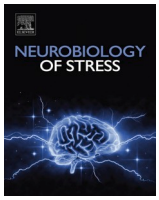
Neurobiology of Stress 27 (2023) 100584

Contents lists available at ScienceDirect

Neurobiology of Stress

journal homepage: www.elsevier.com/locate/ynstr



The double-edged sword of the hippocampus-ventromedial prefrontal cortex resting-state connectivity in stress susceptibility and resilience: A prospective study

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ARTICLE INFO

Keywords:
Hippocampus
Ventromedial prefrontal cortex
Stress susceptibility
Stress resilience

ABSTRACT

The hippocampus has long been considered a pivotal region implicated in both stress susceptibility and resilience. A wealth of evidence from animal and human studies underscores the significance of hippocampal functional connectivity with the ventromedial prefrontal cortex (vmPFC) in these stress-related processes. However, there remains a scarcity of research that explores and contrasts the roles of hippocampus-vmPFC connectivity in stress susceptibility and resilience when facing a real-life traumatic event from a prospective standpoint. In the present study, we investigated the contributions of undirected and directed connectivity between the hippocampus and vmPFC to stress susceptibility and resilience within the context of the COVID-19 pandemic. Our findings revealed that the left hippocampus-left vmPFC connectivity prior to the pandemic exhibited a negative correlation with both stress susceptibility and resilience. Specifically, individuals with stronger left hippocampus-left vmPFC connectivity reported experiencing fewer stress-related feelings during the outbreak period of the epidemic but displayed lower levels of stress resilience five months later. Our application of spectral dynamic causal modeling unveiled an additional inhibitory connectivity pathway from the left hippocampus to the left vmPFC in the context of stress susceptibility, which was notably absent in stress resilience. Furthermore, we observed a noteworthy positive association between self-inhibition of the vmPFC and stress susceptibility, with this effect proving substantial enough to predict an individual's susceptibility to stress; conversely, these patterns did not manifest in the realm of stress resilience. These findings enrich our comprehension of stress susceptibility and stress resilience and might have implications for innovative approaches to managing stress-related disorders.

1. Instruction

Stress susceptibility refers to an individual's inclination or predisposition to experience adverse psychological or physiological reactions when confronted with stressors (Ebner and Singewald 2017). Individuals with a heightened susceptibility to stress might face an increased risk of developing stress-related conditions, such as major depressive disorder (MDD), post-traumatic stress disorder (PTSD), and acute stress disorder (ASD) (Ebner and Singewald 2017). Conversely, many individuals possess the capacity to adapt to stressors and employ adaptive responses, showing resilience (Franklin, Saab et al. 2012; van der Werff et al., 2013). Investigating the neurobiological mechanisms underlying both stress susceptibility and resilience contributes to a deeper understanding of the processes involved in stress-related disorders and might pave the way for new approaches to the prevention and treatment of these conditions (Charney 2004, Long et al., 2023).

The hippocampus, a pivotal brain region, is implicated in stress susceptibility and there is a wealth of evidence supporting the presence of altered hippocampal volume, function, and connectivity with other brain regions induced by acute and chronic stressor (Admon et al., 2013; Chen et al., 2019; Perica et al., 2021; Larosa and Wong 2022). For instance, using the Montreal Imaging Stress Task (MIST) to induce acute stress, Pruessner et al. observed a negative correlation between hippocampal volume and the cortisol response to the stressor, suggesting that

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https://doi.org/10.1016/j.ynstr.2023.100584
Received 13 September 2023; Received in revised form 18 October 2023; Accepted 25 October 2023
Available online 27 October 2023

as hippocampal volume decreased, the susceptibility to stress tended to increase (Pruessner et al., 2005). In individuals with PTSD, disorder severity was negatively predicted by hippocampal volume (Gilbertson et al., 2002; Apfel et al., 2011; Nelson and Tumpap 2017). More interesting, a prospective study revealed that the hippocampal volume of soldiers prior to deployment in Iraq could predict the subsequent onset of PTSD symptoms, suggesting that the hippocampus was not solely impacted by trauma but also functioned as a contributing risk factor for stress susceptibility (Cobb et al., 2023).

Beyond its involvement in stress susceptibility, the hippocampus also assumes a critical role in stress resilience (Pitman et al., 2006; Henningsen et al., 2012; van der Werff et al., 2013; Levone et al., 2015). Specifically, the hippocampus features a dense concentration of mineralocorticoid receptors and glucocorticoid receptors, thereby participating in the mechanism of glucocorticoid feedback inhibition, a pivotal facet of stress regulation (Sandi 2013; Chang and Yu 2019). Employing the Connor–Davidson Resilience scale to assess trait resilience, Van Rooij et al. revealed a positive correlation between hippocampal activation during a response inhibition task and the trait resilience scores in a cohort of highly traumatized women (Van Rooij et al., 2016). Further, heightened hippocampal activity observed during fear extinction shortly after experiencing a traumatic event predicted lower PTSD symptoms three months later (van Rooij et al., 2021). Additionally, studies had shown that individuals diagnosed with PTSD subsequent to trauma exhibited smaller hippocampal volumes compared to those who did not develop PTSD, underscoring the hippocampus's contribution to stress resilience from a structural perspective (Felmingham et al., 2009; Morey et al., 2012; van der Werff et al., 2013).

