Original Article

Nonspecific Effect of Stress on Brain Gray Matter Volume in Drug-naive Female Patients with First Depressive Episode

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Abstract

Background: This study aimed to observe the differences in brain gray matter volume in drug-naive female patients after the first episode of major depression with and without stressful life events (SLEs) before the onset of depression.
Methods: Forty-three drug-naive female patients voluntarily participated in the present study after the first major depressive episode. The life event scale was used to evaluate the severity of the impact of SLEs during 6 months before the onset of the major depressive episode. High-field magnetic resonance imaging (MRI) scans were obtained, and the VBM and SPM8 software process were used to process and analyze the MRI.
Results: Compared to that in patients without SLEs, the volume of brain gray matter was lower in the bilateral temporal lobe, right occipital lobe, and right limbic lobe in the SLE group. However, the gray matter volume did not differ significantly between the two groups after the application of false discovery rate (FDR) correction.
Conclusions: Although the results of the present study suggest the absence of significant differences in brain gray matter volume between female drug-naive patients after the first episode of major depression with and without SLEs after FDR correction, the study provides useful information for exploring the definitive role of stress in the onset of depression.

Key words: First Episode; Gray Matter Volume; Magnetic Resonance Imaging; Major Depression Disorder; Stressful Life Events

Introduction

A considerable proportion of patients with depression previously experienced a certain extent of stressful life events (SLEs) before the onset of depression.[1,2] Previous studies reported that SLEs can cause a decrease in gray matter volume in some key brain regions, such as the anterior cingulate, hippocampus, and parahippocampal gyrus.[3] As is widely known, alterations in gray matter volume are commonly found in depressed patients. For example, Kim *et al*.[4] found that the gray matter volume was decreased in the bilateral caudate nucleus and the thalamus in patients with major depression. Another previous study found that to some extent, the pattern of structural abnormalities observed in the brains of depressed patients is similar to the pattern of abnormalities in patients with posttraumatic stress disorder, a disorder caused by extreme stress.[5] Collectively, the findings of these studies led to the hypothesis that alteration in gray matter caused by stress-related factors may be the neurobiological basis of subsequent depression.

However, other studies have challenged this hypothesis. For example, some epidemiological studies reviewed by Paykel[6] found that not all depression patients experience

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obvious SLEs before the onset of depressive symptoms. These findings suggest that structural alterations in the brains of patients with major depression are intrinsic and independent of whether a patient had experienced an SLE. Unfortunately, to the best of our knowledge, no studies have explored whether brain structural differences exist between depression patients with and without prior SLEs. Thus, the relationships among stress factors, brain structure, and depressive episodes remain unclear.

Based on the results of previous epidemiological studies, we postulated that the experience of SLEs before the onset of depression likely causes brain structural alterations, and these alterations are associated with the subsequent onset of depression. In addition, such alterations are probably different from brain structural alterations found in depression patients without SLE experiences. The aim of this pilot study was to compare the gray matter volume between two groups of drug-naive female patients who had or had not experienced SLEs prior to the onset of major depression by high-field magnetic resonance imaging (MRI) and to provide a foundation for large sample follow-up studies to investigate the associations among stress factors, brain structural alterations, and the onset of depression.

Methods

Patients

This study was approved by the Ethics Committee of Affiliated Hospital of Jining Medical University in Shandong Province, China. Written informed consent was obtained from all participants and their legal guardians when applicable. Both inpatients and outpatients were treated in the Department of Psychiatry of our hospital between February 2011 and February 2013. Due to a previous finding that male depression patients are more likely to be alcohol or nicotine abusers,[7] both of which could confound the MRI results, only female patients were enrolled in this study. All participants were diagnosed by two senior psychiatrists according to the first depressive episode criteria of ICD-10.[8] All participants were right-handed and Han Chinese. The age range was 18–55 years old. None of the participants had ever been treated with anti-depressants, mood stabilizers, or antipsychotics. Patients were excluded from the study if they met any of the following criteria: (1) History of disturbance of consciousness for more than 5 min, (2) diagnosis of neurological disease, (3) depression accompanied by serious psychotic symptoms or substance abuse, (4) presence of physical disease not suitable for an MRI scanning, (5) pregnant or breastfeeding, (6) affected by claustrophobia or other disorders that could affect MRI scanning, and (7) history of alcohol consumption or nicotine use.

