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Research article

Sex-based differences in brain morphometry under chronic stress: A pilot MRI study

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ABSTRACT

Background: Sex-based differences are known to be a significant feature of chronic stress; however, the morphological mechanisms of the brain underlying these differences remain unclear. The present study aimed to use magnetic resonance imaging (MRI) and voxel-based morphometry (VBM) to investigate the effects of sex on gray matter volume (GMV) changes under conditions of chronic stress.

Methods: A total of 32 subjects were included for analysis in the present study: 16 participants experiencing chronic stress and 16 healthy controls. T1-weighted (T1WI) images from a 3 T MRI scanner were extracted from the OpenfMRI database. Images were segmented into gray matter using VBM analysis. A two-way analysis of variance (ANOVA) with a 2 × 2 full factorial design was used to evaluate the main and interaction effects of chronic stress and sex on GMV changes, and then post hoc testing was used to verify each simple effect.

Results: Two-way ANOVA showed a chronic stress × sex interaction effect on GMV. Simple effects analysis indicated that the GMV of the bilateral pre- and post-central gyri, the right cuneus and superior occipital gyrus was decreased in males, whereas that of the bilateral pre- and post-central gyri, the right superior occipital gyrus and the left middle frontal gyrus and orbital middle frontal gyrus was increased in females, under chronic stress. Additionally, in the control group, the GMV of the bilateral pre- and post-central gyri, the right cuneus and superior occipital gyrus was greater in males than females. While in the chronic stress group, the above sex-based differences were no longer significant.

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Conclusions: This study preliminarily shows that there are significant differences in gray matter volume changes between males and females under chronic stress. These findings provide a basis for future studies investigating the volumetric mechanisms of sex differences under chronic stress.

1. Introduction

Chronic stress can have a multitude of adverse physical, financial, and emotional consequences. The World Health Organization (WHO) has designated stress as a "worldwide epidemic" to underscore its deleterious effects [1]. Exposure to stressors typically triggers a complex set of adaptive neuronal, endocrine, and behavioral responses that prepare the body for continued homeostasis. Various physiological and psychopathological symptoms may occur, however, when a stressor appears in a severe, sudden, or chronic manner [2]. There is strong evidence that chronic stress is associated with the onset of major depressive disorder (MDD), bipolar disorder (BD), post-traumatic stress disorder (PTSD), panic disorder (PD), and chronic anxiety [3], which are all linked to increased morbidity and mortality [4].

Animal and human studies have shown that chronic stress can alter cerebral morphology, leading to neuronal loss, dendritic atrophy, and decreased gray matter volume (GMV) in the hippocampus [5,6]. A study regarding cumulative adversity and stress and their relationship to cerebral morphology in young people reported that chronic perceived stress is related to decreased GMV in the prefrontal cortex (PFC), insular cortex, and anterior cingulate cortex (ACC) [7]. Additionally, various cerebral regions, including the amygdala, locus coeruleus (LC), brainstem, cerebellum, occipital cortex, and thalamus, have also been reported to be associated with stress-related psychiatric disorders, such as MDD, PD, and PTSD [8–11].

The prevalence of sex-based differences in many stress-related psychiatric disorders have been identified in epidemiological data. It is evident that men are more prone than women to developing substance-related disorders, such as alcohol and drug abuse [12]. Furthermore, women are approximately twice as likely as men to develop anxiety disorders (e.g., PD) [13] and trauma-related disorders (e.g., PTSD) [14]. The incidence of MDD is also higher in women [15]. Additionally, women are more frequently affected by medical disorders that are comorbid with depression and anxiety, including migraines, insomnia, and irritable bowel syndrome [16–18]. The results of the aforementioned studies indicated that sex-based differences are frequently observed in the underlying biological mechanisms of stress-related psychiatric disorders.