In addition to the hippocampus itself, its functional connectivity with the ventromedial prefrontal cortex (vmPFC) also plays a significant role in stress susceptibility and stress resilience. This critical involvement of the vmPFC, an integral component of the prefrontal cortex (PFC), in these stress-related processes has been consistently underscored by findings from both rodent and human studies (Morey et al., 2016; Sinha et al., 2016; Ginty et al., 2019; Grizzell 2019; Suzuki and Tanaka 2021). Furthermore, numerous studies have reported a negative correlation between the connectivity of the hippocampus and the vmPFC and stress susceptibility (Admon et al., 2013a; Herringa et al., 2013; Birn et al., 2014). For example, a prospective study demonstrated that the functional and structural connectivity between the hippocampus and the vmPFC diminished among soldiers exhibiting heightened post-traumatic stress disorder (PTSD)-related symptoms following stressful military service (Admon et al., 2013a). However, a recent study, aimed at investigating the relationships between hippocampus-PFC connectivity and stress responses related to COVID-19 in a cohort comprising adolescents and young adults, found that heightened connectivity between the vmPFC and the hippocampus corresponded to increased feelings of stress associated with the epidemic, and this effect was most pronounced among the adolescent subset of the cohort (Perica et al., 2021). The inconsistent findings in the literature suggested the need for further research to explore the relationship between the hippocampus-vmPFC connectivity and stress susceptibility. Regarding the stress resilience, previous studies have indicated that a greater connectivity between the hippocampus and the vmPFC was associated with an enhanced capacity to regulate fear responses, which was believed to facilitate resilience (Milad et al., 2007; Admon et al., 2009; Graham and Milad 2011, Admon et al., 2013; Feder et al., 2019; Roeckner et al., 2021). Following military service, an increase in functional connectivity between the hippocampus and vmPFC was associated with a smaller magnitude of increase in stress-related behavioral symptoms (Admon et al., 2009).

While having found the distinct roles of the hippocampus playing in the molecular mechanisms of stress vulnerability and stress resilience in rodent researches (Henningsen et al., 2012; Larosa and Wong 2022, Long et al., 2023), there is a significant lack of studies that has directly assessed and compared the role of the hippocampus, especially its connectivity with the vmPFC, in stress susceptibility versus stress resilience following trauma in humans. However, such investigations are of paramount importance for gaining a comprehensive understanding of these stress-related processes and furthering our knowledge of stress-related disorders (Franklin, Saab et al. 2012). In addition, an ideal approach to investigate the neurobiological mechanisms underlying stress susceptibility and resilience would involve a prospective and longitudinal study design, encompassing a baseline assessment prior to trauma exposure, followed by repeated assessments post-trauma (van der Werff et al., 2013). Such a design would offer valuable insights into whether the identified neurobiological mechanisms were a result of stress induction or represent precursors to stress responses (Vermetten et al., 2003; Admon et al., 2013; van der Werff et al., 2013). The COVID-19 pandemic is one of the largest global pandemics in recent years, rapidly spreading within a short period of time and imposing immense stress on individuals in various aspects of their lives, including their health, academic pursuits, and overall well-being, ultimately resulting in the emergence of mental health issues, such as PTSD and depressive symptoms (Qiu et al., 2020; Tang et al., 2020; He et al., 2021; Perica et al., 2021; Watson 2022). For instance, a study conducted one month after the outbreak of the COVID-19 epidemic assessed the prevalence of PTSD and depression among 2485 Chinese college students from six universities. The findings indicated that 2.7% of participants exhibited symptoms consistent with PTSD, and 9.0% displayed symptoms indicative of depression (Tang et al., 2020). In this prospective study, a cohort of participants, who had previously undergone resting-state functional magnetic resonance imaging (fMRI) prior to the onset of the COVID-19 pandemic, were recruited again to explore the role of the hippocampus during stress susceptibility and resilience in the context of this epidemic.

In this study, firstly, we intended to investigate the distinct contributions of hippocampus-vmPFC connectivity to stress susceptibility and stress resilience related to COVID-19. Moreover, we incorporated spectral dynamic causal modelling (spDCM) to capture the effective connectivity pattern between the hippocampus and the vmPFC. The spDCM, an extension of DCM at resting state, estimates effective connectivity in the frequency domain, offering higher computational efficiency and enhanced sensitivity to group differences (Friston et al., 2014; Razi et al., 2015; Uscătescu et al., 2021; Zhou et al., 2023). Compared with granger causal analysis, DCM is typically employed for addressing questions about the connectivity architectures responsible for observed regional responses after an initial exploratory analysis (Friston 2011). Notably, a recent study implemented spDCM and established a negative correlation between the self-connection of the right amygdala and the experience of stress during the COVID-19 pandemic (Zhou et al., 2023). Based on previous studies (Admon et al., 2013; Feder et al., 2019), we hypothesized that the connectivity between the hippocampus and vmPFC would exhibit a negative correlation with stress susceptibility, while demonstrating a positive relationship with stress resilience. Given the limited availability of relevant literature, we refrained from making explicit hypotheses regarding the outcomes of the spDCM analysis.

