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Gray Matter Volume Abnormalities in Depressive Patients With and Without Anxiety Disorders

Haochen Qi, BE, Yuping Ning, MD, Jie Li, MD, Shengwen Guo, DE, Minyue Chi, BE, Minjian Gao, BE, Yangbo Guo, MD, Yuling Yang, MD, Hongjun Peng, MD, and Kai Wu, MD

Abstract: Comorbidity with anxiety disorder is a relatively common occurrence in major depressive disorder. However, the unique and shared neuroanatomical characteristics of depression and anxiety disorders have not been fully identified. The aim of this study was to identify gray matter abnormalities and their clinical correlates in depressive patients with and without anxiety disorders.

We applied voxel-based morphometry and region-of-interest analyses of gray matter volume (GMV) in normal controls (NC group, $n = 28$), depressive patients without anxiety disorder (DP group, $n = 18$), and depressive patients with anxiety disorder (DPA group, $n = 20$). The correlations between regional GMV and clinical data were analyzed.

The DP group showed decreased GMV in the left insula (INS) and left triangular part of the inferior frontal gyrus when compared to the NC group. The DPA group showed greater GMV in the midbrain, medial prefrontal cortex, and primary motor/somatosensory cortex when compared to the NC group. Moreover, the DPA group showed greater GMV than the DP group in the frontal, INS, and temporal lobes. Most gray matter anomalies were significantly correlated with depression severity or anxiety symptoms. These correlations were categorized into 4 trend models, of which 3 trend models (ie, Models I, II, and IV) revealed the direction of the correlation between regional GMV and depression severity to be the opposite of that between regional GMV and anxiety symptoms. Importantly, the left INS showed a trend Model I, which might be critically important for distinguishing depressive patients with and without anxiety disorder.

Our findings of gray matter abnormalities, their correlations with clinical data, and the trend models showing opposite direction may reflect disorder-specific symptom characteristics and help explain the neurobiological differences between depression and anxiety disorder.

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Abbreviations: AMYG = amygdala, ANG = angular gyrus, ANOVA = analysis of variance, CSF = cerebrospinal fluid, DMPFC = dorsomedial prefrontal cortex, DP = depressive patients without anxiety disorder, DPA = depressive patients with anxiety disorder, GAD = generalized anxiety disorder, GLM = General Linear Model, GMV = gray matter volume, HAMA = Hamilton Anxiety Scale, HAMD = Hamilton Depressive Rating Scale, HIP = hippocampus, IFG = inferior frontal gyrus, IFGtriang = triangular part of the inferior frontal gyrus, INS = insula, ITG = inferior temporal gyrus, LING = lingual gyrus, MDD = major depressive disorder, MRI = magnetic resonance imaging, MTG = middle temporal gyrus, NC = normal controls, PHG = parahippocampal gyrus, PoCG = postcentral gyrus, PreCG = precentral gyrus, REC = rectus, RGMV = regional gray matter volume, ROI = region of interest, ROL = rolandic operculum, SAS = Self-Rating Anxiety Scale, SDS = Zung's Self-Rating Depression Scale, SFGdor = dorsal part of superior frontal gyrus, TGMV = total gray matter volume, VBM = voxel-based morphometry.

INTRODUCTION

Anxious depression is a common, clinically distinct subtype of major depressive disorder (MDD). It has been estimated that 40% to 50% of patients with MDD have at least 1 comorbid anxiety disorder.[1] Twin studies have revealed a similar genetic risk and inheritance pattern for MDD and anxiety disorders.[2] Additionally, family studies have indicated a cosegregation of MDD and anxiety.[3] Given that depression and anxiety respond to the same treatment strategies, they might also have a similar etiology.[4] Many researchers have speculated that a common mechanism may underlie the development of anxious depression because high trait anxiety/neuroticism is a vulnerability factor for MDD[5] and subjects with MDD exhibit enhanced fear conditioning.[6] However, the onset of MDD is often preceded by the development of anxiety disorders, in both children and adults. The comorbid condition of depression and anxiety may differ from MDD in clinical course and characteristics because it has been associated both with worse outcomes[7–10] and with more severe psychopathology.[9–11] Thus, MDD patients with and without anxiety disorders may represent either distinguishable components of the depression spectrum or result

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From the Department of Biomedical Engineering (HQ, SG, MC, KW), School of Materials Science and Engineering, South China University of Technology; Guangzhou Psychiatric Hospital (YN, JL, YG, YY, HP), Affiliated Hospital of Guangzhou Medical University; and School of Computer Science and Engineering (MG), South China University of Technology, Guangzhou, China.
Correspondence: Hongjun Peng, Guangzhou Psychiatric Hospital, Affiliated Hospital of Guangzhou Medical University, Guangzhou 510370, China (e-mail: penghjgz@163.com). Kai Wu, Department of Biomedical Engineering, School of Materials Science and Engineering, South China University of Technology, Guangzhou 510006, China (e-mail: kai.wu.22@gmail.com).
HQ and YN contributed equally to this work.
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from distinct combinations of genetic factors that contribute to both disorders.[1,12]

