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·Original Article·

Grey matter volume abnormalities in patients with bipolar I depressive disorder and unipolar depressive disorder: a voxel-based morphometry study

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ABSTRACT

Bipolar disorder and unipolar depressive disorder (UD) may be different in brain structure. In the present study, we performed voxel-based morphometry (VBM) to quantify the grey matter volumes in 23 patients with bipolar I depressive disorder (BP1) and 23 patients with UD, and 23 age-, gender-, and education-matched healthy controls (HCs) using magnetic resonance imaging. We found that compared with the HC and UD groups, the BP1 group showed reduced grey matter volumes in the right inferior frontal gyrus and middle cingulate gyrus, while the UD group showed reduced volume in the right inferior frontal gyrus compared to HCs. In addition, correlation analyses revealed that the grey matter volumes of these regions were negatively correlated with the Hamilton depression rating scores. Taken together, the results of our study suggest that decreased grey matter volume of the right inferior frontal gyrus is a common abnormality in BP1 and UD, and decreased grey matter volume in the right middle cingulate gyrus may be specific to BP1.

Keywords: bipolar depressive disorder; unipolar depressive disorder; prefrontal cortex; cingulate gyrus; voxel-based morphometry

INTRODUCTION

Bipolar disorder (BP) is characterized by alternating episodes of mania and depression[1] and causes dysfunctions in cognition and emotion[2-4]. BP is a chronic, life-threatening illness affecting over 2% of the general population[5]. A World Health Organization report identified BP as one of ten disorders that most often result in permanent disabilities[6] and it has serious implications for morbidity and mortality[7]. In addition, patients suffering from BP are at high risk of drug abuse and suicide. Therefore, appropriate and timely diagnosis is critical in clinical practice. However, it is difficult for clinicians to diagnose BP. Wolkenstein *et al.*[6] reported that 60% of therapists do not correctly diagnose BP, only 20% of BP patients during a

depressive episode are correctly diagnosed within the first year of seeking treatment[8], and from onset to diagnosis the appropriate treatment averages 5 to 10 years[9, 10]. Nearly 60% of BP patients are misdiagnosed as unipolar depressive disorder (UD)[8]. UD is characterized only by episodes of depression, and its lifetime prevalence ranges from 10% to 30%[11]. Misdiagnosis of BP as UD can lead to inadequate treatment and devastating consequences[12]. Identifying objective biomarkers such as functional and structural brain abnormalities of BP may be helpful for its correct diagnosis.

Both BP and UD belong to the mood disorders. One prevalent hypothesis[13, 14] on the pathophysiology of mood disorders is a loss of top-down control over limbic structures, such as the amygdala, hippocampus, and thalamus[15-18], and cortical regions-of-interest (ROIs) include the inferior frontal gyrus, superior/middle frontal gyrus, and cingulate gyrus[2, 19]. Magnetic resonance imaging (MRI) is a noninvasive clinical tool to detect aberrant brain structures and functions, and has been used to reveal structural abnormalities in patients with BP and UD, albeit with heterogeneous and often conflicting results[20-22]. Arnone *et al*.[20] reported that UD is characterized by reduced brain volume in areas involved in emotional processing, including the frontal cortex, orbitofrontal cortex, cingulate cortex, hippocampus, and striatum. A meta-analysis[23] of studies in UD showed grey matter reductions in the rostral anterior cingulate cortex (ACC) and dorsolateral and dorsomedial prefrontal cortex. Studies in BP have increased in number in recent years, but the results remain contradictory[24]. Two meta-analyses of studies in BP revealed grey matter reductions in the ACC[25], and one meta-analysis reported grey matter reductions in the bilateral frontal cortices, cingulate gyrus, and left middle temporal gyrus, and increases in the basal ganglia[26].