2. Methods

2.1. Participants

Between February 14th and 17th, 2020, the most serious period of the COVID-19 pandemic in China, a cohort of eighty-three participants, who had previously undergone resting-state functional magnetic resonance imaging (fMRI) prior to the pandemic, were invited to complete an online questionnaire survey aimed at capturing and assessing their stress feelings about the prevailing pandemic circumstances. Five participants exhibited excess motion (>2.5 mm in translation or 2.5° in rotation) during the scanning procedure and were excluded, thus yielding 78 participants for the following analyses and second survey (age: 22.000 ± 2.000 years (19–28 years); 47 females; see Table 1). To assess the participants' recovery from stress (i.e., the stress resilience),

Table 1
Demographic characteristics of dataset.

	N	Female		Age (Years)	
		N	%	Mean	SD
First survey	78	47	60.256	22.000	2.000
Second survey	69	41	59.420	22.029	2.000

N, number; SD, standard deviation.

approximately five months later, i.e., during July 18th and 24th, seventy-two out of the 78 participants completed the online questionnaire survey again to evaluate their COVID-19-related stress feelings in the past month (see Fig. 1). During this temporal span, there was no locally-transmitted confirmed COVID-19 cases across the majority of the Chinese mainland, except the Xinjiang Uygur Autonomous Region. To avoid the interference stemming from ongoing anxiety regarding infection risk, three participants from the Xinjiang Uygur Autonomous Region were excluded from subsequent analyses associated with stress resilience (69 participants left, age: 22.029 ± 2.000 years (19–28 years); 41 females; see Table 1). All participants were healthy and without a history of major medical, psychiatric, or neurological disease. They provided written informed consent online according to protocols approved by the South China Normal University Institutional Review Board.

2.2. COVID-19 related stress feelings measures

The stress feelings were assessed using a 5-item self-report questionnaire, initially created during the early stages of the COVID-19 pandemic when dedicated scales for assessing COVID-related stress were limited. The questionnaire was developed based on the input of approximately 15 individuals who were asked to describe the impact of COVID-19 on their lives. The final questionnaire items were selected to minimize participant burden while capturing the most salient aspects of their stressful experiences. For the first survey, the questionnaire included the following items: "To what extent are you experiencing panic related to COVID-19?", "To what extent are you concerned about contracting the novel coronavirus?", "Do you always feel discomfortable (such as fever or shortness of breath) since the onset of the epidemic?", "To what degree are you preoccupied with COVID-19?", "To what extent do you perceive pressure due to this epidemic?". The items in the second survey remained consistent with those in the first survey; however, in order to emphasize the period during which the epidemic was effectively managed, we designated the past month as the temporal frame for each item in the second survey. For example, the first item of the second survey was "To what extent are you experiencing panic related to COVID-19 in the last month?". Each item was rated on a 5-point intensity scale from 1 (not at all) to 5 (extremely).

2.3. Imaging protocol

Brain Images were obtained in a 3-T MRI scanner (Siemens) using a 12-channel head coil. T1-weighted images were collected with the following parameters: repetition time (TR) = 1900 ms, repetition time (TE) = 2.52 ms, field of view (FOV) = 256 × 256 mm, matrix size = 256 × 256, flip angle = 9° and 1 mm^3 isotropic voxel. Functional blood oxygenation level dependent (BOLD) signals were then acquired with a single-shot gradient echo echo-planar imaging (EPI) sequence. Thirty-one axial slices parallel to the AC-PC line covering the whole brain were acquired with TR = 2000ms, TE = 30 ms, FOV = 224 × 224 mm, flip angle = 90°, matrix = 64 × 64, in-plane voxel size = 3 × 3 mm, 31 slices with slice thickness = 3 mm and no gap. Slice scanning order was ascending interleaved. Two hundred and forty images were acquired for the resting state scan. During the resting-state fMRI scanning, participants were instructed to close eyes, keep awake and think of nothing in particular.

2.4. Imaging data processing

We adopted the Statistical Parametric Mapping version 8 (SPM8, Wellcome Department of Imaging Neuroscience, University College London, U.K.) and Data Processing & Analysis for (Resting-State) Brain Imaging (DPABI; http://rfmri.org/DPABI) (Yan et al., 2016) to preprocess and analyze the fMRI data. After discarding the first 10 vol, the remaining 230 fMRI volumes were first slice-time corrected and later motion corrected using a least squares approach and a 24-parameter autoregressive model (Friston 24-parameter model) (Friston et al., 1996). The participants had excess head motion (>2.5 mm in translation or 2.5° in rotation) were excluded. Next, motion-corrected functional data were co-registered to the individual T1-weighted images. The resulting aligned images were segmented into grey matter, white matter, and cerebrospinal fluid (CSF). The 24 head-motion parameters, CSF, white matter and global signals were then regressed out to remove these nuisance signals. The Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra (DARTEL) technique was used to create an average structural brain template from all subject's T1 images (Ashburner 2007). The functional images were normalized into a standardized MNI space using the DARTEL template, re-sampled to 3 mm × 3 mm × 3 mm isotropic voxel, and spatially smoothed with a 6 mm FWHM Gaussian filter. To reduce the effect of very low frequency drift and high frequency physiological noise, the images were temporally band-pass filtered into 0.01–0.1 Hz.

