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The Hippocampal–Ventral Medial Prefrontal Cortex Neurocircuitry Involvement in the Association of Daily Life Stress With Acute Perceived Stress and Cortisol Responses

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ABSTRACT

Objective: Daily life stressors include everyday irritants, hassles, and inconveniences, such as problems in traffic and unexpected work deadlines. A growing body of research has suggested higher daily stress is associated with blunted cortisol response to acute psychosocial stressors. However, so far, the neural mechanism underlying this association has not been elucidated. The current study aimed to examine the role of stress neurocircuitry between the hippocampus and the ventral medial prefrontal cortex in this relationship.

Methods: To this end, as an index of daily stress in 44 young healthy individuals (23 females; mean [standard deviation] age = 19.07 [1.11] years), the total stressful rating score of daily life stress events that occurred in a 24-hour period was quantified. Individuals were then administered a modified version of the Montreal Imaging Stress Task while undergoing functional magnetic resonance imaging scans, and their saliva samples were collected for assessment of the stress hormone cortisol.

Results: Results revealed that a higher level of daily stress was associated with lower salivary cortisol secretion ($r = -0.39$, $p = .008$) and lower activation of the left hippocampus ($t_{peak} = -5.51$) in response to the Montreal Imaging Stress Task. Furthermore, a higher level of daily stress was associated with stronger functional connectivity between the left hippocampus and the ventral medial prefrontal cortex/subgenual anterior cingulate cortex ($t_{peak} = 4.91$, $R^2 = 0.365$).

Conclusions: Taken together, the current study suggested a possible neurocircuitry of the hippocampus and ventral medial prefrontal cortex in the relationship between daily life stress and acute psychosocial stress.

Key words: daily stress, acute psychosocial stress, neurocircuitry, hippocampus, ventral medial prefrontal cortex.

INTRODUCTION

Previous studies have established that acute exposure to stressful stimuli is accompanied by an increased hypothalamic-pituitary-adrenal (HPA) activity, resulting in heightened cortisol levels (1–3). However, these responses to acute stressors are affected by daily background stress (4,5), which refers to the everyday irritants, hassles, and inconveniences, such as problems in traffic, bad weather, and unexpected work deadlines (6–8). Indeed, some studies have found reduced responses to acute stressors due to repeated or prolonged exposure to mild stressful experiences, such as perceived stress at work (9), stress-related to examinations at the end of a semester (10), or daily stress levels as measured by the Perceived Stress Scale (11). These studies have all consistently highlighted a blunted response (physiologically reflected in diastolic blood pressure, heart rate reactivity, and levels of cortisol and dehydroepiandrosterone) to acute stressors in the presence of a mild daily stressor. Researchers have further suggested that the blunted responsiveness of stress hormones to acute psychosocial stressors is a result of stress habituation, which occurs after low-to-medium intensity stimuli presented at an increased frequency of exposure (12). After repeated stress, the stress response system maintains a high activity state resulting in heightened stress hormonal level, which subsequently results in reduced responsiveness to any new stressful stimuli (3,13–15).

Based on the health-neuroscience studies, the brain is the central, top-down regulator of behaviors and parameters of peripheral physiology that impact physical health (16). It is also the critical organ orchestrating adaptive and maladaptive responses to stressors. Specifically, it evaluates whether stimuli are threatening and potentially stressful, then initiating the behavioral and many of the physiological responses to the stressors, which in and of themselves can either be adaptive or damaging (17,18). A very recent study assessed hair cortisol over the last 3 months as a marker of the long-term background stress level and found that higher long-term background stress was associated with lower activation of the dorsal anterior

AAL = anatomical automatic labeling, **DSI** = Daily Stress Inventory, **FDR** = false discovery rate, **fMRI** = functional magnetic resonance imaging, **HPA** = hypothalamic-pituitary-adrenal axis, **MIST** = Montreal Imaging Stress Task, **MNI** = Montreal Neurological Institute, **sgACC** = subgenual region of the anterior cingulate cortex, **vmPFC** = ventromedial prefrontal cortex

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cingulate cortex in response to the acute stressors (19). Notably, although both the long-term stress and the daily life stress could be classified into background stress, the daily stress is more transient and has more proximal physiological and psychological effects than the long-term background stress (7,20,21). However, so far, the neural mechanism underlying the impact of daily life stress on acute stress reactivity has not been elucidated.

The hippocampus is part of the limbic system and is an important component of the neural circuitry that coordinates behavior through modulating neuroendocrine, immune, and autonomic functions for adaptive coping to environmental and psychosocial challenges (22–26). Studies have consistently established that the hippocampus plays an important role in negative feedback inhibition of the HPA axis in response to stressors (1,24). Accordingly, the hippocampal activity will increase to shut down the activated HPA axis when exposed to stressors. Specifically, the stimulation of hippocampus decreases HPA axis activity, whereas hippocampal lesions and total hippocampectomy increase HPA axis activity (1,27–30). In line with this notion, a growing body of research has suggested that there is a stronger activation of hippocampus in the stress compared with the control condition (31–35). Regarding the association between daily life stress and acute stress response, studies have shown that higher daily stress elicited greater basal activity of the HPA axis (daily cortisol secretion) (6,36–38). Individuals with high daily stress may maintain a state of higher level of hippocampus activity, which may subsequently result in a reduced activity to new stressful stimuli.

In addition to the limbic system, stress reactivity is also regulated by the central nervous system through coordinated circuitry integrating the limbic and prefrontal brain regions (1,39). The ventromedial prefrontal cortex (vmPFC), encompassing the subgenual region of the anterior cingulate cortex (sgACC), is thought to be critical both in endocrine regulation, affective regulation, and behavioral coping (40–44). For example, more activation of vmPFC in response to the stressor predicted more positive emotions and less negative emotions during stress recovery (16,45). Moreover, studies have found that activation of the pathway between vmPFC and the hippocampus facilitated the extinction of fearful memory information (40,46–49). A decrease in functional connections between vmPFC and the hippocampus is thought to be a neural marker of inadequate fear extinction ability, which may lead to elevated pathology and stress-related disorder (49,50). Furthermore, stronger hippocampus-vmPFC connectivity was related to weaker stress symptoms after stressful experiences (50,51). Regarding the association between daily life stress and acute stress response, previous studies have found that, after repeated exposure to military stress, the functional connectivity between vmPFC and the hippocampus increased in response to stress cues compared with preexposure (50,51). These findings suggest that higher daily stress may be correlated with higher hippocampus-vmPFC connectivity in response to a new stressor.

In sum, the current study sought to examine the possible neurocircuitry between daily life stress and acute psychosocial stress. Generally, daily stress fluctuates from day to day, and research has found that the daily stress exhibited low consistency for 28 consecutive days (8). Moreover, daily stress is closely related to the spikes in arousal or psychological distress that day (51,52), and its effects and the stress itself are expected to moderate or disappear within a day or two (15,53). Thus, we measured the total stressful rating score of daily life stress events that occurred in the 24 hours before acute stressors as an index of the degree of exposure to daily stress. Individuals also underwent a modified Montreal Imaging Stress Task (MIST) that was used to induce an acute stress response during functional magnetic resonance imaging (fMRI) scanning (52). Here, we hypothesized that a higher level of daily background stress would lead to a blunted cortisol stress response and reduced hippocampal activation in the acute psychosocial stress task. We further hypothesized that a higher level of daily background stress would lead to an enhanced regulatory role of vmPFC/sgACC on negative emotions elicited by the acute stressor, eventually resulting in stronger functional connectivity between the hippocampus and vmPFC/sgACC.

METHODS

Participants

Forty-eight healthy university students were recruited as paid volunteers through Internet advertising. All participants were free of any psychiatric or physical illness, drug abuse, or alcoholism (as indicated by self-report). Four participants were excluded because of excessive head movement during fMRI scanning (translation >2.5 mm or rotation >2.5 degrees) or missing data (resulting from sample contamination or an insufficient volume of saliva), resulting in a final sample of 44 participants (23 females; mean [standard deviation] age = 19.07 [1.11] years). Because the poststress cortisol levels of women in the luteal phase approach those of men, the female participants in the current study were all in their luteal phase (as indicated by self-report) (53). Participants were asked not to smoke on the day of their appointment or engage in any strenuous exercise, drink alcohol or caffeine, eat, or brush their teeth within 1 hour before the testing session. All participants provided written informed consent. The study was approved by the review board of a local university, and all work was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki).

Daily Life Stress

The Daily Stress Inventory (DSI) was used to assess participants' perceived daily life stress. The DSI consists of 58 items that describe various stressful events of daily life, such as "can't finish the assigned work," "was misunderstood by others," or "argued with another person" (7). If the event did not occur in the past 24 hours, participants are asked to denote a "none" response to that item. If the event did occur, participants are asked to indicate the stress level by placing a number from 1 (occurred but was not stressful) to 7 (caused me to panic). There are three indicators to DSI including a) the number of items that are endorsed as having occurred (FREQ), b) the total stress level of items denoted as having occurred (SUM), and c) the average stress level (AIR = SUM divided FREQ). Because FREQ ignores that one's perception of the event may lead to the severity of the stress experienced (54–57), AIR emphasizes the average perception of stressful events ignoring the number of times stressful events are repeated (12), and SUM is a comprehensive index considering both quantity (number) and quality (perception). Thus, in the current study, SUM was quantified as an indicator of daily stress levels.