Although it is widely known that sex-based differences occur in the setting of chronic stress, little is known about the underlying cerebral morphometric mechanisms affecting these changes. A magnetic resonance imaging (MRI) study of patients with exhaustion syndrome caused by daily chronic stress found the following differences in cerebral morphology alterations: enlargement of the relative amygdala volume (amygdala/intracranial volume) was observed only in women, whereas a reduction in the relative caudate volume (caudate/intracranial volume) was observed only in men [19]. Additionally, there are interesting reports regarding stress-processing cerebral circuits, in that stress induces sex-differentiated cerebral activation. Kogler et al. [20] found that females showed greater activation of the left amygdala and right superior temporal gyrus during stress, while males showed greater activation of the putamen more robustly. The results of a meta-analysis of brain activation elicited by acute stress indicated that men display the activation of the thalamus during physiological stress, whereas in women it is the amygdala that is activated [21].

Sex-based differences have been identified as a significant feature of chronic stress; however, the underlying morphological mechanisms behind these changes in the brain remain unclear. The objective of the present study, therefore, was to use MRI and voxel-based morphometry (VBM) to preliminarily investigate the effects of sex on GMV changes in the setting of chronic stress. The primary hypothesis was the occurrence of sex-based changes in GMV due to chronic stress, followed by an interaction effect between chronic stress and sex.

2. Methods

2.1. Participants

Imaging and clinicopathological data were obtained from the open-source Max Planck Institute – Leipzig Mind-Brain-Body (MPILMBB) dataset [22]. Participants were recruited through public advertisements, leaflets, online advertisements, and information events at the University of Leipzig [23]. The primary exclusion criteria were as follows: history of any psychiatric diseases that required inpatient treatment >2 weeks; hypertension without medication intake; and any cardiovascular disease [23]. All participants were evaluated at the Day Clinic for Cognitive Neurology at the University Clinic Leipzig and the Max Planck Institute for Human Cognitive and Brain Sciences (MPI CBS) in Leipzig, Germany, and the sample populations included younger (20–35 years) and older (59–77 years) groups [23]; however, given that there is evidence of age-related decreases in gray matter (GM) and/or white matter (WM) volume in specific cortical regions of the brain [24], only subjects from the younger age group were included in the present analysis. Demographic data, chronic stress status, and original MRI T1 images were extracted from the dataset.

2.2. Data acquisition

Demographic data gathered for analysis included the following: age; sex; education level; handedness; smoking and drinking habits; and relationship status. Chronic stress status was assessed by a German translation [25] of a 20-item short version of the

Perceived Stress Questionnaire (PSQ) [26], which assessed the perception, appraisal, and processing of stressors over the most recent two years. Answers were rated on a 4-point Likert scale, from 1 (almost never) to 4 (usually), with an overall range of 20–80, linearly transformed to values between 0 and 100. Based on the total score cutoffs [27,28], the linear values were differentiated into three groups: 0–45, regular stress; 46–59, moderate stress; and 60–100, high stress. The internal consistency of the scale was good, with Cronbach's α between 0.80 and 0.86 [25]. MRI was performed using a 3 T scanner (MAGNETOM Verio; Siemens Healthcare GmbH, Erlangen, Germany) equipped with a 32-channel head coil. T1-weighted (T1WI) images were acquired using a magnetization-prepared 2 rapid acquisition gradient echoes (MP2-RAGE) sequence and the following parameters: time repeat (TR), 5000 ms; time echo (TE), 2.92 ms; inversion time (TI), 700 ms; flip angle (FA), 4°; echo spacing, 6.9 ms; bandwidth, 240 Hz/pixel; field of view (FOV), 256 mm; voxel size, 1 mm isotropic; generalized autocalibrating partial parallel acquisition (GRAPPA) acceleration factor 3; and slice order, interleaved.

2.3. MRI data processing

T1WI images were preprocessed prior to being downloaded, which included format conversion, background removal, spatial normalization to the Montreal Neurological Institute (MNI) 152 1 mm standard space, and anonymization. VBM was then performed using the CAT12 toolbox (http://www.neuro.uni-jena.de/cat/) implemented in SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/) in MATLAB R2014a (Mathworks, Inc., Natick, MA, USA). In brief, images were first segmented into GM, WM, and cerebrospinal fluid (CSF), after which they underwent spatial registration and modulation with preserved GMV. After visual inspection of the data quality, the images were smoothed with an 8 mm full width at half maximum (FWHM) Gaussian kernel. The total intracranial volume (TIV) was calculated as the sum of the total GM, WM, and CSF volumes, and was used to control for differences in head size among the participants in all analyses.