To further address head motion concerns in resting-state fMRI analyses, we calculated the voxel-specific framewise displacement (FD) (Power et al., 2012; Power et al., 2014). The FD measure indexes the movement of the head from one volume to the next and is calculated as the sum of the absolute values of the differentiated realignment estimates (by backward differences) at every time point (Power et al., 2012). For 78 participants of the first survey, one-sample *t*-test showed that the group mean FD was significantly less than 0.2 mm (Mean ± SD: 0.062 ± 0.028; $t(77) = -43.344, p < 0.001$). The group mean FD was also significantly less than 0.2 mm (Mean ± SD: 0.062 ± 0.029; $t(68) = -39.425, p < 0.001$) for the 69 participants in the second survey. The frames with FD > 0.5 mm were removed ("scrubbing"), and one

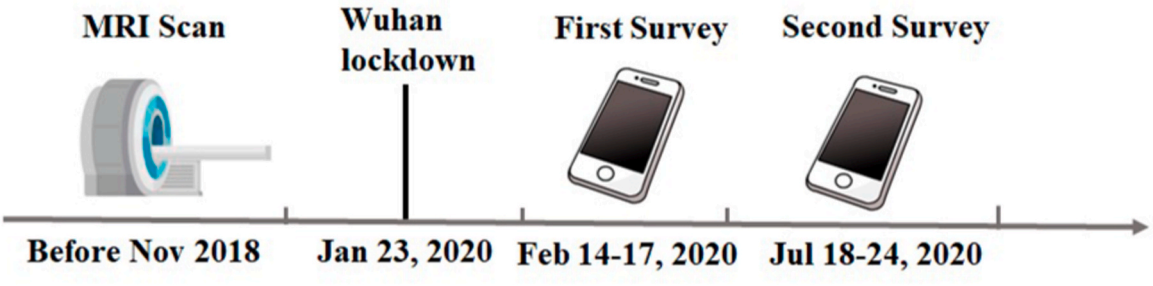

Fig. 1. The time axis of the data collection.

time point before the "bad" time points and two time points after the "bad" time points were deleted for functional connectivity analysis (Li et al., 2016). To further reduce the motion-related artifacts, we added the FD value as a covariate in following analyses.

2.5. Functional connectivity analysis

The ROIs for functional connectivity analysis, i.e., bilateral hippocampus, were defined using the corresponding AAL mask (Tzourio-Mazoyer et al., 2007). We used the DPABI toolbox to conduct the functional connectivity analysis. For each ROI, the correlation coefficient between the averaged time course of this seed region and the time course of the rest brain voxels were computed and thus created r value image maps for individual subjects. Then, these image maps were converted to z score maps by Fisher's z transform (Watts and Jenkins 1968).

We used the stress feelings score obtained in the first survey as an index of stress susceptibility. Additionally, we employed the percentage change in scores between the first and second surveys ((stress feelings score $_{\text{(first survey)}}$- stress feelings score $_{\text{(second survey)}}$)/stress feelings score $_{\text{(first survey)}}$) as an indicator of stress resilience, in order to account for the impact of the initial score in the first survey (Austevoll et al., 2019). To examine the hippocampus-based functional connectivity network which was associated with individual difference in stress susceptibility and resilience respectively, we conducted whole brain multiple regression analyses for each seed by using the z score maps as the dependent variable, and stress feelings score in the first survey or percentage change in scores between the two surveys as the independent variable. To exclude the influence of age, gender and head motion (i.e., FD value), we added them as covariates when conducted the multiple regression analyses. For all reported analyses, the results were evaluated at a threshold of voxel-level family-wise error (FWE) corrected $p < 0.05$ using small volume correction (SVC) on images with an uncorrected voxel threshold of $p < 0.005$. Given the previous works highlighting the role of the vmPFC and its connectivity with the hippocampus in stress susceptibility and resilience (Admon et al., 2009; Morey et al., 2016; Perica et al., 2021), we selected the vmPFC as ROI in our present study, which was defined as an 6 mm sphere centered at MNI (±4, 54, 0) that consistently showed stress-related activity in this specific brain region (Qin et al., 2009; Treadway et al., 2013; Uy and Galván 2017).

It was worth noting that the present study used methods the same as or similar to those in our prior publications (Chang and Yu 2018; Chang and Yu, 2018b; Chang and Yu 2019). Consequently, some text included here was recycled from those sources.