The Montreal Imaging Stress Task

Participants completed a modified version of the MIST, a well-validated psychosocial stress inducer and MRI-adapted protocol to administer during fMRI scanning (52). The MIST used in this study consisted of a block design with three imaging runs. Each run consisted of two conditions: a stressful experimental condition and a nonstressful control condition. Each condition was repeated once per run (order: control-stress-control-stress, 70 seconds for control condition and 140 seconds for stress condition), resulting in a total time of 7 minutes per run.

In both conditions, participants are asked to answer arithmetic questions on a computer screen, to which they have to respond by choosing a one-digit number from a rotary dial using a button mouse. In the stressful experimental condition, the difficulty of arithmetic questions is adapted to participants' performance to yield a 45% to 50% performance range. Participants are asked to answer the arithmetic questions with a time limit, which is presented within a visible progress bar. These settings ensured a higher rate of incorrect responses, and a mock performance indicator on the computer screen shows the poor performance of the participant in comparison to the dummy average others. Moreover, participants are provided with negative verbal feedback via headphones between each run. In this study, to increase participants' feelings of being socially evaluated, the original MIST was modified by creating a monitoring screen with the image of a strict evaluator's face under the experimental stress condition. In the nonstressful control condition, participants are asked to answer arithmetic questions without a time limit and they would not receive any feedback on their performance (Figures 1A, B).

Procedure

Data were collected between September 2017 and March 2018. All experiments were conducted between 1:30 PM and 5:00 PM to control cortisol's circadian rhythm. Figure 1C also outlines the experimental procedure. After participants arrived at the laboratory, they rested for 30 minutes and filled out the questionnaires. Seven saliva samples were collected in total, including the Cort1 sample called *Prescanning*, acquired immediately before participants entered the scanner; the Cort2 sample called *PreMIST*, acquired after the resting-state fMRI and T1 image scanning; the Cort3 sample called *Run1*, acquired after the first run of the MIST; the Cort4 sample called *Run2*, acquired after the second run of the MIST; the Cort5 sample called *Run3*, acquired after the third run of the MIST; the Cort6 sample called *Rest1*, acquired after a 15-minute rest; and the Cort7 sample called *Rest2*, acquired after a further 10-minute rest. To obtain participants' saliva samples in the scanner, the experimenter handed a saliva tube to the participant at the end of each run. Participants put the tube in their mouth and chewed for about 50 seconds. Afterward, participants expelled the tube and handed it back to the experimenter, at which point they were ready for the next experimental task. Participants' subjective stress reports were assessed by oral reports via the microphone in the scanner, just after the saliva sample collection. Each sampling lasted about 3 minutes.

Psychological and Physiological Measures

Self-reported subjective stress was used to rate participants' perceived stress levels on a 7-point Likert scale ranging from 1, corresponding to "not stressful," to 7, corresponding to "terribly stressful." Saliva samples were collected with a specific sampling device (Salivette; SARSTEDT, Nümbrecht, Germany) to assess cortisol levels throughout the experiment. All saliva samples were stored at room temperature until completion of the experiment, after which they were kept in a −20°C freezer until final analysis. Cortisol concentrations were analyzed by an enzyme-linked immunosorbent assay (IBL, Hamburg, Germany) following the manufacturer's instructions. The sensitivity of the cortisol assay was 0.005 μg/dl, and the interassay and intra-assay coefficients of variation for the cortisol assay were 3.2% and 6.1%, respectively.

fMRI Data Acquisition

Functional and anatomical whole-brain images were acquired in a 3 T Siemens Trio MRI scanner. Six hundred fifty-four volume-functional images were acquired from each participant with a T2*-weighted gradient echo-planar imaging sequence. We obtained 32 echo-planar images per volume

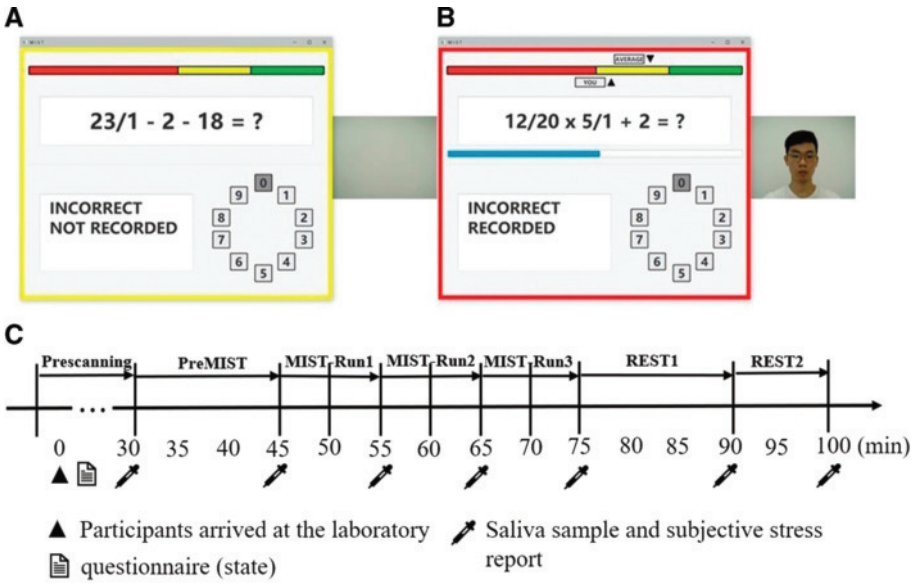

FIGURE 1. Visualization of the MIST and experimental procedure. A, Nonstressful control condition of the modified version of the MIST. Participants are asked to answer arithmetic questions without a time limit, leading to a high number of correct responses. Nothing is shown on the monitoring screen. B, Stressful experimental condition of the modified version of the MIST. Participants answer the arithmetic questions with a time limit and a visible progress bar, leading to a high number of incorrect responses. The image of an evaluator's strict face is shown on the monitoring screen. C, Experimental procedure. After participants arrived at the laboratory, they rested for 30 minutes and filled out the questionnaires. Seven saliva samples were collected in total, including the Cort1 sample called *Prescanning*, acquired immediately before participants entered the scanner; the Cort2 sample called *PreMIST*, acquired after the resting-state fMRI and T1 image scanning; the Cort3 sample called *Run1*, acquired after the first run of the MIST; the Cort4 sample called *Run2*, acquired after the second run of the MIST; the Cort5 sample called *Run3*, acquired after the third run of the MIST; the Cort6 sample called *Rest1*, acquired after a 15-minute rest; and the Cort7 sample called *Rest2*, acquired after a further 10-minute rest. Participants' subjective stress reports and saliva samples were assessed at the same time. MIST = Montreal Imaging Stress Task. Color version of this figure is available online only with this article at www.psychosomaticmedicine.org.

sensitive to blood oxygenation level–dependent contrast (repetition time, 2000 milliseconds; echo time, 30 milliseconds; 64 × 64 matrix with 3 × 3 × 3 mm^3 spatial resolution; field of view, 192 × 192 mm^2). Slices were acquired in an interleaved order and oriented parallel to the AC-PC plane with a 0.99-mm gap. High-resolution T1-weighted three-dimensional fast-field echo sequences were obtained for anatomical reference (176 slices; repetition time, 1900 milliseconds; echo time, 2.52 milliseconds; slice thickness, 1 mm; field of view, 256 mm × 256 mm; voxel size, 1 mm × 1 mm × 1 mm).

fMRI Data Analysis

All preprocessing was performed using the Data Processing & Analysis for (Resting-State) Brain Imaging software (58). The first five volumes were removed. The images were corrected for the acquisition time differences between slices, realigned to the 32nd volume. Individual structural images (T1-weighted magnetization prepared rapid gradient echo) were co-registered to the mean functional image after realignment. To remove the nuisance signals, the Friston 24-parameter model was used to regress out head motion effects from the realigned data. The transformed structural images were then segmented into gray matter, white matter, and cerebral spinal fluid (59). The DARTEL tool (60) was used to compute transformations from individual native space to Montreal Neurological Institute (MNI) space. The signals from white matter and cerebral spinal fluid were regressed out to reduce respiratory and cardiac effects. The images were normalized into the standard T1 MNI template image with a voxel size of 3 × 3 × 3 mm^3. Then, the images were smoothed with a Gaussian kernel of 6-mm full-width-half-maximum.

Other analyses as follows were conducted using SPM12 software (statistical parametric mapping software, SPM; Wellcome Department of Imaging Neuroscience, London, United Kingdom; http://www.fil.ion.ucl.ac.uk). Because of the experimental program settings, when one condition ended, the experimenter had to click a "continue button" to jump to the next condition in a separate run. To avoid unnecessary confusion, we set aside time that acquired eight volumes in total for each run to click the "continue button," so that a "blank condition" was defined to distinguish the button-click trails and other trials. First-level effects were estimated by creating a general linear model that incorporated three conditions (a stressful condition, a control condition, and a blank condition) convolved with the canonical hemodynamic response function and six movement parameters as covariates of noninterest. A high-pass temporal filter with a cutoff period of 256 seconds was applied. The second-level analyses were conducted using random-effects models to assess for any stress effects (stress versus control). To investigate the differences between stressful and nonstressful conditions, a stress versus control contrast was measured. In this study, stress condition was twice as long as the control condition, which can induce a very strong stress effect. Accordingly, to render the results clearly, a relatively strict correction (voxel-level family-wise error corrected $p < .05$) was adopted in this analysis, which was consistent with previous acute stress–related studies (25,61–64). Moreover, to identify the brain regions whose neural responses were associated with daily life stress, the SUM indices of the DSI were entered as a regressor in a whole-brain multiple regression analysis. Significant activation in this whole-brain multiple regression analysis was identified using a widely accepted threshold of voxel-level false discovery rate (FDR) corrected ($p < .05$).

