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Research Paper

Gray Matter Abnormalities in Non-comorbid Medication-naive Patients with Major Depressive Disorder or Social Anxiety Disorder

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ABSTRACT

Background: An overlap of clinical symptoms between major depressive disorder (MDD) and social anxiety disorder (SAD) suggests that the two disorders exhibit similar brain mechanisms. However, few studies have directly compared the brain structures of the two disorders. The aim of this study was to assess the gray matter volume (GMV) and cortical thickness alterations between non-comorbid medication-naive MDD patients and SAD patients.

Methods: High-resolution T1-weighted images were acquired from 37 non-comorbid MDD patients, 24 non-comorbid SAD patients and 41 healthy controls (HCs). Voxel-based morphometry analysis of the GMV (corrected with a false discovery rate of $p < 0.001$) and vertex-based analysis of cortical thickness (corrected with a clusterwise probability of $p < 0.001$) were performed, and group differences were compared by ANOVA followed by post hoc tests.

Outcomes: Relative to the HCs, both the MDD patients and SAD patients showed the following results: GMV reductions in the bilateral orbital frontal cortex (OFC), putamen, and thalamus; cortical thickening in the bilateral medial prefrontal cortex, posterior dorsolateral prefrontal cortex, insular cortex, left temporal pole, and right superior parietal cortex; and cortical thinning in the left lateral OFC and bilateral rostral middle frontal cortex. In addition, MDD patients specifically showed a greater thickness in the left fusiform gyrus and right lateral occipital cortex and a thinner thickness in the bilateral lingual and left cuneus. SAD patients specifically showed a thinner cortical thickness in the right precentral cortex.

Interpretation: Our results indicate that MDD and SAD share common patterns of gray matter abnormalities in the orbitofrontal-striatal-thalamic circuit, salience network and dorsal attention network. These consistent structural differences in the two patient groups may contribute to the broad spectrum of emotional, cognitive and behavioral disturbances observed in MDD patients and SAD patients. In addition, we found disorder-specific involvement of the visual processing regions in MDD and the precentral cortex in SAD. These findings provide new evidence regarding the shared and specific neuropathological mechanisms that underlie MDD and SAD.

1. Introduction

Major depressive disorder (MDD) is typified by depressed mood and loss of interest or pleasure in daily activities, whereas social anxiety disorder (SAD), often referred to as social phobia, is characterized by excessive and persistent fear in social or performance situations. Both are disabling emotional disorders that are highly prevalent (Kessler et al., 2005) and frequently comorbid, with the incidence of comorbidity ranging from 19.5% to >74.5% (Gorman, 1996; Ohayon and Schatzberg, 2010; Koyuncu et al., 2014). Depression is likely to co-occur with one form of anxiety, particularly SAD (Brown et al., 2001). Furthermore, depression and anxiety respond to the same treatment strategies; thus, it has been suggested that they share a similar etiology (Ressler and Mayberg, 2007). There have also been claims that a similar neural, presumably computational, architecture mediates of mood and anxiety symptoms (Martin et al., 2009).

Neuroimaging studies have shown similar neuroanatomical changes and distinct alteration patterns in MDD and SAD. Both gray matter volume (GMV) and cortical thickness were used. The GMV is a product of cortical thickness and surface area and is driven mostly by differences in the cortical surface area rather than cortical thickness (Panizzon et

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al., 2009). Cortical thickness reflects the size, density, and arrangement of neurons, neuroglia, and nerve fibers (Narr et al., 2005); thus, its measurement can provide important and relatively unique information regarding disease-specific neuroanatomical changes. Prior meta-analyses of voxel-based morphometry studies have shown the following chracteristics for anxiety and depression: a smaller GMV in the anterior cingulate cortex (ACC) and prefrontal cortex (PFC) in patients with non-comorbid depression (Du et al., 2012) and patients with non-comorbid anxiety (Shang et al., 2014); an increased GMV in the thalamus and cuneus in patients with non-comorbid depression (Peng et al., 2016a); and a reduced GMV in the middle temporal gyrus and precentral gyrus in patients with anxiety but without comorbid MDD (Shang et al., 2014). Greater GMV in the lingual gyrus, lateral occipital cortex, supplementary motor cortex, premotor cortex, precuneus, and angular gyrus have also been reported in SAD patients (Frick et al., 2014; Irle et al., 2014). A recent meta-analysis showed reduced cortical thickness in the orbitofrontal cortex (OFC), ACC, insula and temporal lobes in MDD patients (Schmaal et al., 2016). There are few cortical thickness studies of SAD patients, and only three original studies have reported cortical thickening in the left insula, right ACC and right temporal pole and cortical thinning in the right post-central cortex (Syal et al., 2012; Frick et al., 2013; Bruhl et al., 2014). However, the results of these studies may be confounded by the presence of medication and comorbid depression and anxiety.