2.6. Spectral dynamic causal modeling

In addition to the results of multiple regression analyses revealing the relationship between left hippocampus-left vmPFC functional connectivity (see Results section) and stress susceptibility and resilience, we adopted the spDCM to further identify whether the commonalities and differences across participants in stress susceptibility and resilience were expressed differently in effective connectivity between left hippocampus and left vmPFC. The spDCM analysis was conducted with the DCM12.5 routine implemented in SPM12. We took the left hippocampal mask from AAL and left vmPFC defined for SVC (i.e., an 6 mm sphere centered at MNI (−4, 54, 0)) as the volume of interest (VOI). After extracting the principal eigenvariate of the VOIs, we created a full and reciprocal connected model for each participant, which included the bidirectional connectivity between the two VOIs and the intrinsic self-connections of them. Unlike DCM under tasks, the spDCM only contained endogenous connectivity (matrix A) (Friston et al., 2014; Crone et al., 2015, Wang et al., 2019). The individual models were jointly estimated based on variational Laplace under the frequency domain. The convolution kernel representation of the models was converted into a spectrum representation and expressed in the frequency domain (Friston et al., 2014; Wang et al., 2019). Having estimated of the connectivity strengths for each participants, we used the Parametric Empirical Bayes (PEB) framework to test the commonalities across participants in effective connectivity and the relationship between connectivity strengths and behavioral indexes (i.e., stress susceptibility and resilience in this study) in second-level analysis (Zeidman et al., 2019). We specified two PEB models with stress susceptibility and stress resilience as regressor respectively. After estimating the PEB model, we used the automatic search to perform model comparison, which will reduce the parameters that have no contribution to the model evidence. The Bayesian Model Average (BMA) was then computed for the two PEB models separately to return the average of the parameters across all models weighed by their posterior probabilities. We focused on the parameters with strong evidence (95% probability) (Zeidman et al., 2019). We further adopted the Leave One Out cross-validation to test whether the connectivity that found having correlation with the behavioral indexes could predict the left-out participant's behavioral performance (Zeidman et al., 2019; Voigt et al., 2020).

3. Results

3.1. Stress feelings results

For the first survey conducted in the outbreak period of epidemic, the stress feelings score for the cohort of 78 participants was 11.423 ± 2.452 (mean ± SD), with a higher score indicating heightened stress susceptibility. The percentage change in stress feelings score for the 69 participants between the first and second surveys was 0.323 ± 0.227 (mean ± SD), which was significantly different from zero ($t(68) = 11.792$, $p < 0.001$), showing that participants' stress feelings decreased significantly during the second survey compared to the first. Furthermore, a higher percentage change indicated a greater level of stress resilience.

3.2. Resting state functional connectivity results

For the left hippocampus seed, the results of multiple regression analysis showed that the connectivity between the seed and the left vmPFC ([−6 54 -3], voxel = 12, $p = 0.010$, SVC corrected) was negatively correlated with the stress feelings score in the first survey (Fig. 2A). Specifically, higher stress feelings score (indicative of heightened stress susceptibility) was associated with diminished connectivity between the left hippocampus and left vmPFC. In addition, we found that the connectivity between the left hippocampus and the left vmPFC ([−3 54 0], voxel = 3, $p = 0.034$, SVC corrected) was also negatively correlated with the percentage change in stress feelings score (Fig. 2B). A greater percentage change, i.e., a higher level of stress resilience, was correlated with weaker connectivity between the left hippocampus and left vmPFC. For the right hippocampus seed, no such results were observed (all $ps > 0.050$).

3.3. Spectral dynamic causal modeling results

Based on the findings of functional connectivity analyses, we further adopted the spDCM to explore the relationship between the left hippocampus-left vmPFC effective connectivity and stress susceptibility and resilience. For stress susceptibility, as showed in Fig. 3A, in common cross participants, there were excitatory connectivity from the left vmPFC to the left hippocampus, self-inhibition in the left hippocampus and inhibitory connectivity from the left hippocampus to the left vmPFC. Notably, we found a positive correlation between the stress feelings score from the first survey and the self-inhibition effect of the left vmPFC, showing that the participant with stronger self-inhibition of the vmPFC experienced more stressful feelings in this epidemic, i.e., was more vulnerable to the stressor. For stress resilience, there was excitatory connectivity from the left vmPFC to the left hippocampus, along with self-inhibition in the left hippocampus across participants. No significant correlation was observed between any effective connectivity