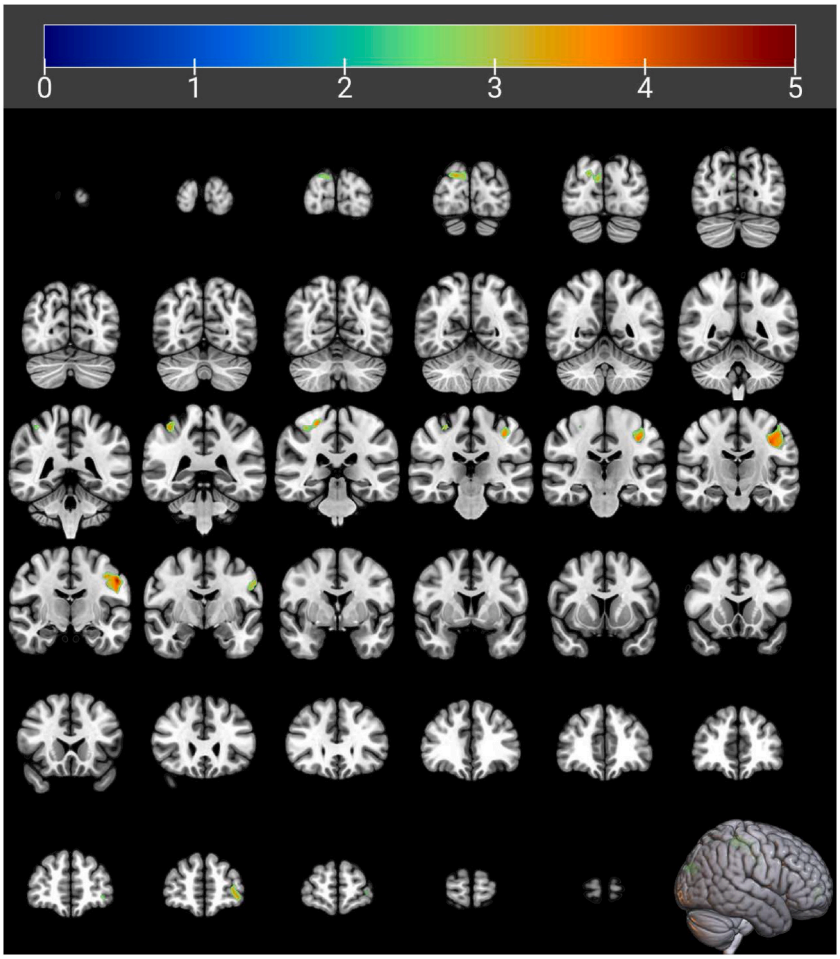

Fig. 1. Areas with significant chronic stress × sex interaction effect in the alteration of gray matter volume (GMV). Results show the Gaussian random field (GRF) -corrected F-map with cluster size >207, voxel $P < 0.005$, cluster $P < 0.05$. The color bar indicates the color window for the F values. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

2.4. Statistical analyses

The demographics, basic living habits, and relationship status of the participants were first reported, and a two-tailed chi-squared test was employed to assess the statistical significance of the variables between the male and female groups. These analyses were processed in SPSS version 26.0, with $P < 0.05$ considered statistically significant. Two-way analysis of variance (ANOVA) was performed using a 2×2 full factorial design, with TIV as a covariable, to explore the main and interaction effects of chronic stress (yes/no) and sex (male/female) on the changes in GMV. Post hoc tests were then performed within a mask showing GMV differences from the ANOVA analysis to verify the simple effects of chronic stress and sex on GMV. These analyses were performed using SPM12. The resulting images were rendered and reported using the viewer component in RESTplus v1.24 [29] with Gaussian random field (GRF) correction, with $P < 0.005$ considered statistically significant for voxel and $P < 0.05$ for cluster.