The connectivity analysis was performed using the CONN toolbox based on SPM12 (CONN; http://www.nitrc.org/projects/conn) (65), which provided task-dependent functional connectivity processing. With the setup step, the data of the first level that was already estimated by creating a general linear model were subsequently used, so that three conditions (the stress, control, and blank) were entered into the design matrix. After that, denoising was performed to define, explore, and remove possible confounds in the blood oxygenation level–dependent signal, including motion, physiological, and other noise sources. A bandpass filter (0.008–0.09) was applied to the data. The seed region of interest was functionally defined by the hippocampus (MNI −24 −6 −15) that showed the effects of daily background stress on neural responses to acute stress in the current study, with a radius of 3 mm. Then, a seed-to-voxel functional connectivity analysis was conducted. Furthermore, to analyze connectivity results across conditions, stress versus control contrast was conducted. In the contrast analysis, a threshold of voxel-level FDR corrected ($p < .05$) was used. Furthermore, to identify brain regions whose functional connectivity with the seed region was associated with daily background stress, the SUM indices of the DSI were entered as a regressor in the second-level (between-subject) covariates setup. To delineate the relevant brain regions that show strong relationship between daily background stress and the neural response to ongoing acute psychosocial stress as comprehensively as possible, significant activation in the seed-to-voxel functional connectivity analysis was identified using a relatively lenient correction method (cluster-level FDR corrected $p < .05$ [uncorrected $p < .001$]).

All the resting-state data collected in the current study have not been analyzed. All the original data and/or code used in the present study are available upon direct request by contacting the corresponding author.

RESULTS

Daily Stress

Descriptive statistics of daily stress are presented in Table 1. A Bayesian independent-samples *t* test revealed no significant sex differences on the total stressful ranking of daily life events ($BF_{10} = 0.46$, error = 0.018).

Acute Stress Response

Participants' subjective stress reports during the MIST are illustrated in Figure 2A. A repeated analysis of variance with time as a within-subject variable revealed a significant effect of time ($F(6,258) = 72.81$, $p < .001$, $\eta_p^2 = 0.63$). A post hoc analysis revealed that participants reported the highest levels of perceived stress after the Run3 session (approximately 30 minutes after the onset of the MIST, $p_{Run3\text{-}Run1} < .001$, $p_{Run3\text{-}PreMIST} < .001$, $p_{Run3\text{-}Prescanning} < .001$, $p_{Run3\text{-}REST1} < .001$, $p_{Run3\text{-}REST2} < .001$, $p_{Run2\text{-}Run1} < .001$, $p_{Run2\text{-}PreMIST} < .001$, $p_{Run2\text{-}Prescanning} < .001$, $p_{Run2\text{-}REST1} < .001$, $p_{Run2\text{-}REST2} < .001$, $p_{Run1\text{-}PreMIST} < .001$, $p_{Run1\text{-}Prescanning} < .001$, $p_{Run1\text{-}REST1} < .001$, $p_{Run1\text{-}REST2} < .001$, $p_{PreMIST\text{-}Prescanning} < .001$, $p_{REST1\text{-}REST2} < .001$).

Participants' salivary cortisol stress responses during the MIST are illustrated in Figure 2B. A repeated analysis of variance with time as a within-subject variable revealed a significant effect of time ($F(6,258) = 3.05$, $p = .029$, $\eta_p^2 = 0.066$). A post hoc analysis revealed that participants' salivary cortisol levels peaked after the Run3 session (approximately 30 minutes after the onset of the MIST, $p_{Run3\text{-}Run2} < .05$, $p_{Run3\text{-}Run1} < .05$, $p_{Run3\text{-}Prescanning} < .05$, $p_{REST1\text{-}Run2} < .05$, $p_{REST1\text{-}Run1} < .05$, $p_{REST1\text{-}Prescanning} < .05$). We also analyzed the area under the curve with respect to increase (AUCi) as the indicator of changes in stress levels. The AUCi is calculated in reference to the baseline measurement, ignoring the

TABLE 1. Descriptive Statistics of Daily Stress Levels

Behavioral Variable	Group	*n*	M	SD	BF_{10}	Error
SUM	All participants	44	56.02	43.29		
	Male	21	61.85	54.05	0.46	0.018
	Female	23	50.69	30.74		

Bayesian independent-samples *t* test was conducted to assess the sex differences on daily stress levels. The total stressful ranking of daily life events is quantified as an indicator of daily stress levels (SUM).

M = mean; SD = standard deviation; BF = Bayesian factor.

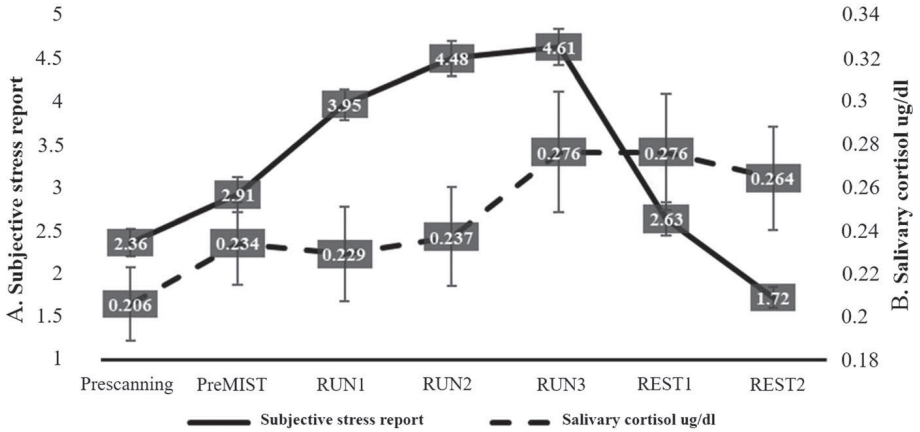

FIGURE 2. Participants' subjective stress reports and salivary cortisol stress responses during the MIST. A, Subjective stress reports showed elevated responses during the MIST (n = 44, post hoc: $p_{\text{Run3-Run1}} < .001$, $p_{\text{Run3-PreMIST}} < .001$, $p_{\text{Run3-Prescanning}} < .001$, $p_{\text{Run3-REST1}} < .001$, $p_{\text{Run3-REST2}} < .001$, $p_{\text{Run2-Run1}} < .001$, $p_{\text{Run2-PreMIST}} < .001$, $p_{\text{Run2-Prescanning}} < .001$, $p_{\text{Run2-REST1}} < .001$, $p_{\text{Run2-REST2}} < .001$, $p_{\text{Run1-PreMIST}} < .001$, $p_{\text{Run1-Prescanning}} < .001$, $p_{\text{Run1-REST1}} < .001$, $p_{\text{Run1-REST2}} < .001$, $p_{\text{PreMIST-Prescanning}} < .001$, $p_{\text{REST1-REST2}} < .001$). B, Participants' salivary cortisol (μg/dl) peaked immediately after Run3 of the MIST (approximately 30 minutes after the onset of the MIST, n = 44, post hoc: $p_{\text{Run3-Run2}} < .05$, $p_{\text{Run3-Run1}} < .05$, $p_{\text{Run3-Prescanning}} < .05$, $p_{\text{REST1-Run2}} < .05$, $p_{\text{REST1-Run1}} < .05$, $p_{\text{REST1-Prescanning}} < .05$). Values and their error bars represent the mean ± SEM. MIST = Montreal Imaging Stress Task; SEM = standard error of the mean.

distance from zero of all measurements, and emphasizes changes over time (66,67). A Bayesian independent-samples t test revealed no significant sex differences in the AUCi of cortisol (BF_{10} = 1.40, error = 0.002).

As for the neural response that induced by the psychosocial stress, compared with the nonstressful control condition, stress induced extensive activation, including of the frontal gyrus, parietal lobule, precuneus, cingulate gyrus, thalamus, insula, hippocampus, parahippocampal gyrus, occipital gyrus, temporal gyrus, and caudate. Deactivation was detected in the temporal gyrus, angular gyrus (all p values <.05, family-wise error) corrected for the whole brain (Table 2 and Figure 3).

Association Between Daily Life Stress Levels and Acute Stress Response

The Correlation Between Daily Stress and Acute Stress Response

After controlling for the effect of sex, participants' daily stress levels were significantly correlated with the cortisol level on the time point of *Prescanning* ($r_{\text{Prescanning}}$ = 0.52, p < .001). Importantly, after controlling for the effect of sex, participants' daily stress levels were significantly correlated with the AUCi of salivary cortisol levels (r = −0.38, p = .012; Figure 4A), but not significantly correlated with the AUCi of their subjective stress reports (r = 0.08, p = .59; Figure 4B).