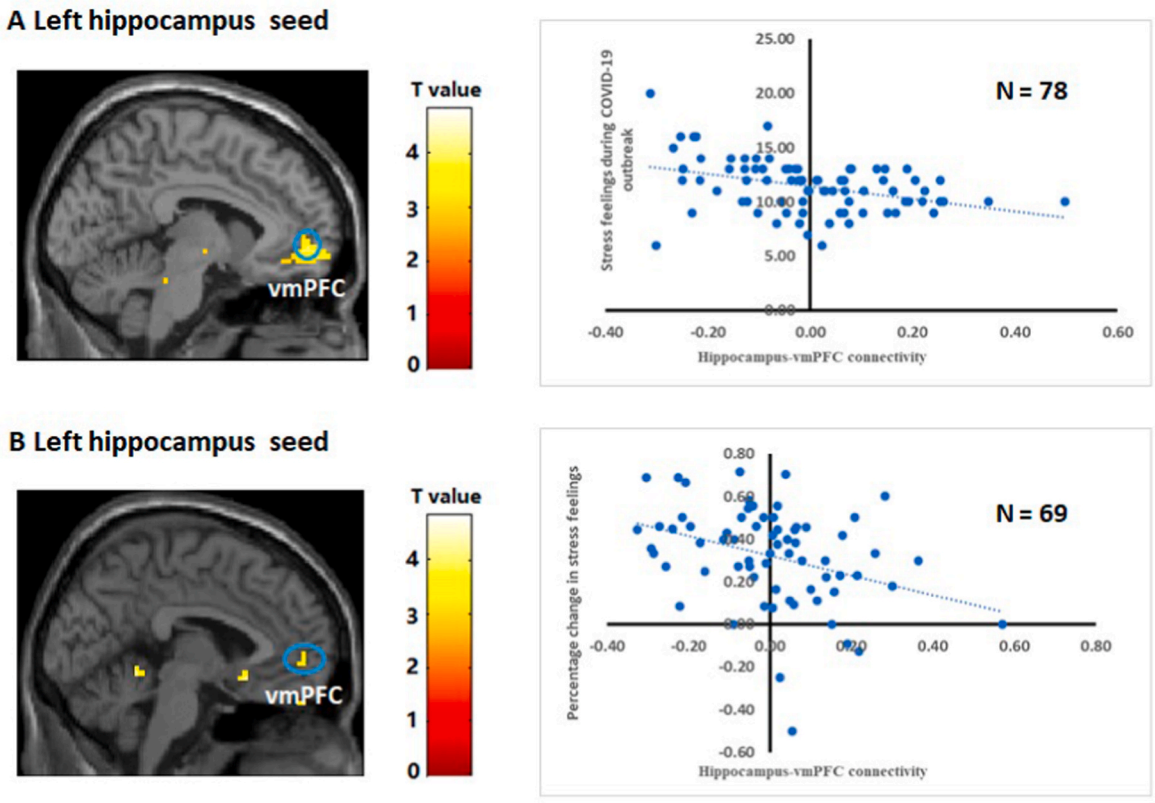

Fig. 2. The results of multiple regression analyses. (A) the connectivity between the left hippocampus and the left vmPFC ([-6 54 -3], voxel = 12, $p = 0.010$, SVC corrected) was negatively correlated with the stress feelings score in the first survey; (B) the connectivity between the left hippocampus and the left vmPFC ([-3 54 0], voxel = 3, $p = 0.034$, SVC corrected) was negatively correlated with the percentage change in stress feelings score. vmPFC, ventromedial prefrontal cortex; N, number.