To date, few neuroimaging studies have compared structural abnormalities in anxiety and depression, and none have compared MDD and SAD. One previous study indicated that the reduced volume in ACC was shared between depressive and anxiety disorders and that the inferior frontal cortex and lateral temporal cortex were disorder-specific for MDD and anxiety disorders, respectively (van Tol et al., 2010). Recent evidence suggests that the neural correlates of SAD differ from those of generalized anxiety disorder (GAD) and panic disorder (PD) (Blair et al., 2008; Buff et al., 2016). Thus, the results may have been confounded when PD, GAD and SAD patients were grouped together in that study. It is important to note that a direct neural comparison of non-comorbid MDD and SAD is necessary to identify both specific and general neural characteristics of these two disorders.

In this study, we conducted a direct comparison of the GMV and cortical thickness among non-comorbid MDD patients, non-comorbid SAD patients and healthy controls to identify general and specific changes to the gray matter in the context of these two disorders. Based on the literature, we hypothesized that MDD and SAD patients manifest common and distinct GMVs and cortical thickness abnormalities, such as specific involvement of the decreased GMV or cortical thickness in the cuneus in MDD, decreased GMV or cortical thickness in the precentral areas in SAD, and decreased GMV or cortical thickness in the OFC and ACC in the context of the two disorders.

2. Materials and Methods

2.1. Participants

Thirty-seven medication-naïve MDD patients and 26 medication-naïve SAD patients were recruited at the Mental Health Center at the West China Hospital of Sichuan University. The diagnoses of MDD and SAD were performed per a SCID (Structured Clinical Interview for DSM Disorders) according to Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria (American Psychiatric Association, 2000). Diagnoses of MDD and SAD were determined by consensus between two experienced clinical psychiatrists. All patients were right-handed, and none of the patients had received any psychotherapy or anti-psychiatric medications before MR scanning. Data from two SAD patients were subsequently excluded because of visual movement artifacts.

Forty-one healthy controls (HCs), matched for age, sex, handedness, and education, were recruited from the local area by poster advertisement and screened using the SCID Non-Patient Version to ascertain the lifetime absence of psychiatric and neurological illness. Two experienced clinical psychiatrists obtained the demographic characteristics and clinical variables of all subjects before MR scanning.

The exclusion criteria for the three groups were as follows: (1) the existence of a neurological disorder or other axis I psychiatric disorders; (2) axis II antisocial or borderline personality disorders (identified using the Structured Clinical Interview for DSM-IV criteria); (3) a history of drug dependence or abuse; (4) pregnancy; and (5) major physical illness such as cardiovascular disease or hepatitis, as assessed by clinical evaluations and medical records. Another exclusion criterion for the two patients group was any other DSM-IV axis I comorbidity. Another exclusion criterion for the HCs group was a history of psychiatric illness in first-degree relatives. T1-weighted and T2-weighted images of the brain were inspected by an experienced neuroradiologist, and no gross abnormalities were observed in any participant.

All MDD patients were evaluated with the Hamilton Anxiety Rating Scale (HAMA) and Hamilton Depression Rating Scale (HAMD). Psychological ratings and clinical symptoms in the SAD patients were evaluated using the Liebowitz Social Anxiety Scale (LSAS). The study procedure and involved risks were explained to the subjects; all the subjects provided written informed consent according to the protocol approved by the Ethics Committee of West China Hospital, Sichuan University.

2.2. MRI Acquisition

The MRI examinations were performed on a whole-body 3.0 T MR scanner (Siemens Trio, Erlangen, Germany) with a 12-channel head coil. Subjects were fitted with soft ear plugs, positioned comfortably in the coil and instructed to relax and remain still. Head motion was minimized with foam pads. High-resolution three-dimensional T1-weighted images were acquired using a spoiled gradient recalled sequence with TR/TE = 1900/2.26 ms, flip angle = 9°, 176 sagittal slices with thickness = 1 mm, FOV = 240 × 240 mm^2 and data matrix = 256 × 256, yielding an in-plane resolution of 0.94 × 0.94 mm^2.