A large number of magnetic resonance imaging (MRI) studies have identified structural brain changes associated with MDD and anxiety. A previous selective review of T1-weighted structural MRI in adult samples of patients with MDD has demonstrated that volumetric reductions of the hippocampus (HIP), basal ganglia, and orbitofrontal and prefrontal cortex are consistently found in patients with MDD.[13] More recently, a meta-analysis of studies applying voxel-based morphometry (VBM) to MDD indicated that gray matter is significantly reduced in a confined cluster located in the rostral anterior cingulate cortex, dorsolateral prefrontal cortex, and dorsomedial prefrontal cortex (DMPFC).[12] Therefore, although decreased volumes are found in many brain structures, previous findings are not completely consistent.[12,13] Conversely, adult patients with generalized anxiety disorder (GAD) show larger gray matter volume (GMV) in brain regions associated with anticipatory anxiety and emotion regulation, such as the amygdala (AMYG) and DMPFC.[14] MDD patients with anxiety symptoms show greater GMV in the right temporal cortex when compared with MDD patients without anxiety symptoms.[15] Specific involvement of the inferior frontal cortex in MDD and lateral temporal cortex in anxiety disorders without comorbid MDD has been demonstrated and may reflect disorder-specific symptom clusters.[16] However, the unique and shared neuroanatomical characteristics of depression and anxiety have not been fully identified. In this study, we applied a VBM analysis of GMV in normal controls (NC) and depressive patients with and without anxiety disorder. Moreover, we analyzed the correlations between clinical characteristics and regional GMV in brain regions showing significant GMV differences in the group VBM comparisons.

MATERIALS AND METHODS

Subjects

Thirty-eight depressive patients between the ages of 18 and 45 years were recruited from the inpatient and outpatient units at Guangzhou Psychiatric Hospital, Affiliated Hospital of Guangzhou Medical University, Guangdong, China. The structured clinical interview for DSM-IV diagnostic criteria was used to assess the presence or absence of MDD. A 17-item Hamilton Depressive Rating Scale (HAMD) and Zung Self-Rating Depression Scale (SDS) were used to evaluate depression severity.[17–19] A 14-item Hamilton Anxiety Scale (HAMA) and Self-Rating Anxiety Scale (SAS) were used to evaluate anxiety symptoms.[20,21] We used Chinese versions of these measurements that show good reliability and validity.[22] With the exception of anxiety disorder, patients were excluded from the study if they met any of the following criteria: having other psychiatric axis-I or axis-II disorders, another neurological disorder, any substance use within the past 6 months, electroconvulsive therapy, any type of contraindication for MRI, or any other clinically relevant abnormalities in their medical history or laboratory examinations. Therefore, 38 depressive patients were divided into 2 groups: 18 depressive patients without anxiety disorder (the DP group, SAS scores <40, HAMA scores <14) and 20 depressive patients with anxiety disorder (the DPA group, SAS scores ≥ 40, HAMA scores ≥ 14).

In addition, 28 sex and age-matched NC (the NC group) were recruited from the local community. Before enrollment, all subjects were fully informed of the details of the study and written informed consent was obtained. These studies were performed according to the Declaration of Helsinki and approved by the Guangzhou Psychiatric Hospital Ethics Committee.

Image Acquisition

Imaging data were acquired using Philips 3T MR systems (Philips, Best, The Netherlands) located at Guangzhou Psychiatric Hospital, Affiliated Hospital of Guangzhou Medical University. For each subject, an anatomical image was obtained using a sagittal 3-D gradient-echo T1-weighted sequence (TR = 7.6 ms, TED = 3.7 ms, TI = 795 ms, flip angle = 8°, 180 slices, slice thickness = 1 mm, gap = 0 mm, matrix = 256×256, and inversion time = 0).

Image Processing

All T1-weighted magnetic resonance (MR) images were analyzed using SPM8 (Wellcome Institute of Neurology, University College London, UK; http://www.fil.ion.ucl.ac.uk/spm). First, the ''New Segmentation'' algorithm from SPM8 was applied to each T1-weighted MR image to extract tissue maps corresponding to gray matter, white matter, and cerebrospinal fluid. Next, all segmented tissue maps were used to create a customized, population-specific template using the DARTEL template-creation tool.[23] At the end of the process, gray matter map of each subject was warped using its corresponding smooth, reversible deformation parameters to the custom template space, and then to the MNI standard space. All warped gray matter images were then modulated by calculating the Jacobian determinants derived from the special normalization step and multiplying each voxel by the relative change in volume.[24] Finally, all wrapped modulated gray matter images were smoothed with an 8-mm Gaussian kernel before voxel-wise group comparisons.