Clinical assessments

The 24-item Hamilton depression scale[9] was used to evaluate the severity of the depressive symptoms. The life event scale[10] was used to evaluate life events that occurred within 6 months as well as the severity of stress experienced within 6 months before the emergence of the first episode of major depression.

Magnetic resonance imaging sequence and imaging parameters

MRI data were collected using Siemens 3.0T Magetom Trio, A Tim System (Siemens, Germany). The scanning parameters were as follows: (1) For T1-weighted images (T1-WI) sequences: repetition time (TR) = 350 ms, echo time (TE) = 2.5 ms, slice thickness = 5.5 mm, gap = 1.1 m, matrix = 320 × 320, and field of view (FOV) = 230 mm × 230 mm. (2) For T2-WI sequences: TR = 6000 ms, TE = 93 ms, slice thickness = 5.5 mm, gap = 1.1 m, matrix = 320 × 320, and FOV = 230 mm × 230 mm. A 3DT1 sequence was obtained if no organic disease was found in the regular scans and TR/TE = 1900 ms/9.5 ms, FOV = 250 mm × 250 mm, matrix = 128 × 128, slice thickness = 0.9 mm, and interval = 0.45 cm.

Magnetic resonance imaging data analysis

SPM8 (The FIL Methods group, UK) and VBM8 (Structural Brain Mapping Group, Germany) software programs were used in both preprocessing and processing for scanned images. The raw Digital Imaging and Communication in Medicine MRI data were converted to NIFTI format using SPM8 running on MATLAB R2010B (The MathWorks Inc., Natick, MA, USA). Brain volume normalizing, bias correcting, and segmentation into gray matter, white matter, and cerebrospinal fluid were performed using VBM8 toolbox. VBM8 toolbox is based on an optimized voxel-based morphometry protocol that helps increase the signal to noise ratio. The total volumes of gray matter, white matter, and cerebrospinal fluid were assessed by calculating the resulting tissue probabilities. Total brain volume was defined as the sum of the gray matter and white matter volumes. The volume images were smoothed using an isotropic Gaussian kernel (full width at half maximum = 8 mm).

Statistical analysis

SPSS 19.0 statistical analysis software (SPSS, Inc., Chicago, IL, USA) was used for statistical analysis. Continuous variables are presented as mean ± standard deviation (SD). Continuous and categorical variables were compared between groups using independent samples *t*-tests and Chi-square analysis. A P value of <0.05 was considered statistically significant.

Results

Demographic characteristics

In total, 43 women participated in the study (23 patients in the SLE group and 20 patients in the non-SLE group). No significant differences in age, education level, or the duration and severity of the depressive symptoms were observed between the two groups. The levels of SLE stimulation were significantly higher in SLE group than in non-SLE group [Table 1]. All patients who reported SLEs noted that they experienced negative events, such as divorce or unemployment.

Comparison of gray matter volume

Compared with that in non-SLE group, the gray matter volume in SLE group was less in the bilateral temporal lobe, right occipital lobe, and right limbic lobe [Table 2 and Figure 1]. However, these differences in gray matter volume were no longer statistically significant after the application of false discovery rate (FDR) correction.

Discussion

To our knowledge, the present study is the first MRI study to compare gray matter volumes in female drug-naive

Table 1: Life events scale comparison between SLE and non-SLE groups

Variables	SLE (n = 23)	Non-SLE (n = 20)	t	P
Age (years)	39.48 ± 11.18	46.10 ± 11.58	−1.96	0.06
Duration of illness (months)	4.17 ± 3.06	5.20 ± 3.75	−0.92	0.36
Education level (years)	7.74 ± 5.22	6.20 ± 5.29	0.96	0.34
HAMD–24	49.30 ± 3.23	48.45 ± 8.60	0.33	0.74
Negative stimuli levels	28.39 ± 8.35	1.85 ± 2.20	13.78	<0.001

Data are shown as mean ± standard deviation. SLE: Stressful life event.