2.3. Imaging Processing

As the surface-based analysis was restricted to the cortical mantle, the GMV was calculated using optimized voxel-based morphometry, following diffeomorphic anatomical registration through exponentiated lie algebra (DARTEL) (Ashburner, 2007) using the Statistical Parametric Mapping software (SPM8, http://www.fil.ion.ucl.ac.uk/spm). DARTEL has been recommended in favor of standard SPM normalization or the SPM-unified segmentation approaches for whole-brain and regional analysis without segmenting regions of interest (Ashburner and Friston, 2009; Yassa and Stark, 2009). Preprocessing of VBM-DARTEL was performed in four steps. (1) All original images were manually aligned on the anterior-posterior commissure line. (2) MR images were segmented into GM, white matter, and cerebrospinal fluid (CSF) using the standard unified segmentation model in SPM8. (3) The DARTEL approach was applied for registration, normalization, and modulation, leaving the images in the DARTEL space (In this approach, a DARTEL template was created based on the deformation fields that were produced during the segmentation procedure, and all individual deformation fields were subsequently registered to this template). Normalization was achieved through non-linear warping of the GM images to the DARTEL GM template in the MNI space, whereas the modulation was used for ensuring that the relative volumes of GM were preserved following the spatial normalization procedure. (4) The images were smoothed with an 8-mm, full width at half maximum Gaussian kernel to correct nonlinear gray matter volumes for individual brain size for the statistical analysis. After spatial pre-processing, the smoothed, modulated, normalized GM datasets were used for statistical analysis.

Cortical reconstruction and estimation of cortical thickness were performed using the FreeSurfer package (version 5.1.0, http://surfer.

nmr.mgh.harvard.edu/) (Fischl and Dale, 2000). The reliability of the method was validated against histological analysis of postmortem brains (Rosas et al., 2002) and manual measurements (Salat et al., 2004), and test-retest reliability was high (Han et al., 2006). In brief, the procedure involved automated registration to the Talairach space, normalization of intensity, segmentation of the gray matter, white matter and CSF, tessellation of the gray matter and white matter boundaries, and an automated topology correction and surface deformation following intensity gradients to optimally place the gray/white and gray/CSF borders defined at the location with the greatest shift in signal intensity (Dale et al., 1999; Fischl and Dale, 2000; Fischl et al., 2002; Fischl et al., 2004; Zhang et al., 2015). The results of this segmentation procedure were inspected visually and, if necessary, edited manually by adding control points. Afterward, surface inflation and registration to a spherical atlas were performed (Dale et al., 1999), and the cerebral cortex was parcellated into 34 regions per hemisphere, based on the gyral and sulcal structures (Desikan et al., 2006). Finally, cortical thickness was estimated as the average shortest distance between the white matter boundary and the pial surface. Surface maps were generated following registration of the cortical reconstructions of all subjects to a common average surface and then smoothed using a surface-based, 10-mm, full-width half-maximum Gaussian kernel.

2.4. Statistical Analysis

Demographic and clinical data comparisons were made among groups via one-way analysis of variance (ANOVA), two-sample *t*-tests and chi-square tests, using the Statistical Package for Social Sciences, version 19 (SPSS Inc., USA). Significance was set at $p < 0.05$.

GMV maps were analyzed in the context of the general linear model. A whole-brain voxel-wise analysis tested the main effect of diagnosis (MDD, SAD and HCs) using a factorial design in SPM8. A voxel-wise ANOVA was performed with the threshold set at $p < 0.001$ that was corrected by the false discovery rate (FDR) with the whole brain volume as a covariate of no interest. A contiguous cluster of at least 100 voxels was accepted as significant. Post hoc evaluations of significant ANOVA findings in these regions were then performed with secondary two-tailed independent sample *t*-tests. The GMVs of the regions showing significant differences among the three groups were extracted using the Mars Bar toolbox.

Measurements of cortical thickness were obtained for each vertex and mapped on a common spherical coordinate system. Maps were smoothed with a 10-mm Gaussian kernel, and right and left hemispheres were tested separately. To correct for multiple comparisons, a cluster analysis was conducted using a Monte Carlo simulation smoothed with a 15-mm Gaussian kernel with 10,000 iterations. The vertex-wide threshold was set at $p < 0.0001$ for simulation and clustering, and clusters were considered significant if they survived a clusterwise probability of $p < 0.001$.

2.5. Correlation Analyses

The mean volumes of the regions that showed significant group effects in the GMV after the FDR correction were extracted in common space for each subject. In the MDD patient group, partial correlations (two-tailed) were also used to examine the relationship between the GMV and the illness duration and symptom severity scores (HAMA score and HAMD score) after controlling for age and gender. In the SAD patient group, partial correlations (two-tailed) were also used to examine the relationship between the GMV and the illness duration and symptom severity scores (fear factor score, avoidance factor score, LSAS total score) after controlling for age and gender. Multiple comparisons were also controlled using an FDR of $p < 0.001$.

We then conducted vertex-wise whole brain analyses in the Query Design Estimate Contrast (QDEC) interface of FreeSurfer to test for the effects of illness duration and symptom severity scores, as mentioned above, on cortical thickness measurements using age and gender as covariates in the MDD or SAD patients. Cortical thickness indices were derived from the T1-weighted anatomical images that were smoothed with a kernel of 10. Multiple comparisons were controlled using the Monte Carlo method with a clusterwise threshold for inclusion of $p < 0.001$.