Statistical Analysis

One-way analysis of variance (ANOVA) was used to test the group differences in clinical and demographic characteristics of all subjects using SPSS20.0 software. Post hoc pairwise comparisons were then performed using *t* tests. The gender data were analyzed using the χ^2 test. A value of $P < 0.05$ was considered significant.

Smoothed modulated gray matter images were analyzed with SPM8 utilizing the framework of general linear model. Voxel-wise GMV differences among the 3 groups were investigated using the ANOVA model. Post hoc pairwise comparisons were used to compare differences in GMV between any 2 groups. The covariates included in the model were total gray matter volume (TGMV) calculated from modulated gray matter images, age, gender, and education years. The resulting statistical map was corrected for multiple comparisons to a significance level of $P < 0.05$ by combining individual voxels ($P < 0.001$) and using a cluster size of 173 voxels. This correction was confined within a whole brain mask and determined by Monte Carlo simulations using the AFNI AlphaSim program (http://afni.nih.gov/afni/docpdf/AlphaSim.pdf).

Moreover, we performed a region-of-interest (ROI) analysis of regional gray matter volume (RGMV) in which the ROIs were defined as the significant brain areas found in the voxel-wise analysis of GMV. The partial correlation between the clinical data and the RGMV of each ROI was calculated, controlling for the age, gender, education years, and TGMV.

TABLE 1. Statistical Analysis of Clinical and Demographic Characteristics Among Normal Controls and Depressive Patients With and Without Anxiety Disorders

	NC (n = 28)	DP (n = 18)	DPA (n = 20)	F Value (χ^2)	*P* Value
Age, y	28.61 ± 5.45	31.06 ± 7.39	28.65 ± 8.18	0.812	0.449
Education, y	16.25 ± 4.04	12.56 ± 3.48	11.55 ± 3.38	10.826	<0.0001[a,b]
Gender (F/M)	13/15	11/7	9/11	1.232	0.540[*]
SDS	27.43 ± 5.85	51.67 ± 5.88	51.45 ± 9.19	94.855	<0.0001[a,b]
HAMD	13.50 ± 1.64	22.28 ± 3.30	20.25 ± 3.61	62.047	<0.0001[a,b]
SAS	27.46 ± 5.19	27.67 ± 4.67	47.10 ± 5.26	103.495	<0.0001[b,c]
HAMA	8.93 ± 1.98	8.11 ± 1.88	16.80 ± 3.52	74.077	<0.0001[b,c]

DP = depressive patients without anxiety disorder, DPA = depressive patients with anxietydisorder, HAMA = Hamilton Anxiety Scale, HAMD = Hamilton Depressive Rating Scale, NC = normal controls, SAS = Self-Rating Anxiety Scale, SDS = Zung Self-Rating Depression Scale. Values are showed as the mean ± standard deviation. The comparisons of clinical and demographic characteristics among the 3 groups (NC, DP, and DPA) were performed using a separate one-way ANOVA. Post hoc pairwise comparisons were then performed using *t* test. Statistical significance was set at $P < 0.05$. [*]For the gender distribution among the 3 groups, *P* value was obtained using χ^2 test. [a]Post hoc paired comparisons showed significant group differences between NC versus DP. [b]Post hoc paired comparisons showed significant group differences between NC versus DPA. [c]Post hoc paired comparisons showed significant group differences between DP versus DPA.

TABLE 2. Gray Matter Volume Abnormalities Among Normal Controls, Depressive Patients Without Anxiety, and Depressive Patients With Anxiety

			MNI Coordinates, mm			
Anatomical Region	**Hemisphere**	**Cluster Size (Voxels)**	***x***	***y***	***z***	***t* Value**
DP < NC						
Insula	L	280	−38	17	15	3.327
DPA > NC						
Precentral gyrus	L	1845	−44	−14	59	4.526
Midbrain	L	596	−6	−33	12	4.41
Midbrain	L	581	0	−8	−18	4.449
Superior occipital gyrus	L	350	−20	−77	29	4.426
Orbitofrontal cortex (medial)	L	276	−2	66	−6	3.821
Rolandic operculum	L	224	−48	−20	18	3.766
Precentral gyrus	R	525	27	−24	71	4.508
Precentral gyrus	R	283	59	−6	50	3.792
Postcentral gyrus	R	245	14	−45	77	3.855
DP < DPA						
Insula	L	5362	−26	23	−6	4.592
Inferior temporal gyrus	L	1987	−33	−2	−29	4.381
Precentral gyrus	L	1307	−56	−26	56	4.261
Rectal gyrus	L	611	0	60	−18	4.118
Superior frontal gyrus (dorsal)	L	361	−17	57	14	3.899
Insula	R	6581	36	35	−5	5.214
Lingual gyrus	R	3045	14	−87	−17	4.654
Parahippocampal gyrus	R	2708	35	0	−30	4.570
Middle temporal gyrus	R	970	63	6	−26	4.124
Inferior temporal gyrus	R	590	56	−48	−11	4.079
Rectal gyrus	R	499	8	35	−32	4.404
Supplementary motor area	R	326	11	12	54	3.800
Angular gyrus	R	244	45	−53	23	4.122