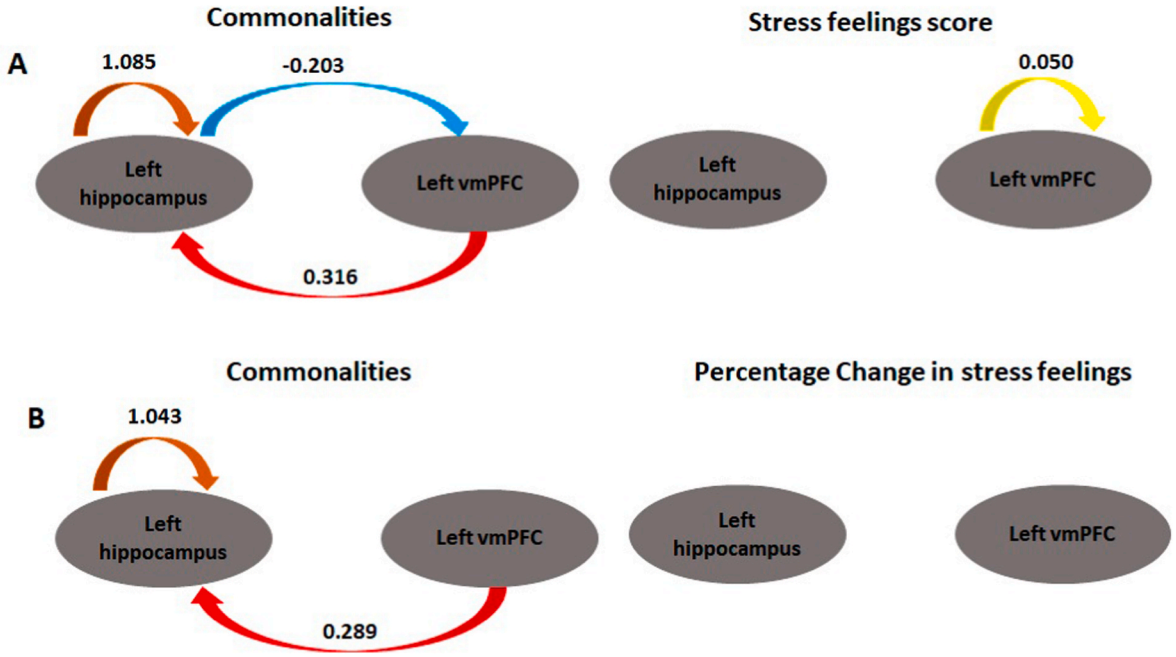

Fig. 3. The results of spectral dynamic causal modeling. (A) Left: the red arrow indicates the excitatory effective connectivity and the blue arrow indicates the inhibitory effective connectivity. The orange arrow represents self-inhibition. The values indicate the connectivity strength; Right: the yellow arrow represents a positive correlation between the self-inhibition of the vmPFC and stress feelings score; (B) Left: the red arrow indicates the excitatory effective connectivity and the orange arrow represents self-inhibition. The values indicate the connectivity strength; Right: none of the effective connectivity values had significant correlation with percentage change in stress feelings. vmPFC, ventromedial prefrontal cortex. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

value and the stress resilience index, defined as the percentage change between the two surveys (Fig. 3B).

We further used leave-one-out cross validation to address whether stress feelings-related effectivity connectivity (i.e., the self-inhibition effect of the left vmPFC) could predict a participant's stress feelings score. The results showed that the Pearson's correlation coefficient between the actual stress feelings score and predicted values for each left-out participant was 0.200 ($p = 0.040$), suggesting that the self-inhibition effect in the vmPFC was large enough to predict a participant's stress susceptibility in COVID-19 outbreak period.

4. Discussion

The present study investigated the role of both undirected and directed connectivity between the hippocampus and vmPFC in relation to stress susceptibility and stress resilience within the context of the COVID-19 pandemic. The findings revealed a negative correlation between hippocampus-vmPFC connectivity and susceptibility to stress. Furthermore, this connectivity was also found to be negatively associated with the level of stress resilience approximately five months later. Additionally, the results of spDCM showed that the self-inhibition of the vmPFC displayed a positive link with stress susceptibility, and the self-inhibition effect was substantial enough to predict an individual participant's susceptibility to stress. Compared with the stress resilience, there was an extra inhibitory connectivity from the left hippocampus to the left vmPFC in the context of stress susceptibility.

In line with the proposed hypothesis, the observed connectivity between the hippocampus and vmPFC exhibited a negative correlation with stress susceptibility, consistent with findings from previous studies (Admon et al., 2013; Herringa et al., 2013; Birn et al., 2014). For instance, the hippocampus-vmPFC connectivity displayed a negative association with scores obtained from the Childhood Trauma Questionnaire, a measure assessing childhood maltreatment experiences (Herringa et al., 2013; Birn et al., 2014). In contrast to these findings, a recent study reported a positive connection between the hippocampus-vmPFC and COVID-19-related stress, with this effect being particularly pronounced among adolescents (Perica et al., 2021). We speculated that the inconsistence might be attributed to differences in the age range of participants. Given the ongoing brain development during adolescence, individuals in this age group process stress using distinct neural patterns compared to adults (Woon and Hedges 2008, Wu et al., 2021). For instance, a previous study demonstrated that perceived stress exhibited a positive correlation with the volume of the orbitofrontal cortex, the insula, and the amygdala in adolescents, while this correlation was reversed in adults (Wu et al., 2021). Both the vmPFC and hippocampus are components of the Default Mode Network (DMN), a neural network associated with self-referential thinking, mind-wandering, and autobiographical memory retrieval (Spreng et al., 2009; Qin and Northoff 2011, Lanius et al., 2015). Connectivity within the DMN had been observed to decrease following exposure to acute and chronic stress, with this decrease being correlated with core symptoms of stress-related disorders, such as disturbances in self-referential mental processing and the recollection of past experiences (Sripada et al., 2014; Lanius et al., 2015; Zeev-Wolf et al., 2019; Zhang et al., 2019). Our findings aligned with these studies and provided additional prospective evidence that healthy individuals with initially weaker connectivity within DMN (i.e., the hippocampus-vmPFC connectivity) experienced more intense stress feelings during a real-life traumatic event.

The observed negative association between hippocampus-vmPFC connectivity and stress resilience in our study contrasted with our original hypothesis. A recent review paper identified individuals with higher levels of resilience exhibiting increased hippocampal-vmPFC coupling prior to trauma, suggesting a potential protective role (Roeckner et al., 2021). It was noteworthy that the trauma types covered in the literature review encompassed various stressors such as military service, childhood maltreatment, and motor vehicle collisions, all of which were actual events experienced by the subjects in those studies. In our study, the participants did not experience actual infection with COVID-19 pneumonia. Consequently, the extent of stress exposure they encountered might have been comparatively milder than the scenarios documented in the literature. This distinction in stress exposure could potentially contribute to the differences observed in our results. The increased connectivity between the hippocampus and vmPFC was found during the episodic future thinking, a cognitive process which had been shown to be related with the symptoms of anxiety (Wu et al., 2015; Campbell et al., 2018; Perica et al., 2021). In addition, the hippocampus played a pivotal role in the persistence of traumatic memories, and its connectivity with the vmPFC was involved in memory retrieval and decision-making processes (Gluth et al., 2015; Postel, Mary et al. 2021). Therefore, as suggested by previous research, increased connectivity between these brain regions following trauma could lead to rumination on trauma-related memories, a symptom often observed in stress-related disorders (Hamilton et al., 2011; Zhu et al., 2017). In light of these findings, participants with heightened hippocampus-vmPFC connectivity in our study might be exhibiting a reduced capacity to adapt to the pandemic, specifically, a lower resilience level.