3. Results

3.1. Demographic and Clinical Data (Table 1)

We enrolled 37 patients with MDD, 24 patients with SAD and 41 HCs. There were no significant differences in the age, gender, education levels and handedness among the 3 groups, but the SAD patients showed longer illness durations than the MDD patients, which may stem from the fact that the onset of anxiety often precedes the onset of the first depressive episode (Beesdo et al., 2007). However, there was no significant correlation between the illness duration and gray matter abnormalities in the two patient groups.

3.2. Voxel-Based Morphometry Analysis of Gray Matter Volume (Table 2, Fig. 1)

Voxel-based morphometry analysis and one-way ANOVA were conducted. The three groups differed in the bilateral lateral OFC, medial OFC, putamen, thalamus, middle frontal cortex (MFC), right temporal pole, and left cuneus ($p < 0.001$, FDR-corrected, extent threshold > 100 voxels) (see Supplementary material Fig. S1). The post hoc analysis showed that both the MDD patients and SAD patients showed GMV reductions in the bilateral OFC, putamen, and thalamus compared to HCs. In addition, MDD patients showed decreased GMV in the right MFC and left cuneus and showed increased GMV in the right temporal pole relative to the HCs. This study detected no regions of increased GMV in the SAD patients compared with the HCs. In addition, no significant difference in the GMV was observed between the MDD and SAD groups.

3.3. Regional Cortical Thickness Measurements (Table 3, Fig. 2)

Supplementary material Fig. S2 and Table S1 show the brain clusters, including the frontal, parietal, insular, temporal, and occipital cortex, which highlights a significant group effect in cortical thickness. Between-group cortical thickness comparisons are presented in Table 3 and rendered in Fig. 2 ($p < 0.001$, cluster-corrected). Both the MDD and SAD groups, relative to the HCs, exhibited significant cortical thickening in the bilateral (rostral and caudal) ACC that extended to the medial superior frontal cortex (SFC), bilateral SFC, bilateral caudal MFC, bilateral insular cortex, left temporal pole, right superior parietal cortex, right supramarginal cortex, and right inferior temporal cortex. Cortical thinning in the left lateral OFC and bilateral rostral MFC was also apparent. In addition, compared with the HCs, the MDD patients showed greater thickness in the left fusiform, right bank superior temporal cortex and right lateral occipital cortex and prominent thinness in the bilateral lingual cortex, left cuneus and left pars orbitalis. Compared with the HCs, the SAD patients showed decreased cortical thickness in the right precentral cortex. Compared with the SAD patients, the MDD patients showed greater thickness in the bilateral SFC and thinness in the left postcentral cortex.

3.4. Correlations with Clinical Variable and Symptomatology

There was no significant correlation between the GMV and the illness duration or symptom severity scores in any of these regions after FDR correction of $p < 0.001$ in the MDD patients and SAD patients (see Supplementary material Table S2). No significant correlations between cortical thickness and the illness duration or symptom severity scores

Table 1
Sociodemographic and clinical features of patients and healthy controls.

	HCs	MDD	SAD	p value
	41	37	24	
Age	27.1 ± 7.2 (18–50)	26.7 ± 7.1 (18–43)	24.5 ± 4.0 (18–32)	0.113[a]
Male: female	26:15	25:12	15:9	0.899[b]
Education (year)	13.3 ± 2.6 (5–17)	13.4 ± 3.0 (7–19.5)	14.0 ± 3.5 (8–21)	0.860[a]
Duration (year)	–	2.0 ± 0.5 (0.6–3.0)	7.6 ± 3.8 (1.0–16.0)	0.000[c]
HAMA	–	28.1 ± 8.8 (12–43)	–	–
HAMD	–	25.0 ± 5.2 (16–36)	–	–
LSAS				
Total scale	–	–	57.0 ± 25.5 (23–115)	–
Fear factor	–	–	28.7 ± 12.5 (13–57)	–
Avoidance factor	–	–	28.4 ± 14.6 (4–58)	–

Values are means ± standard deviations (minimum–maximum).
Abbreviations: HAMA, Hamilton Anxiety Rating Scale; HAMD, Hamilton Depression Rating Scale; HCs, healthy controls; LSAS, Liebowitz Social Anxiety Scale; MDD, major depressive disorder; SAD, social anxiety disorder.
[a] p values obtained by ANOVA model.
[b] p value obtained by two-tailed Pearson chi-square test.
[c] p value obtained by two-sample *t*-test.

after the Monte Carlo correction of $p < 0.001$ were observed in the MDD patients or SAD patients in either the right or the left hemisphere.