Association of Daily Stress With Neural Responses to Acute Stress

Significant inverse relationships between SUM indices and stress-induced neural activity were found in the left parahippocampal gyrus extending into the hippocampus (MNI −24 −6 −15, t_{peak} = −5.51), right cerebellum anterior lobe extending to the left parahippocampal gyrus (MNI 9 −33 −18, t_{peak} = −4.60), left superior temporal gyrus (MNI −48 6 −18, t_{peak} = −5.03), right superior temporal gyrus (MNI 57 −60 21, t_{peak} = −4.46), and right inferior frontal gyrus (MNI 54 42 3, t_{peak} = −4.96; all p values <.05, FDR corrected for the whole brain, cluster voxel size >20; Table 3 and Figure 5).

Association of Daily Stress With Stress-Induced Functional Connectivity

A task-dependent seed-to-voxel functional connectivity analysis with the left hippocampus (MNI −24 −6 −15) as a seed region found that no brain regions (stress versus control) survived after the correction of multiple comparisons. Thus, to identify whether there was stronger functional connectivity between the hippocampus and vmPFC in the stress condition, we conducted a small volume correction within a region of vmPFC that was defined from the anatomical automatic labeling (AAL) template (68). Results showed that, compared with the nonstressful control condition, stress induced stronger functional connectivity between the left hippocampus and vmPFC (MNI 18 32 −16, t_{peak} = 3.39; peak-level FDR corrected p = .059 after a small-volume correction).

Furthermore, a regression analysis was conducted to investigate the correlation between the SUM indices reflective of daily stress levels and the difference of functional connectivity between the stress and control conditions. This revealed a significant positive relationship between the SUM indices and functional connectivity, with the left hippocampus as a seed region to the vmPFC/sgACC (MNI 12 32 −16, t_{peak} = 4.91; all p values <.001 uncorrected, cluster-level FDR corrected p < .05, R^2 = 0.365; cluster voxel size ≥117; Table 4 and Figure 6).

DISCUSSION

To investigate the possible neurocircuitry between daily life stress and acute psychosocial stress, the current study quantified the total stressful rating score of daily life stress events over the course of 1 day as a marker of daily stress level. Meanwhile, participants performed the modified MIST while their brains were undergoing fMRI scanning in the laboratory. Our results were consistent with

TABLE 2. Stress Induced Neural Activation and Deactivation

Contrast	Anatomical Region	Hemisphere	Montreal Neurological Institute Coordinate			k	t_{peak}	Peak $p_{FWE\text{-}corr}$
			X	*Y*	*Z*			
Stress > control	Cluster 1	L/R	−12	−93	12	23,535	14.34	.001
	Cluster 1 subregions							
	Precuneus	L	−15	−66	33	375	9.86	.001
		R	12	−51	51	427	10.67	.001
	Middle frontal gyrus	L	−27	−3	60	55	8.36	.001
		L	−30	39	15	118	7.52	.001
		R	36	−3	54	143	9.56	.001
		R	36	42	24	345	6.51	.001
	Superior frontal gyrus	L	−24	−6	63	140	9.13	.001
		R	15	6	60	292	10.67	.001
		R	27	45	21	64	7.79	.001
	Medial frontal gyrus	L	0	18	42	27	8.95	.001
		R	12	24	45	41	7.78	.001
	Inferior frontal gyrus	L	−39	12	12	27	7.82	.001
		L	−39	18	12	51	8.60	.001
		R	42	3	27	218	9.21	.001
		R	39	24	9	127	8.31	.001
	Precentral gyrus	L	−33	−6	45	428	10.19	.001
		R	39	−6	51	483	10.23	.001
	Middle occipital gyrus	L	−24	−90	15	646	13.73	.001
		R	27	−84	21	285	12.87	.001
	Superior occipital gyrus	L	−12	−93	12	291	14.34	.001
		R	27	−84	24	303	13.76	.001
	Inferior occipital gyrus	L	−33	−75	−9	211	11.42	.001
		R	33	−75	−9	207	12.72	.001
	Middle temporal gyrus	L	−42	−66	9	223	13.11	.001
		R	48	−60	6	378	14.1	.001
	Superior temporal gyrus	L	−54	−45	15	32	7.26	.001
		R	60	−36	18	159	11.18	.001
	Inferior temporal gyrus	L	−42	−60	−9	113	8.13	.001
		R	48	−66	−3	229	10.48	.001
	Inferior parietal lobule	L	−30	−57	51	190	9.00	.001
		R	30	−51	51	214	11.33	.001
	Superior parietal lobule	L	−27	−60	51	250	10.57	.001
		R	15	−54	51	239	11.03	.001
	Lingual gyrus	L	−21	−75	−6	363	14.32	.001
		R	6	−81	−6	392	13.92	.001
	Postcentral gyrus	L	−45	−9	48	313	9.89	.001
		R	24	−48	54	320	8.28	.001
	Cuneus	L	−12	90	15	226	13.10	.001
		R	15	−90	12	97	13.69	.001
		R	18	−66	39	82	9.91	.001
	Thalamus	L	−15	−9	3	259	9.66	.001
		R	15	−21	12	260	10.26	.001
	Insula	L	−39	15	9	292	9.60	.001
		R	36	18	6	218	9.17	.001
	Fusiform gyrus	L	−24	−75	−6	345	13.84	.001

Continued on next page

TABLE 2. *(Continued)*

Contrast	Anatomical Region	Hemisphere	Montreal Neurological Institute Coordinate			k	t_{peak}	Peak $p_{FWE\text{-}corr}$
			X	Y	Z			
		R	30	−78	−9	371	12.90	.001
	Anterior cingulate	L	−9	21	27	155	7.89	.001
		R	12	24	30	186	7.03	.001
	Middle cingulate	L	0	15	42	323	0.961	.001
		R	12	15	42	380	10.76	.001
	Posterior cingulate	L	−9	−42	21	15	7.07	.001
		R	12	−42	18	16	7.05	.001
	Caudate	L	−21	0	24	98	10.42	.001
		R	21	18	18	156	11.61	.001
	Putamen	L	−24	9	15	91	7.55	.001
		R	27	21	0	118	8.54	.001
	Hippocampus	L	−24	−33	0	49	8.81	.001
		R	30	−33	3	72	8.95	.001
	Supramarginal	L	−45	−42	33	95	8.37	.001
		R	48	−39	42	368	9.01	.001
	Angular gyrus	R	27	−54	45	74	10.89	.001
	Cerebellum	L	−27	−60	−21	983	11.11	.001
		-	0	−42	3	20	7.64	.001
	Cluster 1							
Stress < control	Superior temporal gyrus	R	39	15	−30	77	−7.79	.001
	Cluster 2							
	Superior temporal gyrus	L	−33	6	−30	37	−7.90	.001
	Cluster 3							
	Medial frontal gyrus	L	−9	27	−12	20	−6.71	.001
	Cluster 4							
	Medial frontal gyrus	L	−6	57	−9	20	−7.20	.001
	Cluster 5							
	Angular gyrus	R	54	−69	36	66	−9.77	.001
	Cluster 6							
	Angular gyrus	L	−39	−78	42	145	12.05	.001

All p values are <.05, and FWE has been corrected for the whole brain.

FWE = family-wise error; L = left; R = right.

our hypotheses and revealed that a higher level of daily stress was associated with lower salivary cortisol secretion and lower activation of the left hippocampus in response to the MIST. Moreover, a higher level of daily stress was associated with stronger functional connectivity between the left hippocampus and vmPFC/sgACC.

In line with previous work, we found decreased salivary cortisol secretion in response to the MIST in individuals who reported a higher level of daily stress. Studies have demonstrated that mild background stressors, such as perceived stress in one's daily life, overcommitment in one's work, and examination-related stress, may blunt the acute stress response, indicating that higher background stress levels may compromise physiological markers of a healthy stress response to acute stressors, resulting in lower blood pressure, heart rate, and norepinephrine and salivary cortisol levels (5,10,11,69). These reduced acute stress responses may be interpreted as resulting from a process of stress habituation characterized by a reduction of stress responses elicited by exposure to repeated or/and prolonged stressors, especially of low-to-medium intensity (70).

Consistent with this, our results showed that participants' daily stress levels were significantly correlated with the prescanning cortisol level, which may suggest a higher level of daily life stress result in an enhanced baseline cortisol level. Importantly, acute response to a stressor is usually considered an adaptive response because it allows for the reallocation of metabolic resources toward the fight or flight response to the stressor at hand; prolonged exposure to stressors, however, may be deleterious (3,71). After repeated stressors, the stress response system maintains a high activity state resulting in heightened hormonal levels that subsequently