DP = depressive patients without anxiety disorder, DPA = depressive patients with anxiety disorder, L = left, NC = normal control, R = right. The resulting statistical map was corrected for multiple comparisons to a significance level of $P < 0.05$ by combining individual voxels ($P < 0.001$) and using a cluster size of 173 voxels. This correction was confined within a whole brain mask and was determined by Monte Carlo simulations using the AFNI AlphaSim program (http://afni.nih.gov/afni/docpdf/AlphaSim.pdf).

The volumes of extracted brain areas and the partial correlations were calculated by the in-house scripts using MATLAB 2010b.

RESULTS

Clinical and Demographic Characteristics of the Subjects

The demographic characteristics of the subjects are shown in Table 1. The age and gender distribution were not different between the 3 groups ($P > 0.05$). However, the education years in the NC group were significantly higher than those in the DP and DPA groups ($P < 0.0001$). The clinical data for each group are also shown in Table 1. The ANOVAs demonstrated significant group effects in all the test scores ($P < 0.0001$). Specifically, the NC group showed significantly lower scores of SDS and HAMD when compared with the DP and DPA groups. Moreover, the DPA group showed significantly higher scores of SAS and HAMA compared with the NC and DP groups.

GMV Abnormalities

The DP group showed significant gray matter reductions in the left insula (INS) and the left triangular part of the inferior frontal gyrus (IFGtriang), when compared with the NC group (Table 2, Figure 1).

The DPA group showed significant gray matter increases relative to the NC group in the following brain areas: bilateral precentral gyrus (PreCG), bilateral midbrain, left superior occipital gyrus, left medial part of orbitofrontal cortex, left rolandic operculum (ROL), and right postcentral gyrus (PoCG) (Table 2, Figure 2).

The DPA group showed significant gray matter increases when compared with the DP group in the following brain areas: bilateral INS, bilateral inferior frontal gyrus (IFG), bilateral rectus (REC), bilateral ROL, bilateral inferior temporal gyrus (ITG), bilateral middle temporal gyrus (MTG), bilateral parahippocampal gyrus (PHG), bilateral HIP, left PreCG, left dorsal part of superior frontal gyrus (SFGdor), right lingual gyrus (LING), right PoCG, right supplementary motor area, right angular gyrus, and right AMYG (Table 2, Figure 3).

Correlation Between Clinical Data and GMV

We calculated the RGMV of 23 ROIs, which showed significant group differences in the voxel-wise analysis of GMV (as shown in Table 2). Significant partial correlations between the clinical data (including SDS, HAMD, SAS, and HAMA) and the RGMV of ROIs were found, controlling for age, sex, education years, and TGMV (as shown in Table 3). Most ROIs (17 of 23 ROIs) indicated significant correlations ($P < 0.05$) between the RGMV and at least 1 of the clinical evaluation metrics. A significant negative correlation was found only in ROI-3 (the left ITG) and ROI-9 (the right PHG) between the RGMV and HAMD values; all other significant correlations were positive.

Furthermore, we defined 4 trend models (I–IV, as shown in Table 3) according to the correlations between depression severity (SDS or HAMD) and RGMV and those between anxiety symptoms (SAS or HAMA) and RGMV (Figure 4).