4. Discussion

To the best of our knowledge, this study is the first to examine gray matter abnormalities in non-comorbid medication-naive MDD patients and SAD patients without the potentially confounding influences of comorbidity and treatment. We demonstrate shared and specific gray matter abnormalities in the two disorders relative to HCs, which mainly include reduced GMV and thinner cortical thickness in the bilateral orbital prefrontal cortex with increased cortical thickness mainly in the bilateral medial prefrontal cortex (i.e., ACC and medial SFC), insular cortex, posterior dorsolateral prefrontal cortex (DLPFC) (i.e., SFC and caudal MFC), left temporal pole, and right superior parietal cortex. However, the MDD patients manifested more widespread alterations than the SAD patients, including greater thickness in the left fusiform and right lateral occipital cortex and thinner thickness in the bilateral lingual cortex and left cuneus. The SAD patients specifically showed thinner cortical thickness in the right precentral cortex.

Table 2
Differences in gray matter volume among patients and healthy controls.[a]

Brain region	Maxima MNI			Cluster size (voxels)	F/t value[b]	p value
	Coordinate (x, y, z)					
Main-effect						
Bilateral orbital frontal cortex	−3	36	−30	9730	261.11	0.000
Left putamen	−26	0	−5	2001	81.29	0.000
Right putamen	32	−7	−3	1800	59.70	0.000
Bilateral thalamus	5	−10	0	511	42.96	0.000
Left cuneus	−2	−73	−9	1653	32.29	0.000
Left middle frontal cortex	−39	−21	61	168	33.54	0.000
Right temporal pole	38	14	−17	116	30.49	0.000
Right middle frontal cortex	34	−22	63	105	29.92	0.001
Post-hoc (volume reduction in MDD vs. HCs)						
Bilateral orbital frontal cortex	−3	36	−30	9032	20.34	0.000
Left putamen	−26	0	−3	1369	10.75	0.000
Right putamen	27	3	−2	576	9.26	0.000
Bilateral thalamus	−5	−15	3	1081	8.88	0.000
Left middle frontal cortex	−39	−19	61	141	7.87	0.000
Right middle frontal cortex	34	−22	63	103	8.36	0.000
Left cuneus	−2	−73	−9	1666	7.72	0.000
Post-hoc (volume increase in MDD vs. HCs)						
Right temporal pole	39	14	−30	127	7.70	0.000
Post-hoc (volume reduction in SAD vs. HCs)						
Bilateral orbital frontal cortex	−3	36	−30	3933	11.29	0.000
Left putamen	−26	2	−6	1918	10.69	0.000
Right putamen	32	−7	−5	1030	9.10	0.000
Bilateral thalamus	5	−9	0	301	6.86	0.000
Post-hoc (volume increase in SAD vs. HCs)						
No						

Abbreviations: HCs, healthy controls; MDD, major depressive disorder; MNI, Montreal Neurological Institute; SAD, social anxiety disorder.
[a] All effects survived false discovery rate (FDR) correction for multiple comparisons ($p < 0.001$) with a minimum cluster size of 100 voxels.
[b] Data indicate voxel-wise F values for ANOVA analysis and t values for post-hoc analysis.

4.1. Shared Gray Matter Alterations in MDD and SAD

Consistent with our hypothesis, both SAD and MDD shared similar gray matter deficits, particularly reduced GMV in the bilateral OFC, putamen and thalamus, relative to healthy controls, which had been reported in prior independent studies of MDD patients (Nugent et al., 2013; Peng et al. 2016) and SAD patients (Meng et al., 2013; Talati et al., 2013). Furthermore, a direct comparison between MDD and SAD also showed no differences in these regions. The OFC plays important roles in normal social functioning, affect modulation, reward learning and decision making (Kahnt et al., 2012). Therefore, inappropriate function of the OFC could lead to an array of behavioral deficits and psychopathology. The putamen, a part of the dorsal striatum, is implicated in motor and cognitive control, social learning and reward processing (Delgado, 2007). Both MDD patients and SAD patients are associated with serotonin transporter binding dysfunction in the putamen (Frick et al., 2015). The thalamus is an integral part of the emotion modulation, emotional salience and cognitive/executive networks (Yamamura et al., 2016). Indeed, volume reduction of thalamus may help account for the deficits in top-down regulation of negative emotions in individuals who are more prone to experiencing depressive symptoms (Webb et al., 2014). The OFC and thalamus play major roles in the integration of limbic and emotional information for translation into behavioral responses; the striatum and thalamus are required for motivated behaviors (Bonelli and Cummings, 2007). Our imaging data suggest that orbitofrontal-striatal-thalamic circuit dysfunction may be the pathophysiological mechanism for both MDD and SAD.