3. Results

A total of 32 subjects were included in the present analysis, among which 16 were in the chronic stress group (total PSQ score $\geq$46) and 16 were controls (total PSQ score $\leq$45). In order to eliminate interference due to the proportion of men to women in the results, the two groups were assigned equal numbers of males and females, with 8:8 in each group. The demographics and basic living habits of the participants, stratified by sex, are shown in Supplementary Table 1. There were no significant differences in age, handedness, educational status, smoking or drinking status, or emotional status between the male and female groups.

3.1. Sex-based differences in the impact of chronic stress on GMV

Results of the two-way ANOVA of sex and stress in GMV changes showed that significant cerebral regions existed in the main effect of stress, the main effect of sex, and the interaction effect of stress $\times$ sex. As shown in Fig. 1, there were four significant clusters subject to the interaction effect of stress $\times$ sex on GMV (GRF correction, voxel $P < 0.005$, cluster $P < 0.05$). The following were significant cerebral regions: the left pre-central and post-central gyri, the right cuneus and superior occipital gyrus the right pre-central and post-central gyri, and the left middle frontal gyrus and orbital middle frontal gyrus. The specific brain atlas and coordinates are shown in Table 1.

The main effect of chronic stress on GMV was not significant; however, there were four clusters of differences throughout the brain under a less strict correction (GRF correction, voxel $P < 0.05$, cluster $P < 0.05$), including the left inferior temporal gyrus, right brainstem, and midbrain; the right opercular and triangular part of the inferior frontal gyrus; and the right parietal lobe and angular gyrus (Supplementary Fig. 1 and Supplementary Table 2). Significant differences were observed in the main effect for sex, with six altered GMV clusters (GRF correction, voxel $P < 0.005$, cluster $P < 0.05$), including the bilateral lingual gyri and cerebellum, the right middle and inferior occipital gyri, the bilateral opercular and triangular part of the inferior frontal gyrus, the right superior and middle frontal gyri, and the right parietal and frontal lobes (Supplementary Fig. 2 and Supplementary Table 3).

3.2. The simple effect of chronic stress and sex on GMV

The simple effect analysis of chronic stress in the post hoc test indicated a GMV decrease in the bilateral pre- and post-central gyri, the right cuneus and superior occipital gyrus in males (False Discovery Rate(FDR) correction, $P < 0.05$, Fig. 2A), and a GMV increase in the bilateral pre-central and post-central gyri, the right superior occipital gyrus and the left middle frontal gyrus and orbital middle frontal gyrus in females (FDR correction, $P < 0.05$, Fig. 2B).

For the simple effect analysis of sex in the post hoc test, in the control group (Fig. 2C), males had three clusters of GMV > females (FDR correction, $P < 0.05$), including the left pre-central and post-central gyri, the right cuneus and superior occipital gyrus and the right pre-central and post-central gyri. However, in the chronic stress group, the above sex-based differences were no longer significant (FDR correction, $P < 0.05$). The males had only greater GMV than females in the left post-central gyri and the left middle frontal gyrus under less strict correction (cluster level correction, cluster size>45, voxel $P < 0.001$; Fig. 2D). The detailed distribution of the

Table 1
Cluster list for chronic stress * gender interaction effect on GMV.

Cluster index	Cluster size	Peak F value	MNI Coordinate (mm)			Brain areas (AAL)
			x	y	z	
1	1456	4.5959	−54	−12	39	L Postcentral gyrus L Precental gyrus
2	537	3.5824	16.5	−88.5	27	R Cuneus R Superior occipital gyrus
3	473	4.1756	30	−28.5	52.5	R Postcentral gyrus R Precental gyrus
4	253	3.4026	−37.5	57	−4.5	L Middle frontal gyrus, orbital part L Middle frontal gyrus

Note: GMV, gray matter volume; MNI, Montreal Neurological Institute; L, left; R, right; AAL, Anatomical Automatic Labeling; only regions with voxel size>20 are reported.