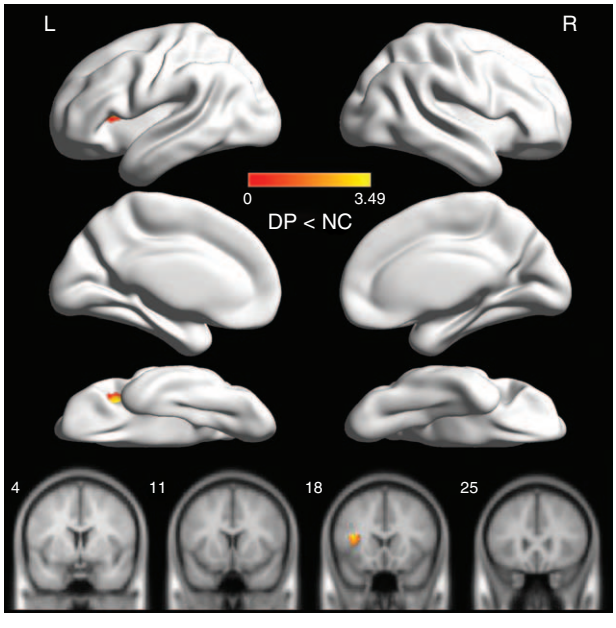

FIGURE 1. Gray matter volume reductions in depression patients without anxiety disorder compared with normal controls. Depression patients without anxiety disorder showed significant gray matter reductions in the left insula and the left triangular part of the inferior frontal gyrus. The resulting statistical map was corrected for multiple comparisons to a significance level of $P < 0.05$ by combining individual voxels ($P < 0.001$) and using a cluster size of 173 voxels. All coordinates are in MNI space. DP = depression patients without anxiety disorder, NC = normal controls.

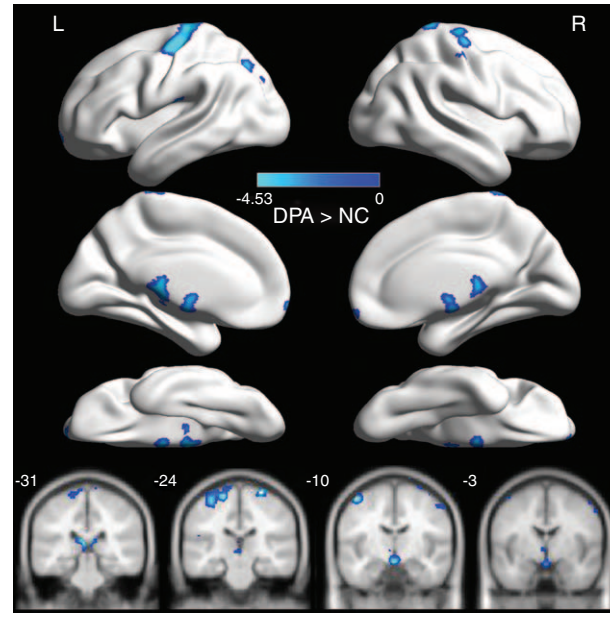

FIGURE 2. Gray matter volume increases in depression patients with anxiety disorder compared with normal controls. Depression patients with anxiety disorder showed significant gray matter increases in bilateral precentral gyrus, bilateral midbrain, left superior occipital gyrus, left medial part of orbitofrontal cortex, left rolandic operculum, and right postcentral gyrus. The resulting statistical map was corrected for multiple comparisons to a significance level of $P < 0.05$ by combining individual voxels ($P < 0.001$) and using a cluster size of 173 voxels. All coordinates are in MNI space. DPA = depression patients with anxiety disorder, NC = normal controls.

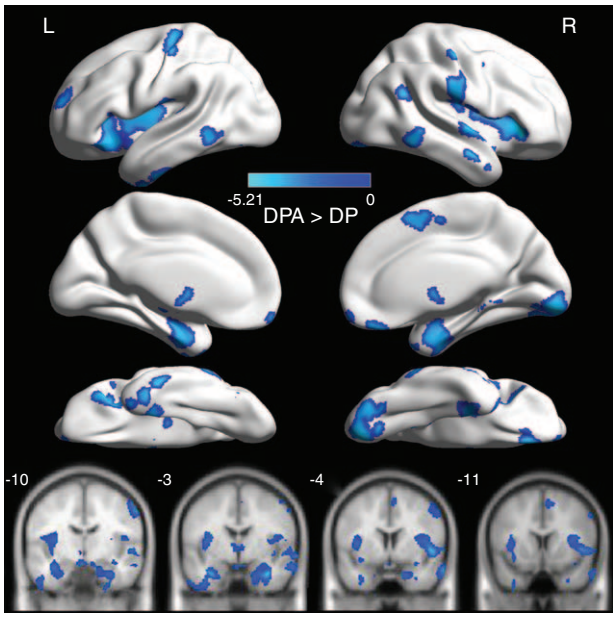

FIGURE 3. Gray matter volume increases in depression patients with anxiety disorder compared with depression patients without anxiety disorder. Depression patients with anxiety disorder showed significant gray matter increases in bilateral INS, bilateral inferior frontal gyrus, bilateral rectus, bilateral rolandic operculum, bilateral inferior temporal gyrus, bilateral middle temporal gyrus, bilateral parahippocampal gyrus, bilateral hippocampus, left precentral gyrus, left dorsal part of superior frontal gyrus, right lingual gyrus, right postcentral gyrus, right supplementary motor area, right angular gyrus, and right amygdala. The resulting statistical map was corrected for multiple comparisons to a significance level of $P < 0.05$ by combining individual voxels ($P < 0.001$) and using a cluster size of 173 voxels. All coordinates are in MNI space. DP = depression patients without anxiety disorder, DPA = depression patients with anxiety disorder, INS = insula.