Furthermore, we unexpectedly detected increased cortical thicknesses of the ACC in both the MDD patients and SAD patients. Recent meta-analyses of structural brain changes have identified low ACC volume as a significant feature of MDD and SAD (Du et al., 2012; Shang et al., 2014; Goodkind et al., 2015), but discrepancies exist. Previous

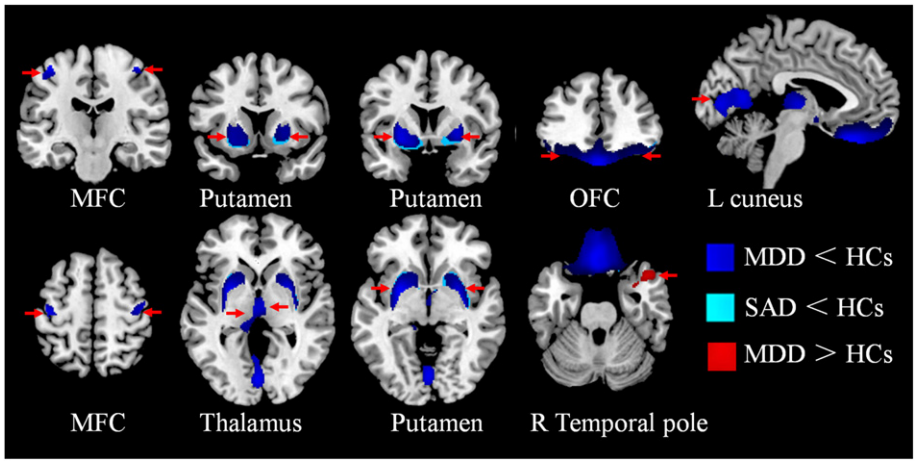

Fig. 1. Between-group results for the gray matter volume. All effects survived the false discovery rate (FDR) correction for multiple comparisons ($p < 0.001$) with a minimum cluster size of 100 voxels. Abbreviations: HCs, healthy controls; L, left; MDD, major depressive disorder; MFC, middle frontal cortex; OFC, orbital frontal cortex; SAD, social anxiety disorder.

studies have also reported increased ACC cortical thickness in MDD (van Eijndhoven et al., 2013) and SAD (Bruhl et al., 2014). The meaning of the greater cortical thickness of the neocortex remains unclear, but several potential explanations can be suggested. First, it is possible that a greater cortical thickness may reflect a compensatory mechanism that is related to inflammation or other aspects of the pathophysiology (Qiu et al., 2014). Second, greater ACC cortical thickness could be the result of both the continuous coping efforts and emotion regulation attempts of MDD and SAD patients (van Eijndhoven et al., 2013; Bruhl et al., 2014).

Compared with controls, both the MDD patients and SAD patients showed increased cortical thickness in the bilateral insular cortex and left temporal pole. The insula monitors internal states and has also been identified as an important structure in the pathophysiology of MDD and SAD (Bruhl et al., 2014; van Eijndhoven et al., 2016). GMV reductions of the insula have also been found in individuals with depression (Peng et al. 2016) and anxiety disorders (Moon and Jeong, 2017). The anterior insula and dorsal ACC have been reported to be common structural changes that occur across a wide variety of neuropsychiatric illnesses, including depression and anxiety (Goodkind et al., 2015). The temporal pole is critical for the evaluation of emotional states (Terasawa et al., 2013). The cortical thickness of the temporal pole has been reported to be positively correlated with the severity of SAD symptoms (Bruhl et al., 2014). The ACC, insular cortex and temporal pole are critical components of the salience network that functions to segregate the most relevant among internal and extrapersonal stimuli to guide behavior (Seeley et al., 2007). Thus, the observation of increased thickness in these regions may reflect an enhanced inability to control internal emotional states in MDD and SAD.

In MDD and SAD, we also observed increased cortical thickness in the bilateral posterior DLPFC and right superior parietal cortex compared with healthy controls. Our findings are partially convergent with prior reports that also describe increased cortical thickness in the DLPFC and superior parietal cortex in SAD patients (Bruhl et al., 2014). However, our observations of increased cortical thickness in the bilateral SFC and caudal MFC are less commonly reported for MDD patients, which might be explained by the fact that all of the enrolled MDD patients in the present study were medication-naïve and non-comorbid. The posterior DLPFC and superior parietal cortex are parts of the dorsal attention network, which is involved in attending to the external environment (Sylvester et al., 2012). Converging data have highlighted abnormal functional connectivities within the dorsal attention networks of MDD patients (Sacchet et al., 2016) and SAD patients (Liao et al., 2010). Taken together, our findings provide additional evidence for the involvement of the dorsal attention network in the pathophysiology of MDD and SAD.

