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 charictarics 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 psycho-therapy 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.