Trend model I indicated a significant positive correlation between anxiety symptoms and RGMV and no significant correlation between depression severity and RGMV. We found 11 of 23 ROIs that were consistent with trend model I, such as the left INS (Figure 4A). Trend model II indicated a significant positive correlation between anxiety symptoms and RGMV and a significant negative correlation between depression severity and RGMV. Only the left ITG fit the pattern of trend model II (Figure 4B). Trend model III indicated a significant positive correlation between RGMV and both anxiety symptoms and depression severity. Four brain regions were classified into trend model III, such as the left REC (Figure 4C). Finally, trend model IV indicated a significant negative correlation between depression severity and RGMV and no significant correlation between anxiety symptoms and RGMV. Only the right PHG showed a pattern consistent with trend model IV (Figure 4D).

DISCUSSION

Our results indicated that the DP group had lower GMV in the left INS and left IFGtriang than the NC group. These results were consistent with several previous studies, which found that patients with MDD had significantly decreased GMV in the left INS[25,26] and in the bilateral INS,[27,28] when compared with healthy controls. However, many previous structural MRI studies have indicated that several brain regions (eg, anterior cingulate cortex, HIP, AMYG, and medial prefrontal cortex) are involved in the emotional and cognitive impairments in MDD.[29–31] Dysfunction of these brain structures, in addition to the INS, forms the basis of the limbic-cortical theory of the pathogenesis of MDD.[32,33] The INS is located deep within the lateral sulcus and has been included in the limbic lobe because of its intimate connections with the cingulate, AMYG, and orbitofrontal cortex.[34] Theoretically, the INS is neuroanatomically well positioned to represent emotional experience because it receives interoceptive inputs from the whole body, and its connections with the prefrontal regions can provide contextual information.[35] The inferior prefrontal cortex plays a major role in the orbitofrontal circuit, which allows the integration of limbic and emotional information into behavioral responses.[36–39] Therefore, abnormalities in the INS and inferior prefrontal cortex might cause changes in social behavior and emotional experiences. Moreover, a previous combined functional and structural MRI study found that patients with MDD show GMV abnormalities in several parts of IFG and that the structural changes result in functional alterations within the emotional circuit.[40]

Interestingly, the DPA group showed increased GMV in a variety of cortical regions, compared to both the NC and DP groups. When compared with the NC group, the DPA group showed GMV increases primarily within areas of the midbrain, medial prefrontal cortex, and primary motor/somatosensory cortex. However, the DPA group showed greater GMV than the DP group principally within regions of the frontal, INS, and temporal lobes. Our results were consistent with previous findings that increased GMV in specific brain structures is associated with anxiety disorders.[14,15,41,42] For example, among patients with MDD, those with anxiety display greater GMV than those without anxiety in the right temporal cortex extending from the mid-posterior superior temporal gyrus into the posterior middle and ITG.[15] Moreover, our results may support the valence-arousal model, which states that depression correlates with decreased activity in the right parietotemporal brain regions associated with arousal properties, whereas anxiety correlates with increased activity.[43] For example, patients with GAD show increased GMV in brain regions (eg, dorsomedial prefrontal cortex) associated with anticipatory anxiety and emotion regulation.[14] In addition, a previous task-related functional MRI study observed frontal and limbic hypoactivation (eg, INS and medial frontal cortex) in patients with depression and comorbid anxiety.[44] Thus, we speculated that abnormalities in these brain structures or the connections between them might result in pathological anxiety, which extensive fear conditioning research has suggested may arise from abnormal interactions between cortical and subcortical regions.[45–47]

We also found significant correlations between gray matter anomalies and depression severity or anxiety symptoms. More importantly, significant correlations can be defined as 4 trend models. Three trend models (Models I, II, and IV; 13 of 17 ROIs) revealed an opposite direction of association between regional brain volumes and either depression or anxiety scores; the values of RGMV were decreased with depression severity but increased with anxiety symptoms. These results further support the findings from our VBM analysis, which showed an opposite direction of RGMV abnormalities for the DP and DPA groups when compared with the NC group. Anxiety disorders are marked by excessive fear (and avoidance), often in response to specific objects or situations and in the absence of