ROI-based method was based on the anatomic knowledge and conventional MRI, by stepwise decreasing the regions of interest. It has potential biases. A number of studies have reported structural abnormalities and dysfunctions in depression. With ROI-based analysis, Liu *et al*.[27] reported that the right parahippocampal gyrus showed an abnormality specific to the BP group, while the right middle frontal gyrus, the right dorsal anterior insula, and the right posterior cingulate cortex showed abnormalities specific to the UD group. Another ROI-based analysis[28] reported that fractional anisotropy of the middle-anterior and middle-posterior cingulum bundle was associated with executive functioning and divided attention in patients with major depression. Voxel-based morphometry (VBM) allows automated voxel-by-voxel examination and avoids potential biases that may occur in ROI-based methods[29]. VBM has been shown to be useful for identifying structural changes associated with various disorders[30, 31]. Previous studies have reported that decreased grey matter volume overlaps in patients with BP[17, 32-34] and UD[35, 36]. While patients with BP and UD express different clinical symptoms, we hypothesized that the grey matter volumes would show altered and differential patterns in patients with BP and UD compared to healthy controls (HCs). To date, the majority of neuroimaging studies assessing patients with BP and UD have used ROI-based methods and compared their findings against those obtained in HCs, but few have examined possible differences in grey matter volumes between BP and UD groups directly using VBM.

The present study aimed to examine and compare the whole-brain grey matter volumes obtained with VBM among patients with bipolar I depressive disorder (BP1) or UD and HCs and to identify common and unique changes in grey matter volumes in patients with BP1 and those with UD. We also examined possible correlations of structural abnormalities with clinical characteristics to clarify their pathological mechanisms.

PARTICIPANTS AND METHODS

Participants

A total of 46 patients diagnosed with BP1 or UD (23 each) were enrolled in the study along with 23 HCs. All patients were recruited from the outpatient and inpatient units of the Department of Psychiatry at the Second Xiangya Hospital of Central South University, Changsha, China, between April 2010 and May 2011. HCs were recruited from the Health Examination Centre of the Second Xiangya Hospital during the same period. The three groups were matched for age, gender, and education. All were right-handed, aged between 18 and 45 years, and had completed >9 years of education. All patients underwent structured clinical interviews by two independent psychiatrists according to the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV)[37] and met the DSM-IV criteria for BP1 or UD.

Patients with UD who had experienced more than three depression episodes and had no family history of BP were considered for this study. Patients with any of the following were excluded: (1) head injury; (2) mental retardation; (3) neurological disorders; (4) history of alcohol, drug abuse, or smoking; (5) failure to meet screening criteria for MRI scan, including heart pacemaker or metal implants, claustrophobia, and pregnancy or breastfeeding; (6) Hamilton anxiety rating scale (HAMA)[38] score >14; (7) Bech-Rafaelsen mania scale (BRMS)[39] score >5; and (8) personal or family history of psychiatric disorders.

The study protocol was reviewed and approved by the Ethics Committee of the Second Xiangya Hospital. All participants were informed of the potential risks and benefits associated with study participation, and gave written informed consent.

Clinical Assessments

The following clinical criteria were used for psychometric assessment: the 17-item Hamilton depression rating scale (17-HAMD)[40], HAMA score, and BRMS. A score >17 on the HAMD scale, >14 on the HAMA scale, or >5 on the BRMS was considered as an episode of depression, anxiety, or hypomania respectively. Psychometric parameter assessment and demographic detail recording were carried out by two psychiatrists on the same day as MRI scanning.

Structural MRI

MRI examinations were conducted using a Philips Gyroscan Achieva 3.0 Tesla MRI Scanner (Philips, Best, The Netherlands) equipped with a SENSE-8 channel head coil. For each patient and HC, high-resolution T1-weighted anatomical images were obtained using a 3-dimensional rapid acquisition gradient echo sequence with the following parameters: repetition time = 7.5 ms, echo time = 3.7 ms, flip angle = 8°; field of view = 256 mm × 256 mm, slice number = 180, and voxel size = 1× 1 × 1 mm^3.

VBM Analysis

Data were analyzed using the default parameters of the SPM8 (Wellcome Department of Cognitive Neurology, London, UK) and the VBM8 toolbox (version 435; http://dbm.neuro.uni-jena.de/vbm8/) in the Matlab 7.8.0 environment (R2009b; Math Works, Natick, MA). Individual structural images were preprocessed with the VBM8 toolbox using the default parameters. T1-weighted images were corrected for bias-field inhomogeneities, spatially normalized to the Montreal Neurological Institute standard template space, and segmented into grey matter, white matter, and cerebrospinal fluid using the segmentation algorithm in SPM8[41], within a unified model including high-dimensional DARTEL normalization. Grey matter segments were modulated by the non-linear components only, which allows comparing the absolute amount of tissue corrected for individual brain size. The voxel resolution after normalization was 1.5 mm × 1.5 mm × 1.5 mm. The homogeneity of grey matter images was verified using the check data quality function. The resulting modulated and warped images were then smoothed with an isotropic Gaussian kernel of 8-mm full-width at half-maximum.