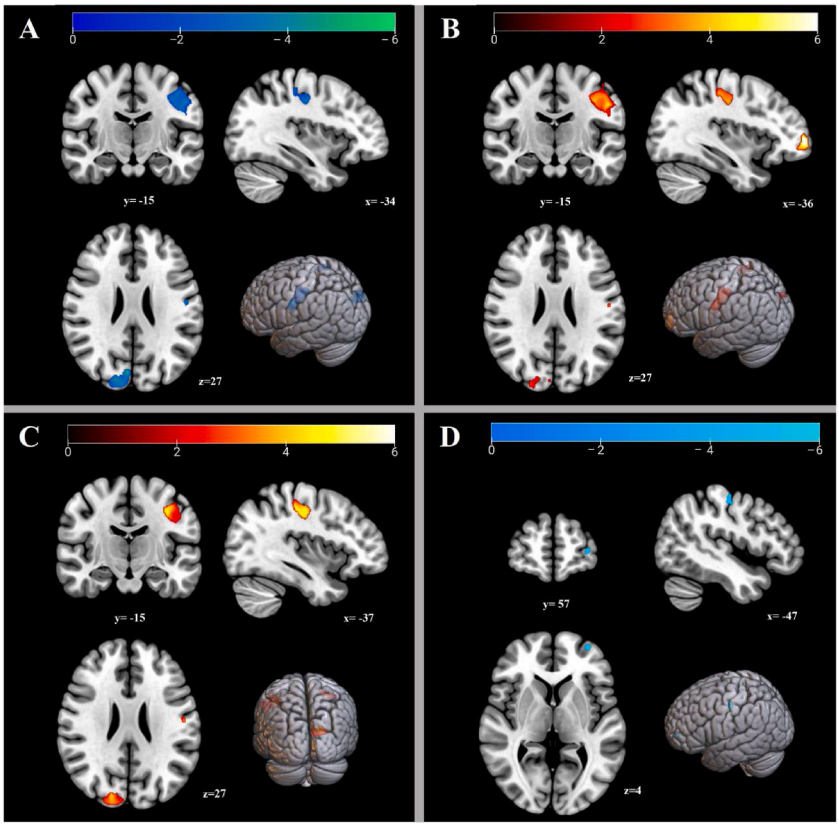

Fig. 2. Areas of altered gray matter volume (GMV) after simple effect analysis. (2A) T-map of GMV changes in males in the setting of chronic stress, with False Discovery Rate(FDR) correction, $P < 0.05$; (2B) T-map of GMV changes in females in the setting of chronic stress, with FDR correction, $P < 0.05$; (2C) T-map of sex differences in GMV without stress (male-female), FDR correction, $P < 0.05$; and (2D) T-map of sex differences in GMV under chronic stress (male-female), cluster level correction, cluster size>45, voxel $P < 0.001$. The color bar indicates the color window for the T values. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

functional brain atlas associated with the simple effects of chronic stress and sex is shown in Table 2.

4. Discussion

Sex differences are considered significant features of chronic stress and other related psychiatric disorders, which were been highlighted during the coronavirus disease 2019 (COVID-19) pandemic era [30,31]. Given the critical gap in current research regarding the cerebral morphology of sex-related differences in the setting of chronic stress, the present study aimed to conduct a pilot investigation. We identified a moderating role of sex in brain plasticity and sex-differentiated GMV changes under chronic stress. Two-way ANOVA showed a chronic stress × sex interaction effect on GMV changes, along with related brain regions. Simple effects analysis indicated that the GMV of the bilateral pre-central and post-central gyri, the right cuneus and superior occipital gyrus decreased in males experiencing chronic stress, whereas that of the bilateral pre-central and post-central gyri, the right superior occipital gyrus and the left middle frontal gyrus and orbital middle frontal gyrus increased in females. Additionally, the left pre-central and post-central gyri, the right cuneus and superior occipital gyrus and the right pre-central and post-central gyri were involved in sex-differentiated GMV changes. GMV was greater in males than in females in the control group. However, there was no significant sex difference under chronic stress.

