships among chronic stress, neural dynamics, and depression symptoms. Longitudinal design studies are needed to investigate how chronic stress affects neural dynamics and depression symptoms. Third, due to the constraints of conducting this study during the COVID-19 pandemic, the limited sample size and the lack of participant biological samples, e.g. saliva, limit the use of cortisol as a comprehensive physiological indicator of stress-induced arousal. Therefore, our findings provided only anecdotal evidence for hypothesis testing. Future research should use a larger sample and incorporate physiological markers of stress response, such as cortisol levels and autonomic measures, to offer more objective measures of stress reactivity and recovery.

6. Conclusion

In conclusion, this study provides novel insights into how chronic stress modulates the neural dynamic patterns of the cortical-limbic circuit (vmPFC-amygdala and vmPFC-hippocampus) during acute stress response and recovery. Our findings demonstrate that individuals with higher levels of chronic stress exhibit blunted neural dynamics during acute stress, particularly in vmPFC-amygdala connectivity. A clinical implication is that such blunted neural dynamics may contribute to an increased vulnerability to depression. The observed moderating effect of chronic stress on brain-symptoms relationships suggests potential neural markers for identifying individuals at risk for stress-related psychopathology, such as depression. Together, these findings advance our understanding of the complex interactions among chronic stress, neural dynamics, and mental health, while offering promising directions in the development of targeted interventions for stress-related disorders.

CRediT authorship contribution statement

Menglu Chen: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Conceptualization. **Mengxia Gao:** Writing – review & editing, Writing – original draft, Data curation. **Robin Shao:** Data curation. **Horace Tong:** Formal analysis, Data curation. **June M. Liu:** Methodology. **Amanda K. Cheung:** Writing – review & editing. **Tatia M.C. Lee:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Ethics statement

This study was approved by the Human Research Ethics Committee (HREC) at The University of Hong Kong (ethics number: EA1909038). All procedures in this study followed the Declaration of Helsinki guidelines, and informed consent was obtained from all the participants.

Declaration of Generative AI and AI-assisted technologies in the writing process

We acknowledge the assistance of Claude (Anthropic) for language editing and proofreading during manuscript preparation. This AI tool was used for improving clarity and readability of the text.

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Declaration of competing interest

The authors have no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary Figure 1 (Fig S1) shows that there are significant differences in both depression symptoms and resilience between High and Low chronic stress groups. Individuals in the High chronic stress group exhibited significantly higher depression symptoms compared to the Low stress group, with depression symptoms showing a positive correlation with chronic stress levels. Conversely, resilience levels were significantly lower in the High chronic stress group, demonstrating a negative correlation with chronic stress. Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2025.120725.

Data availability

The anonymized minimal dataset supporting the conclusions of this study can be obtained upon reasonable request from the corresponding authors, as participants did not provide consent for public sharing of the raw data.

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