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Research Paper

Common and Specific Abnormalities in Cortical Thickness in Patients with Major Depressive and Bipolar Disorders

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ABSTRACT

Major depressive disorder (MDD) and bipolar disorder (BD) are severe psychiatric diseases with overlapping symptomatology. Although previous studies reported abnormal brain structures in MDD or BD patients, the disorder-specific underlying neural mechanisms remain poorly understood. The purpose of this study was to investigate the whole-brain gray matter morphological patterns in unmedicated patients with MDD or BD and to identify the shared and disease-specific brain morphological alterations in these two disorders.

We acquired high-resolution brain structural MRI data from a sample of 36 MDD patients, 32 BD patients, and 30 healthy controls. Using FreeSurfer, we estimated their brain cortical thickness (CT) and compared between-group difference in multiple locations across the continuous cortical surface.

Compared to the healthy controls, both the MDD and BD patient groups showed significantly reduced CT in the left inferior temporal cortex (ITC). However, compared to the MDD patients, the BD patients showed a significantly thinner CT in the left rostral middle frontal region. In addition, compared to the healthy controls, the BD patients displayed thinner CT in the left ITC, left frontal pole (FPO), left superior frontal, right lateral occipital, right pars triangularis (PTRI) and right lateral orbitofrontal regions. Further analysis revealed a significantly positive correlation between the mean CT in the left FPO and the onset age, but a negative correlation between the mean CT in the right PTRI and the number of episodes, in the BD patients.

Our findings revealed that the BD and MDD patients had variations in CT that were in common, but many more that were distinct, suggesting potential differences in their neural mechanisms.

1. Introduction

Major depressive disorder (MDD) and bipolar disorder (BD) are two major types of mood disorder. Although mania or hypomania is a defining feature of BD patients, the presence of subthreshold manic symptoms can be observed in both disorders during a depressive episode (de Almeida & Phillips, 2013). This leads to difficulty in distinguishing BD from MDD patients as they have the same diagnostic criteria for a depressive episode (Phillips & Kupfer, 2013). Actually, misdiagnosing BD as MDD has many potentially deleterious consequences because treatment with antidepressants in the absence of a mood stabilizer carries the risk of precipitating mania and may increase rates of cycling between mood states (Baldessarini et al., 2010). In fact, whether MDD and BD have different neural mechanisms or share some in common remains ambiguous (de Almeida & Phillips, 2013; McGuffin et al., 2003). Neuroimaging studies have identified a number of differences between patients with depressive disorders and healthy controls in brain

Abbreviations: MDD, major depressive disorder; BD, bipolar disorder; BD-I, bipolar I disorder; BD-II, bipolar II disorder; HC, healthy controls; VBM, voxel-based morphometry; SBM, surface-based morphometry; GM, gray matter; WM, white matter; CSF, cerebrospinal fluid; CT, cortical thickness; HDRS, Hamilton Depression Rating Scale; YMRS, Young Mania Rating Scale; FWHM, full-width half-maximum; ANOVA, analysis of variance; GLM, general linear model; RA, relative alteration; ROI, region of interesting; rMFC, rostral middle frontal cortex; ITC, inferior temporal cortex; FPO, frontal pole; SFC, superior frontal cortex; LOC, lateral occipital cortex; PTRI, pars triangularis; lOFC, lateral orbitofrontal cortex; DLPFC, dorsolateral prefrontal cortex; PFC, prefrontal cortex; VPFC, ventral prefrontal cortex; fNIRS, functional near-infrared spectroscopy; SSRI, selective serotonin reuptake inhibitor.

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structure and function. Until now, it is still unclear to what extent specific or common morphological alterations occur in MDD and BD given the paucity of direct comparisons.

Based on brain structural images, brain morphologic characteristics have been studied in various brain diseases (de Vos et al., 2016; van Lutterveld et al., 2014). Using the voxel-based morphometry (VBM) method, some studies detected altered brain GM volume or density in patients with MDD or BD (Redlich et al., 2014) and found between-group difference in GM volume primarily in the prefrontal cortex (PFC), anterior cingulate gyrus (ACG), amygdala, and hippocampus (Redlich et al., 2014; Koutsouleris et al., 2015). Actually, the VBM method is susceptible to several potential confounds, including the accuracy of the brain segmentation, degree of smoothing, strategies used in registration, and the choice of a normalization template (Bookstein, 2001). Especially, VBM analysis is a method of measuring MRI signal alteration in brain tissue rather than a directly technique to detect brain structural alteration about the volume size of a region, CT and cortical surface area (Bookstein, 2001). CT analysis is similar to VBM, albeit the analysis is performed at the nodes of a 3D polygonal mesh rather than on a 3D voxel grid. And the CT analysis has the advantage of providing a direct quantitative index (in unit of mm), rather than qualitative index, of cortical morphology. Therefore, the measurement of CT alteration has been suggested as a way to obtain a complementary indication of alterations in brain GM morphology (Ecker et al., 2013).