The grey matter volumes for clusters showing significant differences in *post-hoc* tests were obtained from each participant using self-developed software[42]. The level of two-tailed statistical significance was set at P <0.05 for all tests.

Statistical Analysis

All statistical analyses were performed with SPSS version 16.0 (SPSS Inc., Chicago, IL). One-way analysis of variance (ANOVA) with least significant difference (LSD) *post-hoc* tests were used to compare demographic and clinical data and the χ^2 test was used for gender comparisons. In addition, grey matter volumes in the three groups were compared using analysis of covariance (ANCOVA); the covariates in the statistical design for imaging data included grey matter volume, and LSD *post-hoc* tests were used to further investigate differences in grey matter volume as a significant main effect of group. Clusters >100 that survived an uncorrected threshold of P < 0.001 were considered significant. To evaluate whether clinical features were associated with brain regions that showed between-group differences in the voxel-wise statistics, correlation analyses between clinical features and brain regions were performed for all patients.

RESULTS

Demographic and Clinical Characteristics

The demographic and clinical characteristics of all three groups are shown in Table 1. There were no significant differences in age, gender, educational level, or BRMS

Table 1. Demographic and clinical characteristics of BP1, UD, and HC groups (mean ± SD)

Variables	BP1 (*n* = 23)	UD (*n* = 23)	HCs (*n* = 23)	F/x^2/*t*	*P*
Age (years)	25.65 ± 6.589	30.00 ± 7.293	28.2 ± 3.781	2.98	0.058
Gender (male/female)	16/7	13/10	13/10	1.095	0.578
Education (years)	10.91 ± 2.172	11.30 ± 2.835	11.78 ± 1.38	0.892	0.415
BRMS score	1.52 ± 0.593	1.43 ± 0.507	1.17 ± 0.984	1.434	0.246
HAMD score	28.52 ± 9.342	29.7 ± 6.197 [a]	6.04 ± 2.9	91.443	<0.001
HAMA score	8.26 ± 3.165	9.22 ± 1.704 [a]	3.87 ± 1.74	35.178	<0.001
Illness duration (years)	6.09 ± 3.667	4.35 ± 2.382	N/A	1.924	0.061
Age at onset (years)	19.7 ± 4.912	25.7 ± 6.825	N/A	−3.422	0.001
Taking lithium (Y/N)	6/17	N/A	N/A	N/A	N/A
Lithium dose (g)	0.542 ± 0.102	N/A	N/A	N/A	N/A
Taking citalopram (Y/N)	6/17	5/18	N/A	0.119	0.73
Citalopram dose (mg)	9.17 ± 3.76	10 ± 5	N/A	−0.316	0.759

[a]*Post-hoc t* tests ANOVA for comparison between BP1 and UD groups. BP1, bipolar I depressive disorder; BRMS, Bech-Rafaelsen mania scale; HAMA, Hamilton anxiety rating scale; HAMD, Hamilton depression rating scale; HCs, healthy controls; UD; unipolar depressive disorder.

scores among all three groups. As expected, we found increased HAMD and HAMA scores in the BP1 and UD groups compared to HCs (P <0.001). There were no significant differences in illness duration, HAMD, or HAMA scores between the BP1 and UD groups. The onset age of BP1 was younger than that of UD (P = 0.001).

Neuroimaging Studies

The volumes of the right inferior frontal gyrus (F = 9.95, P_{uncorr} <0.001) and right middle cingulate gyrus (F = 11.7, P_{uncorr} <0.001) were significantly different among the three groups. Cortical volumes in the right inferior frontal gyrus (Fig. 1A, Table 2) and the right middle cingulate gyrus (Fig. 1B, Table 2) were reduced in BP1 patients compared to the HCs. Besides, a reduction of cortical volume in the right inferior frontal gyrus (Fig. 1C, Table 2) was observed in UD patients compared to the HCs. In addition, compared to the UD patients, a significant reduction of cortical volume was found in the right middle cingulate gyrus (Fig. 1D, Table 2) in BP1 patients. We did not identify any regions with increased grey matter volume in the BP1 group relative to HCs, the UD group relative to HCs, or the BP1 group relative to the UD group. The grey matter volumes for each cluster are provided in Table 2.