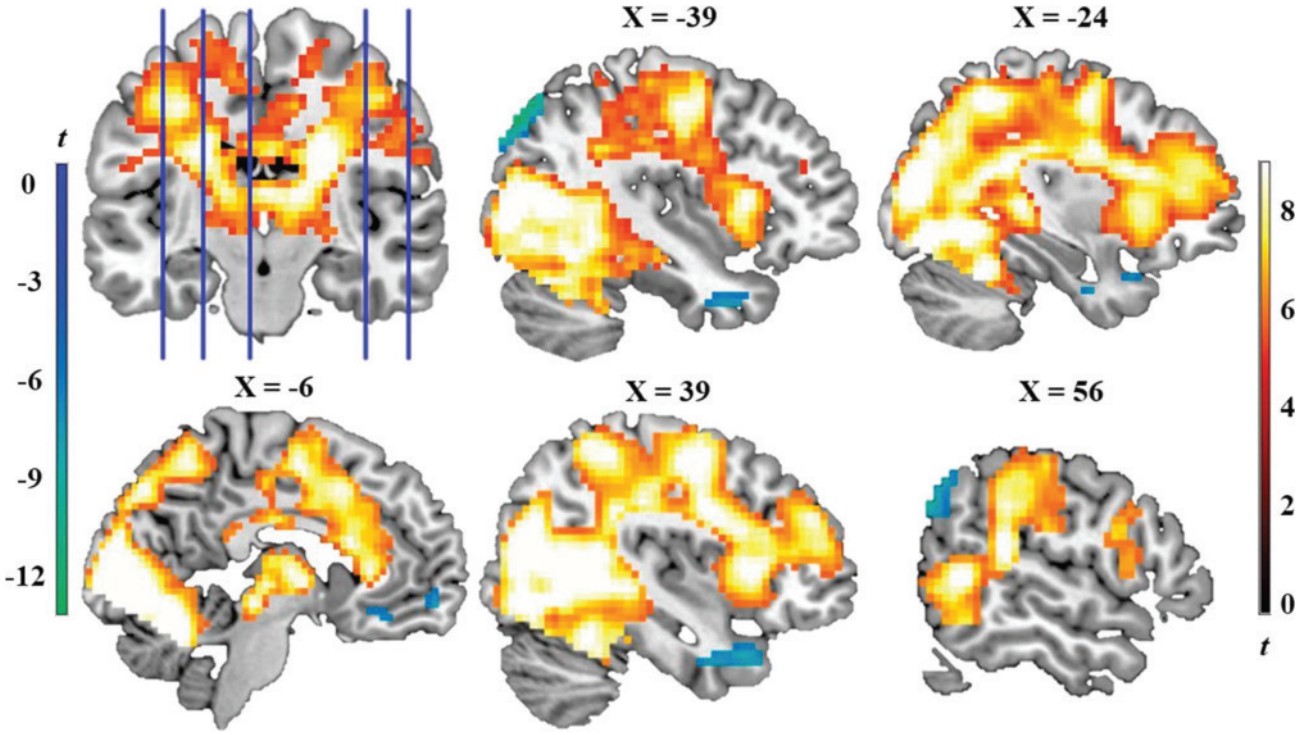

FIGURE 3. Neural responses during the MIST. Compared with the nonstressful control condition, stress induced extensive activation of the brain, including of the frontal gyrus, parietal lobule, precuneus, cingulate gyrus, thalamus, insula, hippocampus, parahippocampal gyrus, occipital gyrus, temporal gyrus, and caudate. Deactivation was detected in the temporal gyrus and angular gyrus. All p values are <.05, and FWE has been corrected for the whole brain. MIST = Montreal Imaging Stress Task; FWE = family-wise error. Color version of this figure is available online only with this article at www.psychosomaticmedicine.org.

result in reduced responsiveness to novel stressful stimuli (3,13–15). Studies have demonstrated that blunted stress responses occur more often in response to low-to-medium intensity stimuli of increasing frequency of exposure (5,12,70). In the current study, the total stressful rating score of stressful events within 1 day, of high frequency and low-to-medium intensity, were quantified as the daily background stress (7). Moreover, an acute stress response in this study was elicited by the MIST, which is considered to be a mild laboratory stressor (52,72). Accordingly, the acute stress response seems to be blunted in individuals who had experienced significant levels of daily stress of a similar perceived and experienced nature.

Considering the impact of daily stress on the neural mechanisms of acute stress responses, our results demonstrate that individuals who experience a greater number of stressful events over the course of the past day show less hippocampal activation in response to the MIST. Because glucocorticoid receptors and mineralocorticoid receptors both play crucial roles in the negative feedback inhibition of the HPA axis and are highly expressed in the hippocampus (73), we speculate that the blunted hippocampal response after acute stressors may reflect a decrease in the negative feedback inhibition of the HPA axis resulting from high exposure levels to daily stress. Notably, the daily stress level was associated with the left hippocampus but not with the right hippocampus. The

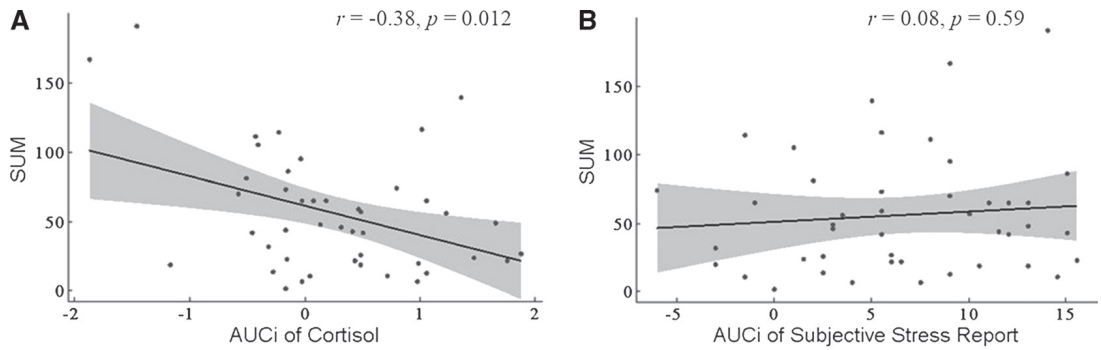

FIGURE 4. Correlations between SUM and acute stress response during MIST. A, the AUCi of salivary cortisol levels. B, the AUCi of subjective stress levels. The AUCi denotes the area under the curve with respect to an increase and as such represents changes in stress levels. SUM = total stress level of items denoted as having occurred; MIST = Montreal Imaging Stress Task.

TABLE 3. Brain Regions Showing an Association Between SUM and Stress-Induced Neural Activity

Anatomical Region	Hemisphere	Montreal Neurological Institute Coordinate			k	t_{peak}	Peak $p_{FDR\text{-}corr}$
		X	Y	Z			
Parahippocampal gyrus/hippocampus/amygdala	L	−24	−6	−15	60	−5.51	.032
Right cerebellum anterior lobe/left parahippocampal gyrus	R/L	9	−33	−18	70	−4.60	.032
Inferior frontal gyrus	R	54	42	3	39	−4.96	.032
Superior temporal gyrus	L	−48	6	−18	32	−5.03	.032
Superior temporal gyrus	R	57	−60	21	28	−4.46	.033

All p values <.05, FDR corrected for the whole brain, cluster voxel size >20.

SUM = total stress level of items denoted as having occurred; FDR = false discovery rate; L = left; R = right.

right hemisphere of the brain is more involved in the process of emotional cognition and expression, and the left hemisphere is more associated with coping, that is, the fight/flight response (74). Moreover, the left hemisphere is linked to activation of catecholamines and directed fight/flight vigilance, and it sets the stage to deal with challenges (74,75). Furthermore, previous evidence has suggested that a reduced left hippocampal volume was associated with clinical pathology like first-episode psychosis (76,77), major depression (78), and posttraumatic stress disorder (79). Therefore, the laterality of the hippocampus in the current study may suggest an important role of left hippocampus involved in stress coping.

Importantly, we also found that higher levels of daily stress were associated with stronger functional connectivity between the left hippocampus and vmPFC/sgACC. Studies have found that the vmPFC/sgACC is related to the inhibition and extinction of negative emotional information (43,46,48). The stronger functional connectivity between the hippocampus and vmPFC/sgACC may reflect an enhanced stress regulation function when facing stressful events again under high background stress. Moreover, studies also found that the activation of vmPFC is associated with behavioral control and stress-resilient coping in the middle and later stages of the stress response (80). This evidence suggests an enhanced adaptive regulation mechanism of the vmPFC when facing stressful events again under high daily stress. This reciprocal relationship between medial PFC and mesotemporal limbic cortices is of interest in the context of previous neuroimaging studies. In relation to the current findings, this reciprocal relationship between the vmPFC and hippocampus cortices may represent a greater top-down modulation of vmPFC to hippocampus in individuals who have experienced a greater level of stress over the course of the day.