Although the hippocampus-vmPFC connectivity had negative correlation with both stress susceptibility and stress resilience, two distinct differences came to light upon comparing the respective spDCM result. Firstly, in the context of stress susceptibility, we identified inhibitory connectivity originating from the left hippocampus to the left vmPFC. Secondly, we uncovered a positive correlation between self-inhibition of the vmPFC and stress susceptibility, with this effect demonstrating significant predictive power regarding a left-out individual's susceptibility to stress. In summation, these findings pointed to heightened suppression of the vmPFC within the realm of stress susceptibility. The vmPFC, serving as a pivotal mediator of individual variations in stress responses, had been extensively implicated in stress modulation (Yang et al., 2018; Grizzell 2019). Notably, higher vmPFC engagement during acute stress has been linked to diminished hypothalamic-pituitary-adrenal reactivity and decreased self-reported stressfulness and arousal rating (Sinha et al., 2016). The vmPFC's significant role in stress modulation is further underscored by its robust connectivity with the amygdala. Specially, the vmPFC is believed to exert top-down inhibitory control over the amygdala, leading to the extinction of conditioned fear and the suppression of negative emotions (Phelps et al., 2004; Urry et al., 2006; Motzkin et al., 2015). In the context of stress-related disorder, like MDD and PTSD, it is proposed that dysfunctional vmPFC activity compromised the inhibition of the amygdala, leading to unregulated amygdala activity and pathological distress (Shin et al., 2006; Johnstone et al., 2007; Koenigs and Grafman 2009, Stevens et al., 2013). Taken together with these previous studies, the observed heightened inhibition of the vmPFC in stress susceptibility in our study might suggest the deficiency of the stress modulation, and thus was linked to increased feelings of stress during this pandemic.

While our study had provided valuable insights, it is crucial to acknowledge several limitations that require careful consideration. Firstly, we did not investigate the role of the amygdala, a well-established brain region implicated in stress responses (Roozendaal et al., 2009; McEwen et al., 2016; Chang and Yu 2018). While its involvement in stress susceptibility is well-documented, the amygdala's role in stress resilience remains less clear. For instance, in a rodent study, it was found that, unlike the hippocampus, which played a role in both stress vulnerability and resilience, the amygdala was primarily associated with stress vulnerability (Long et al., 2023). Similar results had been observed in human cohorts, where the amygdala and its associated connectivity network were linked to stress responses during the COVID-19 pandemic but did not demonstrate the same significance in stress resilience (Zhou et al., 2023). In our study, which aimed to explore and compare the neural mechanisms underlying stress susceptibility and stress resilience, we opted not to include the amygdala as a region of interest. Secondly, we did not investigate the impact of crucial

environmental factors contributing to individual variations in stress susceptibility and stress resilience, such as social status and social support (Eisenberger et al., 2007; Muscatell et al., 2016; Nitschke et al., 2021; Laymon 2023). For instance, in the context of social evaluation stress, individuals with lower subjective social status displayed more pronounced increases in inflammation, indicating heightened stress susceptibility (Muscatell et al., 2016). In addition, lower levels of self-reported perceived stress, along with diminished general and COVID-19-specific concerns, were linked to increased social connectedness during the lockdown period, indicative of enhanced stress resilience (Nitschke et al., 2021). Future research endeavors could incorporate these environmental factors to thoroughly and comprehensively explore the neural mechanisms that underlie both stress susceptibility and resilience. Thirdly, it is essential to acknowledge that our study employed a simplified self-report questionnaire for assessing stress feelings, which does not represent a standardized or structured scale for measuring stress-related outcomes. Its application allowed for initial insights into the stress experiences of our participants during a unique and challenging period—the early stages of the COVID-19 pandemic. By emphasizing the preliminary nature of our findings, we underscore the need for future research to employ more comprehensive stress assessment tools, a step that will contribute to a deeper understanding of the neural mechanisms underlying stress susceptibility and resilience.

Funding

We acknowledge Natural Scientific Foundation of China (No. 32100873) and the Fundamental Research Funds for the Central Universities (No. 2072021132) to J. Chang for financial support. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

CRediT authorship contribution statement

Jingjing Chang: developed the study, Conceptualization, collected, analyzed and interpreted the data under the, Supervision, of, Writing – original draft, the manuscript. **Di Song:** collected, analyzed and interpreted the data under the, Supervision, of, Writing – original draft, the manuscript, All authors approved the final version of the manuscript for submission. **Rongjun Yu:** developed the study, Conceptualization, Writing – original draft, the manuscript, provided critical revisions.

Declaration of competing interest

The authors declared that they had no conflicts of interest with respect to their research, authorship or the publication of this article.

Data availability

Data will be made available on request.

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