Correlations

We performed Pearson correlation analyses for clinical characteristics and grey matter volumes in the right middle cingulate gyrus and the right inferior frontal gyrus in the BP1 and UD groups. We found that the grey matter volume in the right middle cingulate gyrus of BP1 patients was negatively correlated with HAMD score (r = –0.670, U = 21, P <0.001, Fig. 2A), and the grey matter volume in the right inferior frontal gyrus of UD patients was negatively correlated with HAMD score (r = –0.611, U = 21, P = 0.002, Fig. 2B). It should be noted that there was no correlation between the grey matter volume of this area and age, educational level, or illness duration.

DISCUSSION

To the best of our knowledge, this is the first study to examine and compare whole-brain volumetric differences among BP1, UD, and HC groups using VBM. The results showed significant differences in three main aspects. First, there was an evident reduction of the grey matter volume in the right inferior frontal gyrus in the BP1 and UD groups compared to HCs. Second, there was an evident reduction of the grey matter volume in the right middle cingulate gyrus

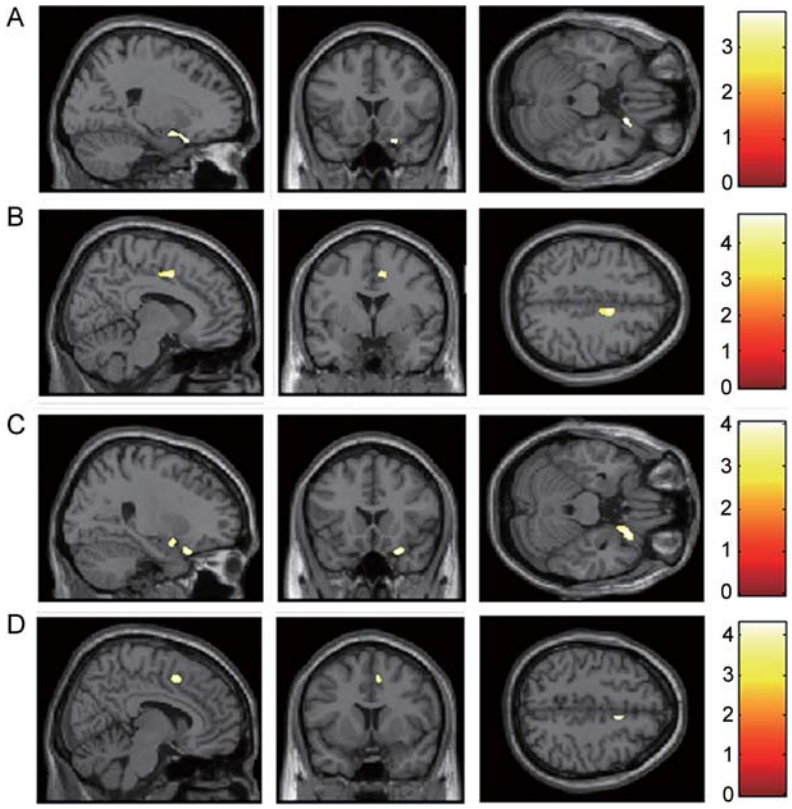

Fig. 1. Significant volumetric differences were found among the three groups (on sagittal, coronal, and axial planes). Patients with BP1 exhibited reduced volumes in the right inferior frontal gyrus (A) and right middle cingulate gyrus (B) compared to HCs, patients with UD had a reduced volume in the right inferior frontal gyrus (C) compared to HCs, and patients with BP1 exhibited a reduced right middle cingulate gyrus (D) volume compared to patients with UD (*P* <0.001 uncorrected, voxels >100).