The cerebellum contributes significantly to the motor system, and has also been reported to be involved in the processing of emotion in the cerebral regions, including the limbic system and prefrontal cortex [32]. Evidence from neuropsychiatric disorders further supports the involvement of the cerebellum in emotional dysregulation, with studies involving individuals with schizophrenia, autism, and depression collectively revealing the structural or functional abnormalities in the cerebellum [33,34]. Rabellino et al. [33] found decreased functional connectivity between the PFC and the posterior cerebellum, which is involved in emotional regulation, in patients with PTSD compared to controls. Seo et al. [35] reported sex-opposite patterns in the association between activity in the occipital gyrus and cerebellum and stress-induced anxiety, with positive associations in females but negative associations in males, indicating a different utility of neural resources in females and males under stress.

The pre-central and post-central gyri represent the primary motor and somatosensory cortices, respectively. Interestingly, the

Table 2
Brain regions of the simple effect of chronic stress and gender on GMV.

Pattern	Cluster index	Cluster size	Peak T value	MNI Coordinate (mm)			Brain areas (AAL)
				x	y	z	
M(CS-Con)	1	1308	−5.0533	−55.5	−10.5	40.5	L Postcentral gyrus
							L Precentral gyrus
	2	532	−4.9502	6	−79.5	27	R Cuneus
							R Superior occipital gyrus
	3	462	−5.8066	31.5	−28.5	52.5	R Postcentral gyrus
							R Precental gyrus
							R Inferior parietal
F(CS-Con)	1	1370	4.5667	−52.5	−13.5	34.5	L Postcentral gyrus
							L Precentral gyrus
	2	359	3.6514	24	−31.5	61.5	R Postcentral gyrus
							R Precental gyrus
	3	253	6.513	−36	58.5	−1.5	L Middle frontal gyrus, orbital part
							L Middle frontal gyrus
	4	130	2.8773	24	−91.5	25.5	R Superior occipital gyrus
Con(M-F)	1	1045	5.6259	−37.5	−24	43.5	L Postcentral gyrus
							L Precentral gyrus
	2	376	5.2589	16.5	−87	33	R Cuneus
							R Superior occipital gyrus
	3	241	4.2636	25.5	−30	55.5	R Postcentral gyrus
							R Precental gyrus
CS(M-F)	1	54	−5.358	−48	−15	52.5	L Postcentral gyrus
	2	45	−4.8703	−34.5	57	4.5	L Middle frontal gyrus

Note: M, male; F, female; CS, chronic stress; Con, control; GMV, gray matter volume; MNI, Montreal Neurological Institute; L, left; R, right; AAL, Anatomical Automatic Labeling; only regions with voxel size>20 are reported.

amygdala has also been reported to contain a wide range of projective cerebral areas involved in sensory and motor processing, including the pre-central and post-central gyri [36]. There is evidence of the existence of a limbic-motor interface, which is likely to be involved in the emotional modulation of complex functions, such as spatial perception and movement computation [37]. A resting regional cerebral perfusion study on PTSD reported that regional cerebral flow in the right precentral cortex was higher in patients with PTSD than in healthy controls [38]. Owing to the important role of the precentral cortex in learning, preparation, and execution of motor tasks, the heightened activation of this area observed in the PTSD group may be indicative of sustained preparatory motor activation, which in turn could result in elevated basal anxiety and arousal levels [38]. This potentially supports our findings that chronic stress might activate the motor system and trigger "fight or flight" responses.

Recently, a structural neuroimaging study of women with PTSD reported that a greater severity of active avoidance symptoms was associated with greater cortical thickness in the postcentral gyrus [39]. Abnormal activity in the postcentral gyrus and somatosensory cortex has been reported in patients with depression [40]. Abnormalities in the function of the postcentral gyrus impair the primary cognitive networks, along with the auditory and sensorimotor networks. Women are more emotionally aware and rely more on emotional content when processing information, leading to an increased activation of the somatosensory cortex [40,41]. An alternative explanation for this finding is that the increase in GMV in the posterior central gyrus may be related to women's excessive attention and interpretation of emotional content and somatic symptoms during stress [42]. This is also consistent with previous studies on patients with depression, in which Yao et al. [43] reported that the weight loss degree of women is positively correlated with the mean low-frequency oscillation (ALFF) value of the postcentral gyrus, indicating increased activity in the postcentral gyrus in women with more serious physical symptoms.