4.2. Specific Gray Matter Alterations in MDD and SAD

Although MDD and SAD share most brain deficits, we also detected specific alterations to the gray matter in the MDD group relative to the control group mainly in regions of the visual recognition network (Tao et al., 2013), including the cuneus, lingual cortex, fusiform, and lateral occipital cortex. The visual recognition network is involved in emotional facial processing, which is crucial for social functioning. Depression has been associated with structural alterations in these regions, such as decreased cortical thickness in the lingual cortex (Tu et al., 2012), decreased GMV in the cuneus (Qiu et al., 2014), and increased surface area in the right lateral occipital cortex (Zorlu et al., 2017). A previous study has suggested that the function of the fusiform in memory processing may contribute to cognitive vulnerability in MDD patients (van Wingen et al., 2010). An altered structural topological organization within the region of the visual recognition network might be related to impaired selective attention and working memory in MDD (Desseilles et al., 2009). Thus, our results, together with previous findings of structural and functional alterations, strongly suggest the involvement of the visual processing region in the pathogenesis of MDD.

Compared with the HCs, a thinner cortical thickness in the right precentral cortex was evident in the SAD patients, and it was specific to the SAD patients. A prior meta-analysis of voxel-based morphometry studies has identified a reduced right precentral gyrus in anxiety patients without comorbid MDD (Shang et al., 2014). The precentral gyrus is involved in motor and somatosensory functions and the modulation of anticipatory threat and anxiety symptoms (Strawn et al., 2012). Patients with generalized anxiety disorder have clearly longer reaction times in the word-recognition tasks with neutral and anxiety-inducing words and show a negative correlation between the precentral gyrus volume and reaction time (Moon et al., 2017). Furthermore, neuroticism with exaggerated responses to anxiety has been reported to be associated with abnormal activation of the precentral gyrus (Drabant et al., 2011). Therefore, our finding of decreased cortical thickness in the precentral cortex provides additional evidence for the involvement of precentral cortex dysfunction in the pathophysiology of SAD.

4.3. Limitations

Several limitations should be considered before considering the results of this study. (1) None of the MDD patients were evaluated using the LSAS, and none of the SAD patients were evaluated using the HAMA and HAMD rating scales. The two patient groups were recruited for two different projects previously, which is why we were not able to evaluate all subjects using the same assessment scales. Our findings

Table 3
Regions of significant cortical thickness abnormalities among patients and healthy controls.

Region	Maximum vertex difference, −log10 (p value)	Size, mm^2	p value for CWP
Post-hoc (cortical thickness increase in MDD vs. SAD)			
Left superior frontal	7.353	218.52	0.0005
Right superior frontal	5.258	214.13	0.0005
Post-hoc (cortical thickness reduction in MDD vs. SAD)			
Left postcentral	−5.482	215.89	0.0002
Post-hoc (cortical thickness increase in MDD vs. HCs)			
Left temporal pole	23.007	3830.84	0.0001
Left anterior and posterior cingulate/superior frontal	21.451	6787.56	0.0001
Left insula	15.743	2029.58	0.0001
Left caudal middle frontal	11.906	703.53	0.0001
Left inferior temporal	6.741	393.58	0.0001
Right inferior temporal	30.812	984.94	0.0002
Right anterior and posterior cingulate/superior frontal	21.805	6599.11	0.0002
Right insula	19.971	2894.75	0.0002
Right superior parietal	10.689	486.91	0.0002
Right caudal middle frontal	10.32	632.35	0.0002
Right bank superior temporal	9.748	1183.56	0.0002
Right lateral occipital	5.074	251.45	0.0002
	4.914	271.19	0.0002
Post-hoc (cortical thickness reduction in MDD vs. HCs)			
Left lateral orbitofrontal	−11.21	236.46	0.0001
Left rostral middle frontal	−11.089	2055.74	0.0001
Left cuneus	−8.172	473.8	0.0001
Left lingual	−8.11	715.28	0.0001
Left pars orbitalis	−6.714	214.67	0.0002
Right rostral middle frontal	−9.278	880.36	0.0002
Right lingual	−8.847	777.32	0.0002
Post-hoc (cortical thickness increase in SAD vs. HCs)			
Left temporal pole	17.591	2716.13	0.0001
Left insula	15.057	1555.83	0.0001
Left anterior and posterior cingulate/superior frontal	14.978	3289.24	0.0001
Left superior frontal	13.078	711.18	0.0001
Left caudal middle frontal	9.28	490.23	0.0001
Right inferior temporal	24.633	757.28	0.0002
Right insula	16.495	1971.99	0.0002
Right anterior and posterior cingulate/superior frontal	15.515	3098.16	0.0002
Right superior frontal	14.562	750.8	0.0002
Right supramarginal	11.768	244.96	0.0002
Right caudal middle frontal	8.618	512.8	0.0002
Right superior parietal	6.765	308.93	0.0002
Post-hoc (cortical thickness reduction in SAD vs. HCs)			
Left rostral middle frontal	−8.706	316.54	0.0001
Left lateral orbitofrontal	−7.682	294.85	0.0001
Left rostral middle frontal	−6.999	398.28	0.0001
Right precentral	−9.605	373	0.0002
Right rostral middle frontal	−5.528	255.23	0.0002

All regions survived clusterwise-correction ($p < 0.001$). Abbreviations: CWP, clusterwise probability; HCs, healthy controls; MDD, major depressive disorder; SAD, social anxiety disorder.