Table 2. ANCOVA comparison of grey matter volumes among BP1, UD, and healthy control subjects

Brain regions	BA	Cluster size	Z-score	P_{uncorr}	MNI coordinate		
					x	y	z
Main effect of group							
Rt middle cingulate gyrus	24	243	3.9	<0.001	10	0	45
Rt inferior frontal gyrus	47	207	3.57	<0.001	24	18	–24
BP1<HCs							
Rt inferior frontal gyrus	47	596	3.57	<0.001	22	17	–23
Rt middle cingulate gyrus	24	520	4.4	<0.001	10	0	45
UD<HCs							
Rt inferior frontal gyrus	47	1330	3.8	<0.001	26	19	–24
BP1<UD							
Rt middle cingulate gyrus	24	198	4.03	<0.001	8	9	48

BA, Brodmann areas; BP1, bipolar I depressive disorder; HCs, healthy controls; MNI, Montreal Neurological Institute; Rt, right; UD, unipolar depressive disorder.

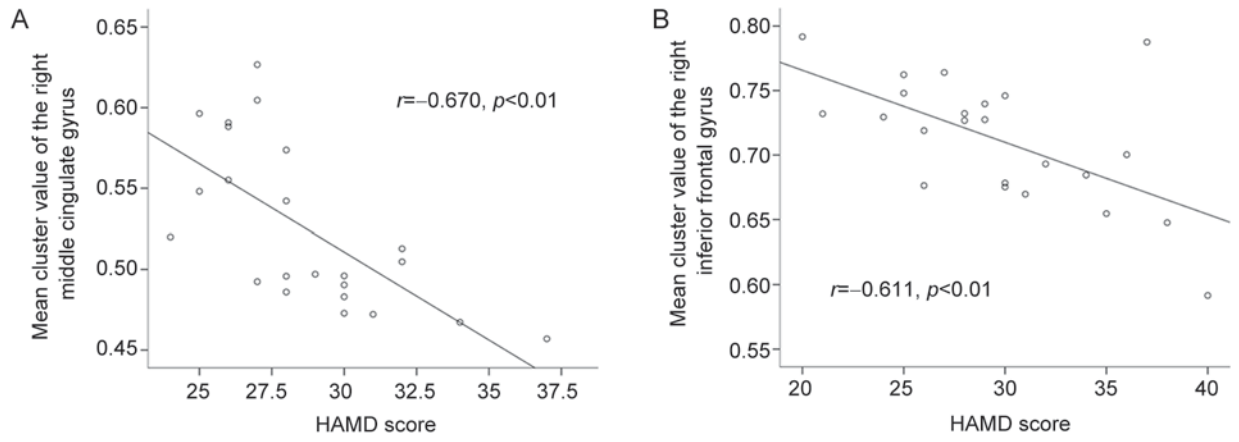

Fig. 2. Scatter plots showing negative correlations between grey matter volume in the right middle cingulate gyrus and HAMD scores in patients with BP1 (A) (*n* = 23), and between grey matter volume in the right inferior frontal gyrus and HAMD scores in patients with UD (B) (*n* = 23).

in patients with BP1 compared to the UD and HC groups. No grey matter volume abnormalities were detected in the cingulate gyrus in patients with UD compared to HCs. Finally, we found that the grey matter volume in the right middle cingulate gyrus of patients with BP1 was negatively correlated with the HAMD score, and the grey matter volume in the right inferior frontal gyrus of patients with UD was negatively correlated with the HAMD score. Along with the common and distinct changes in grey matter volume between the BP1 and UD groups, we found that patients with BP1 had a younger onset age than patients with UD. This result is consistent with a previous report[43].

It is interesting that the significant changes occurred in the right hemisphere. This is consistent with the known cortical asymmetry in BP[44]. Similarly, right hemisphere hyperactivity has been reported in depression[45]. Although we did not further assess this result, it is an interesting topic to explore in future studies.