TABLE 3. Correlation Between the Clinical Data and the RGMV of ROIs

ID of RIOs	Anatomical Region	Hemisphere	Cluster Size (Voxels)	Partial Correlation#				Trend model
				SDS	HAMD	SAS	HAMA	
1	Insula	L	280	n.s.	n.s.	n.s.	n.s.	
2	Insula	L	5362	n.s.	n.s.	0.285*	**0.382****	I
3	Inferior temporal gyrus	L	1987	n.s.	−0.280*	n.s.	0.311*	II
4	Precentral gyrus	L	1307	n.s.	n.s.	**0.330****	0.279*	I
5	Rectal gyrus	L	611	0.272*	**0.397****	0.301*	**0.342****	III
6	Superior frontal gyrus (dorsal)	L	361	0.290*	0.295*	0.303*	0.250*	III
7	Insula	R	6581	n.s.	n.s.	**0.330****	**0.334****	I
8	Lingual gyrus	R	3045	n.s.	n.s.	0.296*	**0.346****	I
9	Parahippocampal gyrus	R	2708	n.s.	−0.322*	n.s.	n.s.	IV
10	Middle temporal gyrus	R	970	n.s.	n.s.	n.s.	n.s.	
11	Inferior temporal gyrus	R	590	n.s.	n.s.	0.260*	n.s.	I
12	Rectal gyrus	R	499	n.s.	n.s.	n.s.	**0.364****	I
13	Supplementary motor area	R	326	n.s.	n.s.	n.s.	n.s.	
14	Angular gyrus	R	244	n.s.	n.s.	**0.369****	n.s.	I
15	Precentral gyrus	L	1845	n.s.	n.s.	0.266*	n.s.	I
16	Midbrain	L	596	n.s.	n.s.	n.s.	n.s.	
17	Midbrain	L	581	n.s.	n.s.	0.322*	0.327*	I
18	Superior occipital gyrus	L	350	0.310*	n.s.	0.281*	0.264*	III
19	Orbitofrontal cortex (medial)	L	276	**0.398****	**0.543****	0.323*	**0.345****	III
20	Rolandic operculum	L	224	n.s.	n.s.	0.268*	n.s.	I
21	Precentral gyrus	R	525	n.s.	n.s.	n.s.	n.s.	
22	Precentral gyrus	R	283	n.s.	n.s.	**0.343****	n.s.	I
23	Postcentral gyrus	R	245	n.s.	n.s.	n.s.	n.s.	

HAMA = Hamilton Anxiety Scale, HAMD = Hamilton Depressive Rating Scale, n.s. = not significant, RGMV = regional gray matter volume, ROI = region of interest, SAS = Self-Rating Anxiety Scale, SDS = Zung Self-Rating Depression Scale, TGMV = total gray matter volume. #The partial correlation between the clinical data and the RGMV of each ROI was calculated, controlling for the age, gender, education years, and TGMV. *Statistical significance was set at $P < 0.05$. **Statistical significance was set at $P < 0.01$ (shown in bold).

true danger.[47] However, MDD is a prevalent mental health concern and is associated with significant disability and suffering.[48,49] Thus, our trend model findings (Models I, II, and IV) may help to explain the neurobiological differences between depressive patients with and without anxiety. Importantly, the left INS cortex showed a trend Model I with a strong positive correlation between the RGMV and HAMA. The INS cortex is associated with modulating subjective feeling states and interoceptive awareness.[50] Moreover, the INS is known to play a key role in the process whereby an increased prediction signal of a prospective aversive body state triggers an increase in anxious affect, worrisome thoughts, and other avoidance behaviors.[34] Finally, heightened activation of the insular cortex has been observed in many of the anxiety disorders.[47] Given this evidence, we speculated that the left insular cortex might be critically important for distinguishing depressive patients with anxiety from those without anxiety.

There are several limitations of the present study. First, the depressive patients with and without anxious disorder in this study were using a selective serotonin reuptake inhibitor—escitalopram. A previous study has indicated the effects of antidepressant treatment on functional connectivity in patients with MDD at a circuit level using resting-state functional MRI.[51] Besides, a recent study has demonstrated that early age at onset may increase the likelihood of distinguishable MDD subtype, and age at onset of the first episode MDD is a promising clinical indicator for the clinical presentation, course, and outcome of MDD.[52] To better explore the neuroanatomical characteristics of depression and anxiety disorders, it would be useful to recruit drug-naive, first-episode patients of depression and anxiety disorders in the future study. Second, the results of our VBM analyses were inconsistent with many previous studies. However, comparing data across studies is difficult because of variations in study design, assessment, and the use of inconsistent definitions to diagnose anxious depression.[1] Therefore, the inconsistent results between the current and previous studies might be attributed to several factors: the VBM analyses with relatively small sample sizes in this study might have insufficient statistical power and a risk of false-positive errors[53]; and the clinical and demographic differences between the samples (eg, illness severity, medication, age, sex, and family history of mental illness) that affect the impact on regional volume of brain tissues.[13] Third, we defined 4 trend models with different patterns of correlation between RGMV and depression severity or anxiety symptoms. Although the analysis of trend models was not quantitative, further studies could apply a data-driven technique, such as multivariate pattern analysis, to discriminate psychiatric patients from healthy controls.[54–57]

CONCLUSION

In this study, we demonstrated that depressive patients with and without anxiety disorder showed gray matter abnormalities in a variety of brain structures and that the abnormalities