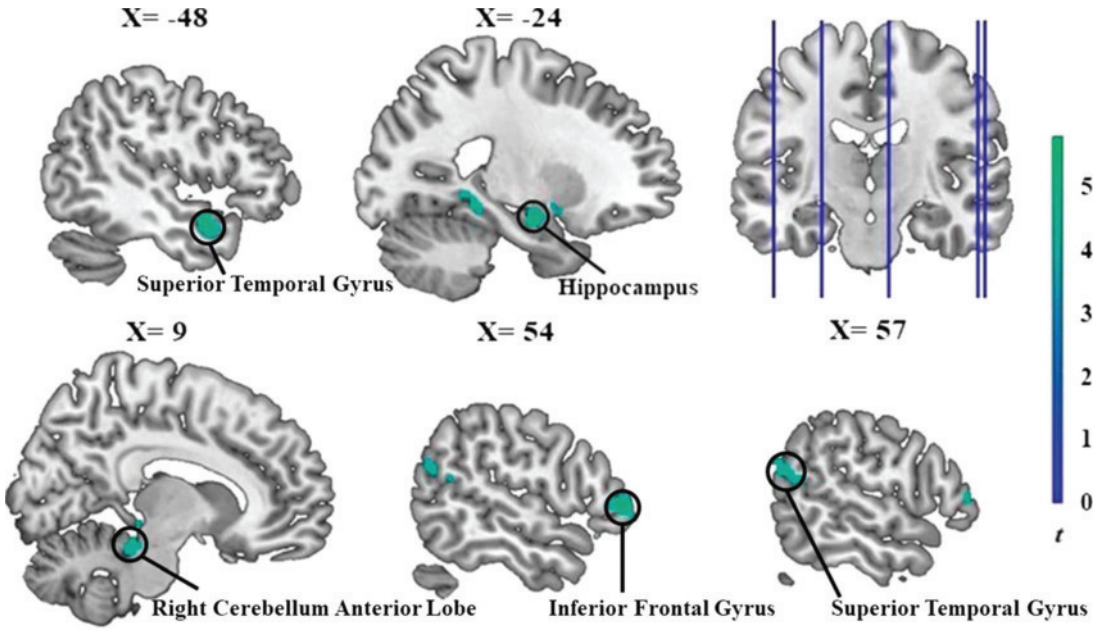

FIGURE 5. Association between SUM and stress-induced neural activity. Inverse relationships between SUM indices and stress-induced neural activity were found in the left parahippocampal gyrus extending to the hippocampus (MNI −24 −6 −15, t_{peak} = −5.51), right cerebellum anterior lobe extending to the left parahippocampal gyrus (MNI 9 −33 −18, t_{peak} = −4.60), left superior temporal gyrus (MNI −48 6 −18, t_{peak} = −5.03), right superior temporal gyrus (MNI 57 −60 21, t_{peak} = −4.46), and right inferior frontal gyrus (MNI 54 42 3, t_{peak} = −4.96). All p values <.05, FDR corrected for the whole brain, cluster voxel size >20. SUM = total stress level of items denoted as having occurred; MNI = Montreal Neurological Institute; FDR = false discovery rate. Color version of this figure is available online only with this article at www.psychosomaticmedicine.org.

TABLE 4. Association of SUM Indices With Stress-Related Functional Connectivity Between the Left hippocampus (MNI −24 −6 −15) and vmPFC/sgACC

Anatomical Region	Hemisphere	Montreal Neurological Institute Coordinate			k	t_{peak}	Cluster $p_{FDR\text{-}corr}$	R^2
		X	*Y*	*Z*				
Medial frontal gyrus/subgenual anterior cingulate	R	12	32	−16	117	4.91	.006	0.365

SUM = total stress level of items denoted as having occurred; Montreal Neurological Institute; vmPFC = ventromedial prefrontal cortex; sgACC = subgenual region of the anterior cingulate cortex; FDR = false discovery rate; R = right.

Humans often face various stressors, trauma, and aggression in their daily life. These stressful experiences physically alter the structure and function of brain regions involved in controlling HPA and autonomic responses to stress (24,81). Individuals with long-term trauma and life stress typically show hippocampal volume reduction (82). Individuals with a high level of cumulative adversity show an increased hippocampal activation and vulnerability to adverse health consequences (83). However, things do not always have to turn bad. Some studies have suggested that reduced limbic deactivation in an individual with childhood trauma may reflect a type of counterregulatory adaptation after sustained exposure to stressors during development (84). In the current study, individuals seemed to exhibit an adaptive response after experiencing high levels of daily background stress throughout the day, illustrated by the reduced neuroendocrine responses and increased regulation role of vmPFC.

Notably, Sandner et al. (19) measured hair cortisol over the last 3 months as a marker of the long-term background stress level, and they found that individuals with higher hair cortisol had lower reactivity in response to an acute psychosocial stressor involving cognitive and social-evaluative challenges. In a similar vein, we found that high daily stress on a self-report level predicts low stress response. Results of these two studies may suggest that both the long-term background stress and the daily background stress might blunt an individual's response to acute psychosocial stressors; however, some empirical studies found opposite patterns. Because of a reduction in coping mechanisms and resulting responses, chronic exposure to stressors could result in a heightened acute response. Consistently, residents living in a crowded living environment showed a significantly greater increase in their stress response (85); in addition, poor social support has also been associated with heightened stress reactivity (86,87). Overall, it seems that the relationship between one's acute stress response and levels of background stress remains complex, naturally contingent on a number of critical factors such as the type of acute stressor and the type, intensity, and duration of the background stressors (5). Moreover, chronic stress was found to differentially affect anticipatory and reactive cortisol response (88,89). Thus, the conflicting results could also be due to the failure to distinguish the cortisol response stage.

This study has several limitations. First, we did not measure the levels of chronic background stress and major life stress, both of which are associated with daily hassles and cortisol response to acute stressors (4,5,21,90–92). Accordingly, levels of chronic background stress and major life stress may confound our results. For example, Serido et al. (21) found that, even after controlling for the effects of chronic stress, higher levels of daily hassles predicted higher levels of psychological distress, suggesting that daily hassles and chronic stressors are different types of stressors with unique contributions to psychological distress. However, they also found that chronic stress moderated the relationship between daily hassles and psychological distress. These results suggest that the presence of chronic stressors on days when individuals experience minor hassles may exacerbate the reaction to hassle and thus influence the stress response. Second, the daily background stressors

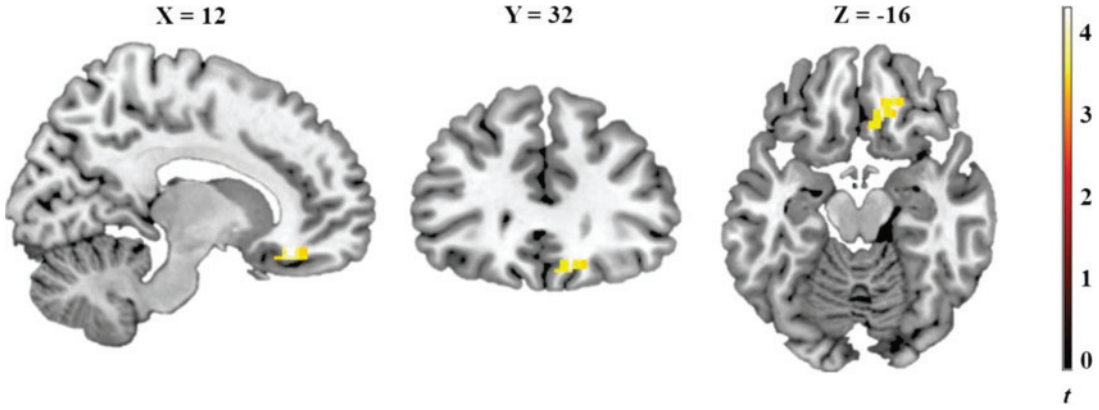

FIGURE 6. Associations of SUM indices with stress-related functional connectivity between the left hippocampus and vmPFC/sgACC. The SUM indices were significantly associated with functional connectivity with the left hippocampus (MNI −24 −6 −15) as a seed region to the vmPFC/sgACC (MNI 12 32 −16, t_{peak} = 4.91; all p values <.001 uncorrected, cluster-level FDR corrected $p < .05$, cluster voxel size ≥117). SUM = total stress level of items denoted as having occurred; vmPFC = ventromedial prefrontal cortex; sgACC = subgenual region of the anterior cingulate cortex; MNI = Montreal Neurological Institute; FDR = false discovery rate. Color version of this figure is available online only with this article at www.psychosomaticmedicine.org.

were of the same type as the acute stressors in the current study. Although we provide evidence of a blunted acute stress response as a result of high daily stress levels, the relationship between one's acute stress response and levels of background stress is still influenced by many factors such as the type of acute stressor and the type, intensity, and duration of the background stressors (5). Therefore, caution to the generalizability of results should be made. Third, as an important indicator of HPA function, basal cortisol levels comprehensively reflect the effects of daily stress on the stress response system. Future studies should consider measuring the cortisol awakening response or rhythmic cortisol levels. Fourth, in this modified version of the MIST, a monitoring screen with the image of a strict evaluator's face is built into the experimental stress condition, but not in the control condition. To avoid unnecessary confusion, future studies should consider building a face without social evaluation threat in the control condition. Moreover, to increase the experimental effect of stress condition, this study canceled the resting condition and added this part of time into the stress condition, which might pose problems in fitting models (93). This problem deserves consideration in future studies. Fifth, female participants were recruited in our study while their information about oral contraceptives was not collected. Given that some medications like anti-inflammatory medication or oral contraceptives might affect cortisol measures, future studies should rule out the potential impact of these factors. Lastly, because sleeping hours might influence cortisol measures, future studies should use a proper method to control participants' sleep-wake cycle.

CONCLUSIONS

Overall, the current study examined the associations of 24-hour daily stress level with the neuroendocrinological response to a laboratory-induced acute stress and found that daily stress level was negatively associated with salivary cortisol and hippocampal responses to acute stress but positively associated with hippocampus-vmPFC functional connectivity during acute stress. These results suggested a possible neuromodulatory pathway in the relationship between daily stress and acute stress, which further provides a new insight into the resilience role of hippocampus-vmPFC in the development of blunted stress system–related psychopathology.