For depressive disorders, previous studies focused primarily on CT alteration in just one of the depressive disorders, comparing the patients with healthy controls (Redlich et al., 2014; Maller et al., 2014), but ignoring the abnormal CT between the two disorders. Several studies of BD patients reported subtle but widespread CT abnormalities and showed decreased CT in the left anterior cingulate/paracingulate, left superior temporal gyrus and prefrontal regions (Rimol et al., 2010, 2012; Hanford et al., 2016). And several studies of MDD patients reported reduced CT in the medial orbitofrontal gyrus and pars opercularis (van Eijndhoven et al., 2013; Tu et al., 2012), and a study reported increased CT in similar regions (Qiu et al., 2014). By now, very few studies have directly compared the difference in brain CT between MDD and BD patients (Lan et al., 2014; Fung et al., 2015), and those that did obtained partially inconsistent results. For example, Lan et al. (2014) investigated the difference in CT between 18 BD patients and 56 MDD patients and reported thinner CT in the right caudal middle frontal cortex, left inferior parietal cortex, and right precuneus in a mixed group of BD-I and BD-II patients. However, Fung et al. (2015) failed to find any brain regions with differences in CT between MDD and BD patients. Notably, in these two studies, the analyses were performed on patients who were taking medications, which may have influenced the results.

The CT analysis may be affected by several factors, such as sample sizes, medication status (Lanzenberger et al., 2012; Foland-Ross et al., 2011), or heterogeneity in the patient samples. Most studies published to date have included patients who were taking medications. Although the effects of medication on brain morphology are not yet fully understood, several studies have indicated that the use of psychotropic medications, such as lithium, may cause an increase in GM volume in the cortical and subcortical regions (Foland-Ross et al., 2011; Brooks et al., 2009). Lanzenberger et al. (2012) and Benmansour et al. (1999) reported that the alteration of brain structure may be resulted from the use of selective serotonin reuptake inhibitors (SSRI). The heterogeneity of patient samples included the age of the participants, their mood states at the time of scanning, and mixing the types of BD patients. As for BD patient, BD-II might have a genetic etiology distinguishable from BD-I (Huang et al., 2010). BD-II is especially difficult to diagnose accurately because of the difficulty in differentiating this disorder from recurrent MDD (recurrent depressive episodes) in depressed patients (Phillips & Kupfer, 2013). Unfortunately, no study has yet directly compared differences in CT between MDD patients and BD-II, although a few studies compared brain CT in combined samples of BD-I, BD-II and BD not otherwise specified (BD-NOS) patients with MDD patients (de Almeida & Phillips, 2013; Lan et al., 2014).

In this study, our goal was to detect alteration of CT in the unmedicated adult MDD and BD-II patients who were in a depressive episode, and compare to the healthy controls to assess morphometric differences and similarities that may reflect common and/or distinct brain regions in affective disorders. Considering the similarities and differences in the clinical symptoms and brain alterations revealed in previous studies (de Almeida & Phillips, 2013; Lan et al., 2014), we hypothesized that depressive episode unmedicated adult MDD and BD-II patients would not only have CT abnormalities that they shared in common but also abnormalities in CT that are specific to each disease. Considering the similarities and differences in clinical symptoms and brain alterations revealed in previous studies (de Almeida & Phillips, 2013; Lan et al., 2014), we hypothesized that the depressive unmedicated adult MDD and BD-II patients would not only have CT abnormalities that they shared in common but also abnormalities in CT that are specific to each disorder. And these abnormal regions would likely be the key brain structures involving in depression symptoms, such as the limbic and prefrontal regions. In addition, as BD is considered to have more complexity and severity than MDD, we supposed that the BD patients had more widespread CT abnormalities than the MDD patients.

2. Methods and Materials

2.1. Subjects

A total of 68 currently unmedicated depressed patients and 30 healthy controls were recruited from the Psychiatry Department of the First Affiliated Hospital of Jinan University (FAHJU), Guangzhou, China, during July 2013–August 2015. All the subjects were determined to have no abnormalities on conventional MRI by two experienced radiologists (Y.W. and Y.S.) and were right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971). The three groups of subjects, MDD (17M/19F, aged 18–43 years old), BD (15M/17F, aged 18–50 years old), healthy controls (17M/13F, aged 19–44 years old), were matched on age and gender. The study was approved by the Institute Review Board of the First Affiliated Hospital of Jinan University, China. Each subject signed a written informed consent form after a full written and verbal explanation of the study. Table 1 lists the detailed demographics for all the subjects in this study.

The MDD and BD patients were diagnosed according to the DSM-IV criteria and the Structured Clinical Interview for DSM-IV Axis I Disorders-Patient Edition (SCID-I/P) (Steinberg, 1994). All patients fulfilled the criteria for either MDD or BD. Diagnosis of patients was determined by two experienced clinical psychiatrists (Y.J. and S.Z., with 20 and 5 years of experience in clinical psychiatry, respectively). Current depressive symptoms were assessed by using the 24-item Hamilton Depression Rating Scale (HDRS) (Williams, 1988) and current manic symptoms were assessed by the Young Mania Rating Scale (YMRS) (Young et al., 1978) during the 7-day period before the imaging session. All patients with BD or MDD were diagnosed with depression (a YMRS score < 7 and a total HDRS score > 21). The exclusion criteria for the patients were other Axis-I psychiatric disorders, a history of organic brain disorder or neurological disorders, mental retardation, cardiovascular diseases, pregnancy, or any physical illness. None of the subjects had lifetime substance use disorders, including alcohol abuse, marijuana use, and cocaine abuse. None of the patients had ever received electroconvulsive therapy prior to participating in this study. The exclusion criteria for the healthy controls were same to the patients, in addition to any history of psychiatric illness in first-degree relatives and current or past significant medical or neurological illness. At the time of the scanning, 37 patients (18 BD and 19 MDD) were medication-naïve; they had never been diagnosed or did not want to take medication. While for the others, the recruited patients generally visited their physicians (psychiatrist/general practitioner) because of depressive relapse

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