Structural and functional alterations in the limbic system (hippocampus, cingulate gyrus, amygdala, and insula) have been widely reported in stress-related psychiatric disorders, resulting in impaired emotional regulation and self-control. Ganzel et al. [44] found that GMV decreased in the amygdala, anterior cingulate, and hippocampus of post-traumatic individuals, and that there was a significant positive correlation between recent stressful events and reduced GMV in the amygdala. Ansell et al. [7] found that the greater the intensity of stressful life events, the smaller the GMV of the cingulate cortex, ventral PFC, and insula. Reduced GMV in the bilateral ACC is also associated with substance use disorder (SUD) [45].However, the present study did not find hippocampi or amygdala volume alterations, which consistent with some previous studies [46]. This is partly due to smaller sample size and differences in the definition and measurement of stress, which may lead to neuroimaging results differences.

The present study does, however, have several limitations. First, although this pilot study investigated sex-based differences in brain morphometry under chronic stress, the sample size should only be considered moderate. The primary reason for the smaller sample size was that older adults were not included in the analysis to prevent age confusion although there were fewer younger adults in the MPILMBB project. Additionally, other projects were not included to ensure the homogeneity of the scanning parameters and behavioral data. Secondly, the cross-sectional design of the present study hampered the investigation of potentially reversible cerebral changes.Thirdly, this pilot study aimed to investigate the brain regions associated with gender differences under chronic stress as much as possible due to the lack of evidence in this area. A less-strict but still acceptable threshold for the GRF correction was used in this study, which may increase the probability of false positives.

5. Conclusions

The present study showed sex-based alterations in the GMV in the setting of chronic stress, with decreased GMV in the bilateral pre- and post-central gyri, the right cuneus and superior occipital gyrus observed in males, and increased GMV in the bilateral pre- and post-central gyri, the right superior occipital gyrus and the left middle frontal gyrus and orbital middle frontal gyrus in females. The study's results provide preliminary evidence that gender and chronic stress may interact to affect brain GMV. However, it is crucial to acknowledge that the present study has a small sample size from the OpenfMRI database. Therefore, to enhance the robustness of the results in the future, it is necessary to replicate the findings using an independent dataset with a larger sample size.

Ethics approval and consent to participate

This data was obtained from the OpenfMRI database. Its accession number is ds000221. All participants who were included in the study are said to have provided written informed consent. Analysis of this data is approved by the ethics committees of Naval Medical University.

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Data availability statement

All data used in the generation of the results presented in this manuscript will be made available upon reasonable request from the corresponding author.

Abbreviations

Abbreviation	Definition
MRI	Magnetic Resonance Imaging
VBM	Voxel-Based Morphometry
GMV	Gray Matter Volume
T1WI	T1-Weighted Images
ANOVA	Analysis Of Variance
MDD	Depressive Disorder
BD	Bipolar Disorder
PTSD	Post-Traumatic Stress Disorder
PD	Panic Disorder
PFC	Prefrontal Cortex
ACC	Anterior Cingulate Cortex
GM	Gray Matter
WM	White Matter
CSF	Cerebrospinal Fluid
PSQ	Perceived Stress Questionnaire
MNI	Montreal Neurological Institute
TIV	Total Intracranial Volume
GRF	Gaussian Random Field
FDR	False Discovery Rate

CRediT authorship contribution statement

Zhilei Shang: Writing – review & editing, Visualization, Methodology, Formal analysis. **Nianqi Liu:** Writing – original draft, Methodology. **Hui Ouyang:** Writing – review & editing, Methodology. **Xiaojie Cai:** Writing – review & editing, Methodology. **Wenjie Yan:** Investigation, Data curation. **Jing Wang:** Methodology, Formal analysis. **Jingye Zhan:** Methodology, Data curation. **Yanpu Jia:** Investigation, Data curation. **Chenqi Xing:** Formal analysis. **Lijun Huang:** Supervision, Project administration. **Lili Wu:** Supervision, Project administration, Conceptualization. **Weizhi Liu:** Validation, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to

influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e30354.

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