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REFERENCES

1. Herman JP, Ostrander MM, Mueller NK, Figueiredo H. Limbic system mechanisms of stress regulation: hypothalamo-pituitary-adrenocortical axis. Prog Neuropsychopharmacol Biol Psychiatry 2005;29:1201–13.
2. Kirschbaum C, Pirke KM, Hellhammer DH. The 'Trier Social Stress Test'—a tool for investigating psychobiological stress responses in a laboratory setting. Neuropsychobiology 1993;28(1–2):76–81.
3. McEwen BS. Protective and damaging effects of stress mediators. N Engl J Med 1998;338:171–9.
4. Chida Y, Hamer M. Chronic psychosocial factors and acute physiological responses to laboratory-induced stress in healthy populations: a quantitative review of 30 years of investigations. Psychol Bull 2008;134:829–85.
5. Gump BB, Matthews KA. Do background stressors influence reactivity to and recovery from acute stressors? J Appl Soc Psychol 1999;29:469–94.
6. Stawski RS, Cichy KE, Piazza JR, Almeida DM. Associations among daily stressors and salivary cortisol: findings from the National Study of Daily Experiences. Psychoneuroendocrinology 2013;38:2654–65.
7. Brantley PJ, Waggoner CD, Jones GN, Rappaport NB. A Daily Stress Inventory: development, reliability, and validity. J Behav Med 1987;10:61–73.
8. Larsson G, Berglund AK, Ohlsson A. Daily hassles, their antecedents and outcomes among professional first responders: a systematic literature review. Scand J Psychol 2016;57:359–67.
9. Lennartsson A-K, Theorell T, Kushnir MM, Bergquist J, Jonsdottir IH. Perceived stress at work is associated with attenuated DHEA-S response during acute psychosocial stress. Psychoneuroendocrinology 2013;38:1650–7.
10. Loft P, Thomas MG, Petrie KJ, Booth RJ, Miles J, Vedhara K. Examination stress results in altered cardiovascular responses to acute challenge and lower cortisol. Psychoneuroendocrinology 2007;32:367–75.
11. Allen C, Ashley AK, Hromas R, Nickoloff JA. More forks on the road to replication stress recovery. J Mol Cell Biol 2011;3:4–12.
12. Groves PM, Lee D, Thompson RF. Effects of stimulus frequency and intensity on habituation and sensitization in acute spinal cat. Physiol Behav 1969;4:383–8.
13. Bamberger CM, Schulte HM, Chrousos GP. Molecular determinants of glucocorticoid receptor function and tissue sensitivity to glucocorticoids. Endocr Rev 1996;17:245–61.
14. Appels A. Exhausted subjects, exhausted systems. Acta Physiol Scand Suppl 1997; 640:153–4.
15. Wirtz PH, Von KÄnel R, Schnorpfeil P, Ehlert U, Frey K, Fischer JE. Reduced glucocorticoid sensitivity of monocyte interleukin-6 production in male industrial employees who are vitally exhausted. Psychosom Med 2003;65:672–8.
16. Erickson KI, Creswell JD, Verstynen TD, Gianaros PJ. Health neuroscience: defining a new field. Curr Dir Psychol Sci 2014;23:446–53.
17. McEwen BS. Physiology and neurobiology of stress and adaptation: central role of the brain. Physiol Rev 2007;87:873–904.
18. Cunningham-Bussel AC, Root JC, Butler T, Tuescher O, Pan H, Epstein J, Weisholtz DS, Pavony M, Silverman ME, Goldstein MS, Altemus M, Cloitre M, Ledoux J, McEwen B, Stern E, Silbersweig D. Diurnal cortisol amplitude and fronto-limbic activity in response to stressful stimuli. Psychoneuroendocrinology 2009;34:694–704.
19. Sandner M, Lois G, Streit F, Zeier P, Kirsch P, Wüst S, Wessa M. Investigating individual stress reactivity: high hair cortisol predicts lower acute stress responses. Psychoneuroendocrinology 2020;118:104660.
20. Almeida DM. Resilience and vulnerability to daily stressors assessed via diary methods. Curr Dir Psychol Sci 2005;14:64–8.
21. Serido J, Almeida DM, Wethington E. Chronic stressors and daily hassles: unique and interactive relationships with psychological distress. J Health Soc Behav 2004;45:17–33.
22. Herman JP, Mueller NK. Role of the ventral subiculum in stress integration. Behav Brain Res 2006;174:215–24.
23. Pruessner JC, Dedovic K, Khalili-Mahani N, Engert V, Pruessner M, Buss C, Renwick R, Dagher A, Meaney MJ, Lupien S. Deactivation of the limbic system during acute psychosocial stress: evidence from positron emission tomography and functional magnetic resonance imaging studies. Biol Psychiatry 2008;63: 234–40.
24. Ulrich-Lai YM, Herman JP. Neural regulation of endocrine and autonomic stress responses. Nat Rev Neurosci 2009;10:397–409.
25. Lederbogen F, Kirsch P, Haddad L, Streit F, Tost H, Schuch P, Wüst S, Pruessner JC, Rietschel M, Deuschle M, Meyer-Lindenberg A. City living and urban upbringing affect neural social stress processing in humans. Nature 2011;474:498–501.
26. Albert K, Pruessner J, Newhouse P. Estradiol levels modulate brain activity and negative responses to psychosocial stress across the menstrual cycle. Psychoneuroendocrinology 2015;59:14–24.
27. Fendler K, Karmos G, Telegdy G. The effect of hippocampal lesion on pituitary-adrenal function. Acta Physiol Acad Sci Hung 1961;20:293–7.
28. Knigge KM. Adrenocortical response to stress in rats with lesions in hippocampus and amygdala. Proc Soc Exp Biol Med 1961;108:18–21.
29. Knigge KM, Hays M. Evidence of inhibitive role of hippocampus in neural regulation of ACTH release. Proc Soc Exp Biol Med 1963;114:67–9.
30. Sapolsky RM, Krey LC, McEwen BS. Glucocorticoid-sensitive hippocampal neurons are involved in terminating the adrenocortical stress response. Proc Natl Acad Sci U S A 1984;81:6174–7.
31. Chung KC, Springer I, Kogler L, Turetsky B, Freiherr J, Derntl B. The influence of androstadienone during psychosocial stress is modulated by gender, trait anxiety and subjective stress: an fMRI study. Psychoneuroendocrinology 2016;68:126–39.
32. Eckenrode J. Impact of chronic and acute stressors on daily reports of mood. J Pers Soc Psychol 1984;46:907–18.
33. Lazarus RS. Puzzles in the study of daily hassles. In: RK Silbereisen, K Eyferth, G Rudinger, editors. Development as Action in Context. Berlin, Heidelberg: Springer; 1986:39–53.
34. Dedovic K, Duchesne A, Andrews J, Engert V, Pruessner JC. The brain and the stress axis: the neural correlates of cortisol regulation in response to stress. Neuroimage 2009;47:864–71.