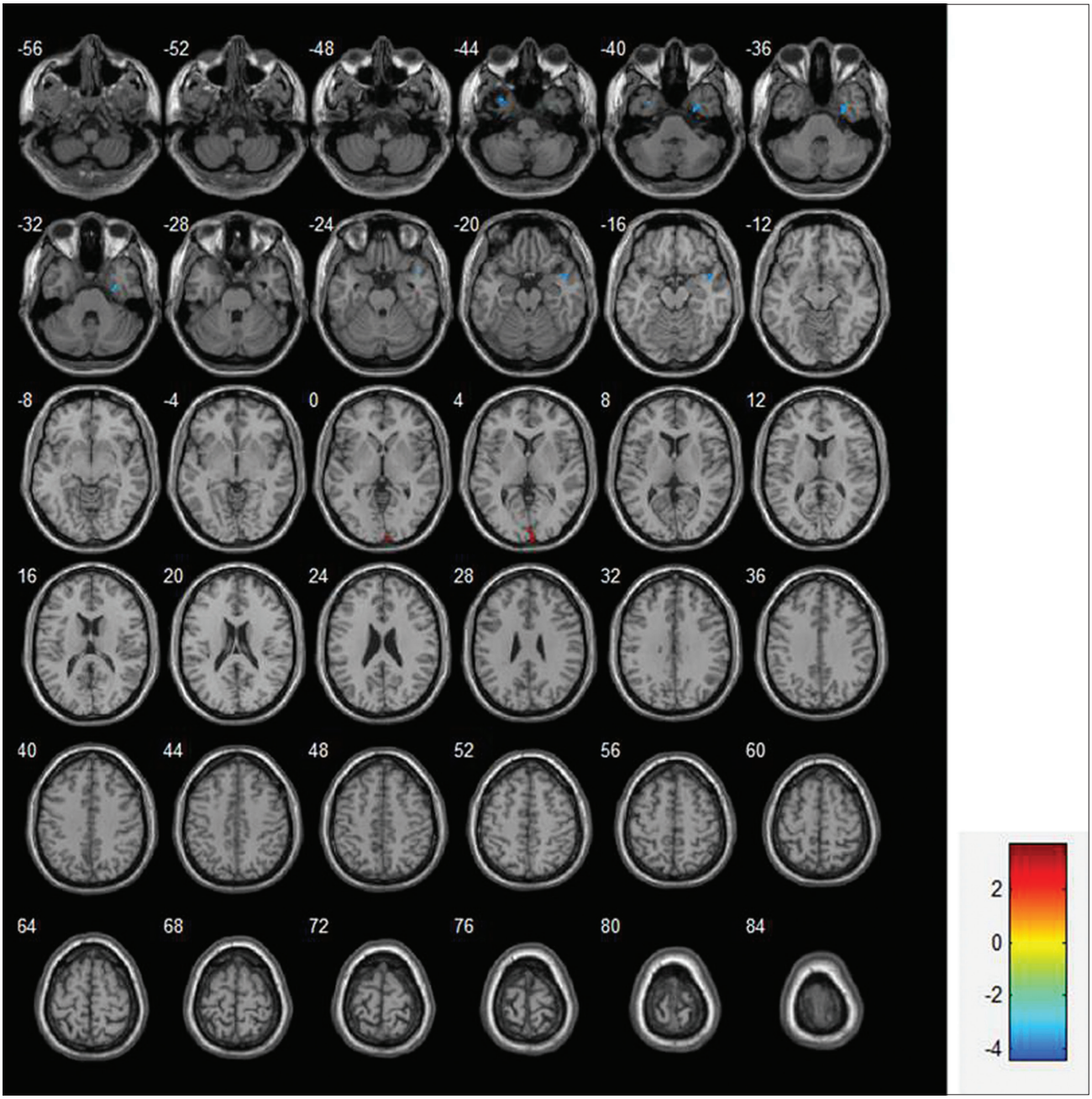

Figure 1: Regions of decreased gray matter volume displayed by xjView (without false discovery rate correction). Blue color indicates decreased brain volume, and the number to the left of each image represents the layer location. A color scale for the T value is displayed on the right.