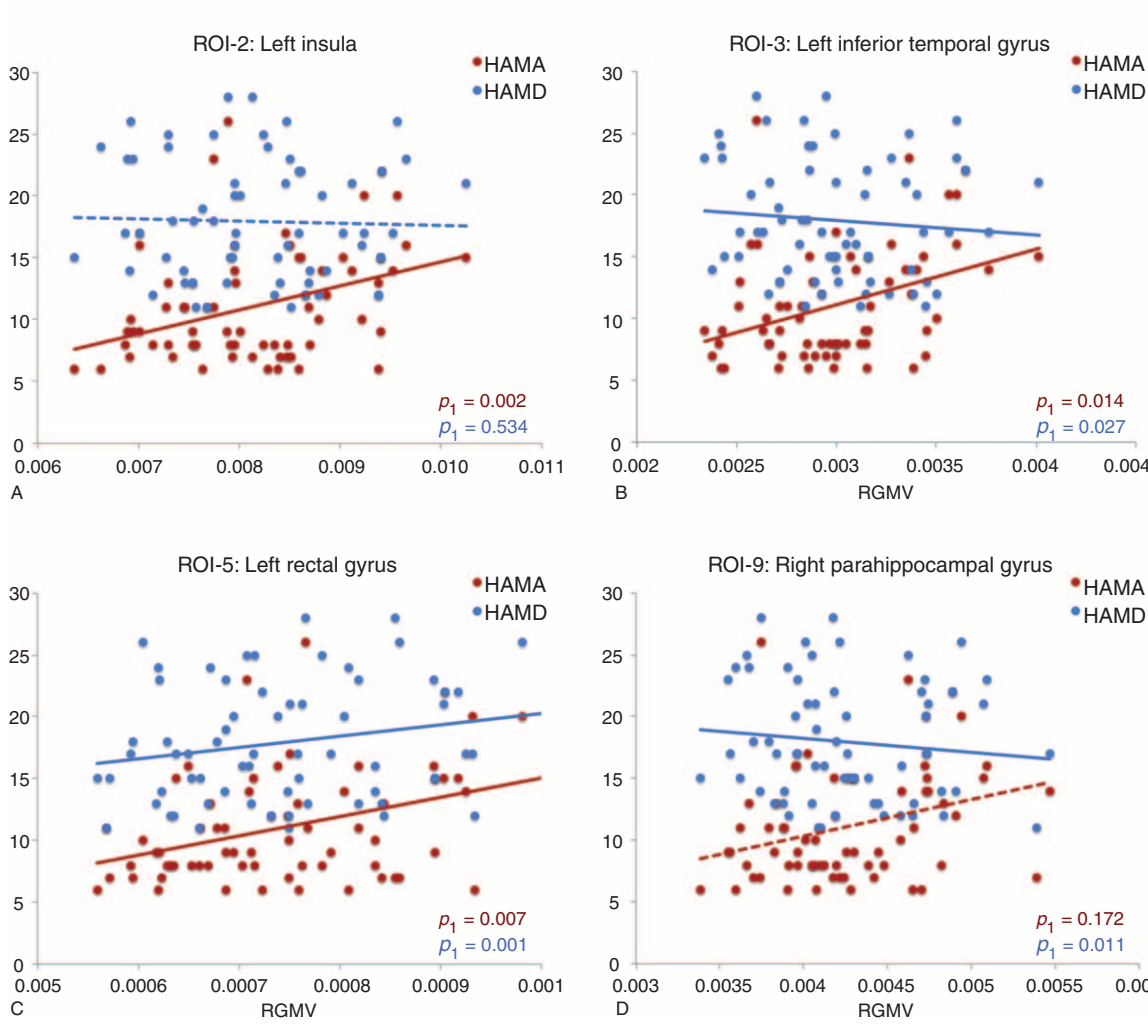

FIGURE 4. Partial correlation between the clinical data and the RGMV of selected ROIs was calculated, controlling for the age, gender, education years, and TGMV. (A) ROI-2: left insula. (B) ROI-3: left inferior temporal gyrus. (C) ROI-5: left rectal gyrus. (D) ROI-9: right parahippocampal gyrus. The solid lines indicate significant correlations with $P < 0.05$. The dashed lines indicate insignificant correlations. HAMD = Hamilton Depressive Rating Scale, HAMA = Hamilton Anxiety Scale, RGMV = regional gray matter volume, ROI = region of interest, TGMV = total gray matter volume.

of some brain structures were significantly correlated with clinical data. Based on the correlations with either HAMD or HAMA, 4 trend models were defined and might reflect disorder-specific symptom characteristics. The existence of distinct neuroanatomical profiles associated with depressive patients with or without anxiety disorder may provide a potential biomarker for disease diagnosis.

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