35. Kogler L, Gur RC, Derntl B. Sex differences in cognitive regulation of psychosocial achievement stress: brain and behavior. Hum Brain Mapp 2015;36:1028–42.
36. Hanson MD, Chen E. Daily stress, cortisol, and sleep: the moderating role of childhood psychosocial environments. Health Psychol 2010;29:394–402.
37. Smyth J, Ockenfels MC, Porter L, Kirschbaum C, Hellhammer DH, Stone AA. Stressors and mood measured on a momentary basis are associated with salivary cortisol secretion. Psychoneuroendocrinology 1998;23:353–70.
38. Peeters F, Nicholson NA, Berkhof J. Cortisol responses to daily events in major depressive disorder. Psychosom Med 2003;65:836–41.
39. Davis EG, Humphreys KL, McEwen LM, Sacchet MD, Camacho MC, MacIsaac JL, Lin DTS, Kobor MS, Gotlib IH. Accelerated DNA methylation age in adolescent girls: associations with elevated diurnal cortisol and reduced hippocampal volume. Transl Psychiatry 2017;7:e1223.
40. Roy M, Shohamy D, Wager TD. Ventromedial prefrontal-subcortical systems and the generation of affective meaning. Trends Cogn Sci 2012;16:147–56.
41. Critchley HD, Nagai Y, Gray MA, Mathias CJ. Dissecting axes of autonomic control in humans: insights from neuroimaging. Auton Neurosci 2011;161(1–2):34–42.
42. Delgado MR, Nearing KI, LeDoux JE, Phelps EA. Neural circuitry underlying the regulation of conditioned fear and its relation to extinction. Neuron 2008;59:829–38.
43. Etkin A, Egner T, Kalisch R. Emotional processing in anterior cingulate and medial prefrontal cortex. Trends Cogn Sci 2011;15:85–93.
44. Gianaros PJ, Wager TD. Brain-body pathways linking psychological stress and physical health. Curr Dir Psychol Sci 2015;24:313–21.
45. Yang X, Garcia KM, Jung Y, Whitlow CT, McRae K, Waugh CE. vmPFC activation during a stressor predicts positive emotions during stress recovery. Soc Cogn Affect Neurosci 2018;13:256–68.
46. Lesting J, Narayanan RT, Kluge C, Sangha S, Seidenbecher T, Pape HC. Patterns of coupled theta activity in amygdala-hippocampal-prefrontal cortical circuits during fear extinction. PLoS One 2011;6:e21714.
47. Moustafa AA, Gilbertson MW, Orr SP, Herzallah MM, Servatius RJ, Myers CE. A model of amygdala-hippocampal-prefrontal interaction in fear conditioning and extinction in animals. Brain Cogn 2013;81:29–43.
48. Bukalo O, Pinard CR, Silverstein S, Brehm C, Hartley ND, Whittle N, Colacicco G, Busch E, Patel S, Singewald N. Prefrontal inputs to the amygdala instruct fear extinction memory formation. Sci Adv 2015;1:e1500251.
49. Milad MR, Pitman RK, Ellis CB, Gold AL, Shin LM, Lasko NB, Zeidan MA, Handwerger K, Orr SP, Rauch SL. Neurobiological basis of failure to recall extinction memory in posttraumatic stress disorder. Biol Psychiatry 2009;66: 1075–82.
50. Admon R, Leykin D, Lubin G, Engert V, Andrews J, Pruessner J, Hendler T. Stress-induced reduction in hippocampal volume and connectivity with the ventromedial prefrontal cortex are related to maladaptive responses to stressful military service. Hum Brain Mapp 2013;34:2808–16.
51. Admon R, Lubin G, Stern O, Rosenberg K, Sela L, Ben-Ami H, Hendler T. Human vulnerability to stress depends on amygdala's predisposition and hippocampal plasticity. Proc Natl Acad Sci 2009;106:14120–5.
52. Dedovic K, Renwick R, Mahani NK, Engert V, Lupien SJ, Pruessner JC. The Montreal Imaging Stress Task: using functional imaging to investigate the effects of perceiving and processing psychosocial stress in the human brain. J Psychiatry Neurosci 2005;30:319–25.
53. Kajantie E, Phillips DI. The effects of sex and hormonal status on the physiological response to acute psychosocial stress. Psychoneuroendocrinology 2006;31:151–78.
54. Cohen S, Wills TA. Stress, social support, and the buffering hypothesis. Psychol Bull 1985;98:310–57.
55. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav 1983;24:385–96.
56. Avison WR, Turner RJ. Stressful life events and depressive symptoms: disaggregating the effects of acute stressors and chronic strains. J Health Soc Behav 1988; 29:253–64.
57. Terrill AL, Gjerde JM, Garofalo JP. Background stress inventory: developing a measure of understudied stress. Stress Health 2015;31:290–8.
58. Yan C-G, Wang X-D, Zuo X-N, Zang Y-F. DPABI: data processing & analysis for (resting-state) brain imaging. Neuroinformatics 2016;14:339–51.
59. Ashburner J, Friston KJ. Unified segmentation. Neuroimage 2005;26:839–51.
60. Ashburner J. A fast diffeomorphic image registration algorithm. Neuroimage 2007;38:95–113.
61. Streit F, Haddad L, Paul T, Frank J, Schäfer A, Nikitopoulos J, Akdeniz C, Lederbogen F, Treutlein J, Witt S. A functional variant in the neuropeptide S receptor 1 gene moderates the influence of urban upbringing on stress processing in the amygdala. Stress 2014;17:352–61.
62. Wheelock MD, Harnett NG, Wood KH, Orem TR, Granger DA, Mrug S, Knight DC. Prefrontal cortex activity is associated with biobehavioral components of the stress response. Front Hum Neurosci 2016;10:583.
63. Tomova L, Majdandžić J, Hummer A, Windischberger C, Heinrichs M, Lamm C. Increased neural responses to empathy for pain might explain how acute stress increases prosociality. Soc Cogn Affect Neurosci 2017;12:401–8.
64. Dahm A-S, Schmierer P, Veer IM, Streit F, Görgen A, Kruschwitz J, Wüst S, Kirsch P, Walter H, Erk S. The burden of conscientiousness? Examining brain activation and cortisol response during social evaluative stress. Psychoneuroendocrinology 2017;78:48–56.
65. Whitfield-Gabrieli S, Nieto-Castanon A. Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. Brain Connect 2012;2:125–41.
66. Pruessner JC, Kirschbaum C, Meinlschmid G, Hellhammer DH. Two formulas for computation of the area under the curve represent measures of total hormone concentration versus time-dependent change. Psychoneuroendocrinology 2003; 28:916–31.
67. Fekedulegn DB, Andrew ME, Burchfiel CM, Violanti JM, Hartley TA, Charles LE, Miller DB. Area under the curve and other summary indicators of repeated waking cortisol measurements. Psychosom Med 2007;69:651–9.
68. Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, Mazoyer B, Joliot M. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage 2002;15:273–89.
69. Wirtz PH, Siegrist J, Rimmele U, Ehlert U. Higher overcommitment to work is associated with lower norepinephrine secretion before and after acute psychosocial stress in men. Psychoneuroendocrinology 2008;33:92–9.
70. Grissom N, Bhatnagar S. Habituation to repeated stress: get used to it. Neurobiol Learn Mem 2009;92:215–24.
71. Dallman MF. Modulation of stress responses: how we cope with excess glucocorticoids. Exp Neurol 2007;206:179–82.
72. Corbett B, Weinberg L, Duarte A. The effect of mild acute stress during memory consolidation on emotional recognition memory. Neurobiol Learn Mem 2017; 145:34–44.
73. Han F, Ozawa H, Matsuda K, Nishi M, Kawata M. Colocalization of mineralocorticoid receptor and glucocorticoid receptor in the hippocampus and hypothalamus. Neurosci Res 2005;51:371–81.
74. Silberman EK, Weingartner H. Hemispheric lateralization of functions related to emotion. Brain Cogn 1986;5:322–53.
75. Davidson RJ, Ekman P, Saron CD, Senulis JA, Friesen WV. Approach-withdrawal and cerebral asymmetry: emotional expression and brain physiology: I. J Pers Soc Psychol 1990;58:330–41.
76. Steen RG, Mull C, Mcclure R, Hamer RM, Lieberman JA. Brain volume in first-episode schizophrenia: systematic review and meta-analysis of magnetic resonance imaging studies. Br J Psychiatry 2006;188:510–8.
77. Mondelli V, Pariante CM, Navari S, Aas M, D'Albenzio A, Di Forti M, Handley R, Hepgul N, Marques TR, Taylor H, Papadopoulos AS, Aitchison KJ, Murray RM, Dazzan P. Higher cortisol levels are associated with smaller left hippocampal volume in first-episode psychosis. Schizophr Res 2010;119(1–3):75–8.
78. Vythilingam M, Heim C, Newport J, Miller AH, Anderson E, Bronen R, Brummer M, Staib L, Vermetten E, Charney DS, Nemeroff CB, Bremner JD. Childhood trauma associated with smaller hippocampal volume in women with major depression. Am J Psychiatry 2002;159:2072–80.
79. Bremner JD, Randall P, Vermetten E, Staib L, Bronen RA, Mazure C, Capelli S, McCarthy G, Innis RB, Charney DS. Magnetic resonance imaging-based measurement of hippocampal volume in posttraumatic stress disorder related to childhood physical and sexual abuse—a preliminary report. Biol Psychiatry 1997;41:23–32.
80. Sinha R, Lacadie CM, Constable RT, Seo D. Dynamic neural activity during stress signals resilient coping. Proc Natl Acad Sci 2016;113:8837–42.
81. De Kloet ER, Joëls M, Holsboer F. Stress and the brain: from adaptation to disease. Nat Rev Neurosci 2005;6:463–75.
82. Hull AM. Neuroimaging findings in post-traumatic stress disorder. Systematic review. Br J Psychiatry 2002;181:102–10.
83. Seo D, Tsou KA, Ansell EB, Potenza MN, Sinha R. Cumulative adversity sensitizes neural response to acute stress: association with health symptoms. Neuropsychopharmacology 2014;39:670–80.
84. Grimm S, Pestke K, Feeser M, Aust S, Weigand A, Wang J, Wingenfeld K, Pruessner JC, La Marca R, Böker H, Bajbouj M. Early life stress modulates oxytocin effects on limbic system during acute psychosocial stress. Soc Cogn Affect Neurosci 2014;9:1828–35.
85. Fleming I, Baum A, Davidson LM, Rectanus E, McArdle S. Chronic stress as a factor in physiologic reactivity to challenge. Health Psychol 1987;6:221–37.
86. Knox SS. Perception of social support and blood pressure in young men. Percept Mot Skills 1993;77:132–4.
87. Roy MP, Steptoe A, Kirschbaum C. Life events and social support as moderators of individual differences in cardiovascular and cortisol reactivity. J Pers Soc Psychol 1998;75:1273–81.
88. Elzinga BM, Roelofs K, Tollenaar MS, Bakvis P, van Pelt J, Spinhoven P. Diminished cortisol responses to psychosocial stress associated with lifetime adverse events: a study among healthy young subjects. Psychoneuroendocrinology 2008;33:227–37.
89. Aschbacher K, O'Donovan A, Wolkowitz OM, Dhabhar FS, Su Y, Epel E. Good stress, bad stress and oxidative stress: insights from anticipatory cortisol reactivity. Psychoneuroendocrinology 2013;38:1698–708.
90. Wagner BM, Compas BE, Howell DC. Daily and major life events: a test of an integrative model of psychosocial stress. Am J Community Psychol 1988;16:189–205.
91. DeLongis A, Coyne JC, Dakof G, Folkman S, Lazarus RS. Relationship of daily hassles, uplifts, and major life events to health status. Health Psychol 1982;1:119.
92. Xin Y, Yao Z, Wang W, Luo Y, Aleman A, Wu J. Recent life stress predicts blunted acute stress response and the role of executive control. Stress 2020;23:359–67.
93. Maus B, van Breukelen GJ, Goebel R, Berger MP. Optimization of blocked designs in fMRI studies. Psychometrika 2010;75:373–90.