Table 2: MNI coordinate of the decreased gray matter volume regions in the SLE group compared to that in the non-SLE group without false discovery rate correction

Brain region	Cluster size	T value	MNI coordinate		
			X	Y	Z
Left temporal lobe	71	−4.30	−31.5	4.5	−43.5
Right occipital lobe	97	4.58	6.0	−100.5	3.0
Right limbic lobe	160	−3.92	−28.5	−3.0	−37.5
Right temporal lobe	65	−4.08	45.0	6.0	−18.0

SLE: Stressful life event.

depression patients who did or did not experience SLEs before the onset of depression. In patients with SLEs, the gray matter volume was less in the temporal lobe, right occipital lobe, and right limbic lobe in comparison to that in the non-SLE patients. However, these differences were no longer statistically significant after FDR correction. These results indicated that stressful experiences before the onset of depression did not lead to changes in brain gray matter volume. This finding challenges our primary hypothesis that patients who experience SLEs before the onset of major depression likely exhibit specific alterations in brain gray matter that may be related to both previous SLEs and subsequent onset of depression.

At first glance, our findings seem counterintuitive to some degree but they are not incredible. Previous studies have reported that there may be no changes in gray matter in the first episode depression patients. For example, Guo *et al*.[11] observed abnormalities only in local brain functional activities but not in brain gray matter volume in drug-naive first episode depression patients compared to healthy controls. Their results suggest that there may be no gray matter changes within the early stage of the onset of depression and support the results of our present study to some extent.

In addition, Kim *et al*.[12] reported that a change in gray matter volume is influenced by the brain-derived neurotrophic factor Val66Met single nucleotide polymorphism and related to the patients' resilience to SLEs. Thus, genetic factors may help explain, to some extent, the inconsistency between our results and the findings of other studies although further studies are needed to provide experimental evidence for this theory.

In addition, several previous studies have suggested a direct association between stress and brain structural alterations in patients with major depression.[13-16] Qiao *et al*.[14] reported a positive association between sensitivity to individual life events and the regional gray matter volume in the ventrolateral prefrontal cortex, and Kronmüller *et al*.[15] found a significant negative association between life events and hippocampal volumes in patients after the first episode of depression. In addition, Zhang *et al*.[16] reported that gray matter volume was reduced in the left precentral gyrus and right fusiform gyrus in patients with depressive cognitive tendencies compared to that in healthy controls. Of note, these previous studies[13-16] drew their conclusions from comparisons of characteristics between patients and healthy controls rather than between patients with different histories of SLEs. Also, the results of the previous studies are inconsistent and even contradictory in some cases. In the present study, we compared observations in two categories of depression patients with different histories of SLEs, and this difference in the patient samples may be one factor explaining the discrepancy between our results and the results of these previous studies.

Our study has some limitations and longitudinal clinical studies with large and genetically varied patient samples are needed to overcome these limitations and effectively elucidate the definitive relationship between SLEs and the subsequent onset of depression. First, this study included menopausal women who are reported to be prone to depression, which may affect the results. Second, clinical studies should be designed with collection of MRI and genetic data from the following four groups with sufficient numbers of cases in each: (1) individuals who experienced SLEs but did not develop depression, (2) patients who experienced SLEs and subsequently developed depression, (3) patients who experienced a first episode of major depression without prior experience of SLEs, and (4) healthy controls without SLEs. Although such a study will be extremely challenging and costly, it will offer the ability to elucidate the definitive relationship between stress and the onset of depression and provide important information for the prevention of depression.

In conclusion, although the results of the present study suggests that after FDR correction, there are no significant differences in brain gray matter volume between patients who have previously experienced SLEs and those who have not, this study still provides useful information for further exploration of the definitive role of stress in the onset of depression.

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Conflicts of interest

There are no conflicts of interest.

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