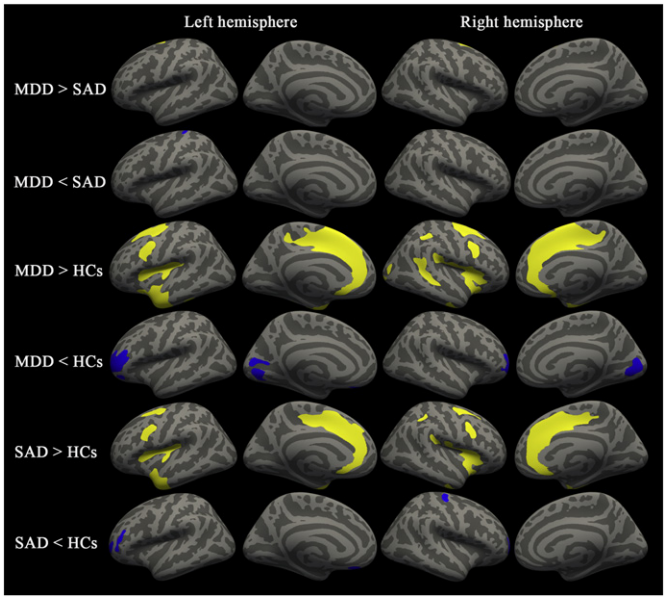

Fig. 2. Between-group results for cortical thickness analyses representing regions that survived the clusterwise correction ($p < 0.001$). Rows 1–2, MDD patients compared with SAD patients; Rows 3–4, MDD patients compared with the HCs group; Rows 5–6, SAD patients compared with the HCs group. Abbreviations: HCs, healthy controls; MDD, major depressive disorder; SAD, social anxiety disorder.

provide preliminary evidence of common and specific gray matter changes in MDD and SAD patients. Future studies will benefit from the use of assessment scales to quantify all participant anxiety and depression symptoms and their relationships to brain structure and functional changes. (2) The relatively small sample size might limit the interpretation of our results. Because anxiety and MDD frequently co-occur, it is difficult to gather large, non-comorbid cases. The results must be interpreted with caution. (3) The lack of an MDD/SAD co-morbid group limits a complete description and delineation of our categorical model for MDD and SAD. (4) The SAD patients were diagnosed using DSM-IV. However, we didn't restrict the patient LSAS scores when the patients were enrolled, causing the LSAS scores for the SAD group to be low compared with other SAD studies. Thus, the enrolled SAD patients may not be completely representative of the general population of SAD patients.

4.4. Conclusions and Future Directions

In conclusion, MDD patients manifested more widespread gray matter alterations than SAD patients. Our results indicated that MDD and SAD share a common pattern of gray matter abnormalities in the orbitofrontal-striatal-thalamic circuit (i.e., OFC, putamen, and thalamus), salience network (i.e., ACC and insula) and dorsal attention network (i.e., DLPFC and superior parietal cortex). These consistent structural differences in the two patient groups may contribute to the broad spectrum of emotional, cognitive and behavioral disturbances observed in MDD patients and SAD patients. In addition, we found disorder-specific involvement of the visual processing regions (i.e., cuneus, lingual cortex, fusiform, and lateral occipital cortex) in MDD and disorder-specific involvement of the precentral cortex in SAD. Future studies will benefit from the use of the same assessment scales to quantify all participant anxiety and depression symptoms and explore their relationships to brain structure and functional changes. Longitudinal studies and prospective studies should clarify the relationship between the GMV and cortical thickness changes and whether these structural abnormalities result from the disease process or represent a vulnerability factor for the development of anxiety and depression.

Conflicts of Interest

The authors declare no competing interests.

Author Contributions

S Lui and QY Gong developed the study design, provided methodological advice, and supervised the conduct of the study. YJ Zhao, W

Zhang, WH Kuang, Q Yue, ZY Jia, HR Zhu and ML Yuan collected the data. YJ Zhao, LZ Chen, and WJ Zhang performed the data analysis. YJ Zhao, Y Xiao and HQ Sun generated the figures and tables. Chandan Shah proofread the article. YJ Zhao and S Lui wrote the article, which all authors reviewed and approved for publication.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ebiom.2017.06.013.

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