The highest regional grey matter volume loss occurred in the inferior frontal gyrus. The inferior frontal gyrus (Brodmann area 47) belongs to the ventral lateral prefrontal cortex[44], an area critical in the integration of emotional information and the regulation of emotional intensity[45]. Our finding of a grey matter volume decrease in the right inferior frontal gyrus in the BP1 and UD groups relative to HCs is consistent with the results of previous brain imaging studies[12, 32, 46, 47]. For instance, Lyoo *et al.*[32] reported decreased grey matter density in the right inferior frontal gyrus in patients with BP1 compared with HCs, and Lopez-Larson *et al.*[46] also reported a reduction in the right inferior frontal gyrus volume in patients with BP. Two meta-analyses of functional neuroimaging studies and structural voxel-based MRI studies in adult patients with BP1 yielded similar results, showing lower neural activation and decreased grey matter in the inferior frontal gyrus in patients with BP1[12]. In addition, functional neuroimaging and magnetic resonance spectroscopy investigations in patients with BP suggested the existence of functional and biochemical abnormalities in the inferior frontal gyrus[48]. Meanwhile, a meta-analysis[23] reported grey matter reduction in the right inferior frontal cortex in patients with UD compared with HCs. The present results support the fact that the reduction of grey matter volume in the right inferior frontal gyrus is a common pathophysiology of patients with BP1 and UD. Grey matter volume reduction in the right inferior frontal cortex may be associated with depressive episodes.

Another striking finding in our study was that patients with BP1 also showed decreased grey matter volume in the right middle cingulate gyrus compared with the UD and HC groups. The cingulate gyrus plays a major role in the neurophysiological basis of complex emotional behaviors, and it is considered to be a part of a putative circuit involved in emotional expression and cognitive functions in humans[49-51]. The study finding of decreased grey matter volume in the right middle cingulate gyrus in BP1 is consistent with previous reports[25, 52-54]. Bora *et al.*[25]

reported grey matter reductions in the anterior cingulate gyrus in patients with BP1 in a meta-analysis of grey matter abnormalities, and Ellison-Wright and Bellmore[24] also reported a reduction in the cingulate gyrus volume in patients with BP1. Bearden *et al.*[55] found that reduced grey matter density in the cingulate gyrus was rescued in lithium-treated patients with BP1. In addition, a deficit in γ-amino-butyric acid, a major inhibitory neurotransmitter, was reported in the cingulate gyrus of patients with BP1[53]. Grey matter volume reduction in the right middle cingulate gyrus may be associated with bipolar disorder. In addition to the right inferior frontal gyrus, the right middle cingulate gyrus may be another key brain region implicated in BP1 pathophysiology. Our study did not find cingulate gyrus grey matter reductions in UD compared with BD and HCs, which is consistent with the results of Frodl *et al.*[56] but inconsistent with the findings of Bora *et al.*[23] and Lai[57]. This discrepancy may be associated with research methods and the heterogeneity of samples.

On the other hand, it should be noted that there were no differences in the grey matter volumes of the amygdala and hippocampus in the BP1 and UD groups relative to HCs. This could be attributed to the homogeneity of the study samples. Bora *et al.*[25] reported that grey matter volume in the amygdala was reduced in patients with UD who had co-morbid anxiety disorders and also in first-episode/drug-free subjects, while in the present study of BP1 and UD groups with HAMA scores <14, there was no significant difference between the two groups. Our result is consistent with a previous report of no significant grey matter volume loss in the hippocampus or amygdala in patients with depression[47]. Reduced grey matter volume in the hippocampus has been revealed in patients with Alzheimer's disease[58] but rarely in mood disorders. Our results suggest that the amygdala and hippocampus may not be key brain regions associated with UD or BP1.

Our findings suggest that reduced grey matter volume in the right inferior frontal gyrus is a common pathophysiological alteration in BP1 and UD, while decreased grey matter volume in the right middle cingulate gyrus is a distinctive change in patients with BP1. Therefore, the abnormal grey matter volume of the right middle cingulate gyrus may be an important neuroimaging marker of BP1, which may enable clinicians to distinguish BP1 from UD. Further work is required to understand the significance of these volumetric changes, including prospective studies and studies that integrate fMRI and DTI data.

The present study had a number of limitations. First, some patients had taken antidepressant medications and/or mood stabilizers, although the impact of medication intake on brain structures remains unclear. Sassi *et al.*[53] reported that lithium treatment might increase cingulate gyrus volume in patients with BP, so lithium treatment could have affected our findings. Second, the sample heterogeneity and variations in illness duration, number of episodes, and age at scanning might have influenced the results to some extent. Further studies with larger sample sizes are needed to verify our results and explore the pathophysiological mechanisms underlying BP1 and UD.

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