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 mm³.

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 $\pm$ SD)

Variables	BP1 (<i>n</i> = 23)	UD (<i>n</i> = 23)	HCS (<i>n</i> = 23)	<i>F</i> / χ^2 / <i>t</i>	<i>P</i>
Age (years)	25.65 $\pm$ 6.589	30.00 $\pm$ 7.293	28.2 $\pm$ 3.781	2.98	0.058
Gender (male/female)	16/7	13/10	13/10	1.095	0.578
Education (years)	10.91 $\pm$ 2.172	11.30 $\pm$ 2.835	11.78 $\pm$ 1.38	0.892	0.415
BRMS score	1.52 $\pm$ 0.593	1.43 $\pm$ 0.507	1.17 $\pm$ 0.984	1.434	0.246
HAMD score	28.52 $\pm$ 9.342	29.7 $\pm$ 6.197 ^a	6.04 $\pm$ 2.9	91.443	<0.001
HAMA score	8.26 $\pm$ 3.165	9.22 $\pm$ 1.704 ^a	3.87 $\pm$ 1.74	35.178	<0.001
Illness duration (years)	6.09 $\pm$ 3.667	4.35 $\pm$ 2.382	N/A	1.924	0.061
Age at onset (years)	19.7 $\pm$ 4.912	25.7 $\pm$ 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 $\pm$ 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 $\pm$ 3.76	10 $\pm$ 5	N/A	-0.316	0.759

^aPost-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 ($F = 9.95$, $P_{\text{uncorr}} < 0.001$) and right middle cingulate gyrus ($F = 11.7$, $P_{\text{uncorr}} < 0.001$) 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.

ACKNOWLEDGEMENTS

This work was supported by grants from the National Natural Science Foundation of China (81171286 and 91232714), and National Basic Research Development Program (973 program) of China (2013CB835100 and 2009CB918303).

Received date: 2014-05-11; Accepted date: 2014-09-14

REFERENCES

- [1] Singh MK, Chang KD, Chen MC, Kelley RG, Garrett A, Mitsunaga MM, *et al.* Volumetric reductions in the subgenual anterior cingulate cortex in adolescents with bipolar I disorder. *Bipolar Disord* 2012, 14: 585–596.
- [2] Phillips ML, Ladouceur CD, Drevets WC. A neural model of voluntary and automatic emotion regulation: implications for understanding the pathophysiology and neurodevelopment of bipolar disorder. *Mol Psychiatry* 2008, 13: 829, 833–857.
- [3] Robinson LJ, Ferrier IN. Evolution of cognitive impairment in bipolar disorder: a systematic review of cross-sectional evidence. *Bipolar Disord* 2006, 8: 103–116.
- [4] Malhi GS, Ivanovski B, Hadzi-Pavlovic D, Mitchell PB, Vieta E, Sachdev P. Neuropsychological deficits and functional impairment in bipolar depression, hypomania and euthymia. *Bipolar Disord* 2007, 9: 114–125.
- [5] Merikangas KR, Akiskal HS, Angst J, Greenberg PE, Hirschfeld RM, Petukhova M, *et al.* Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. *Arch Gen Psychiatry* 2007, 64: 543–552.

- [6] Wolkenstein L, Bruchmuller K, Schmid P, Meyer TD. Misdiagnosing bipolar disorder--do clinicians show heuristic biases? *J Affect Disord* 2011, 130: 405–412.
- [7] Pini S, de Queiroz V, Pagnin D, Pezawas L, Angst J, Cassano GB, *et al.* Prevalence and burden of bipolar disorders in European countries. *Eur Neuropsychopharmacol* 2005, 15: 425–434.
- [8] Hirschfeld RM, Lewis L, Vornik LA. Perceptions and impact of bipolar disorder: how far have we really come? Results of the national depressive and manic-depressive association 2000 survey of individuals with bipolar disorder. *J Clin Psychiatry* 2003, 64: 161–174.
- [9] Baethge C, Tondo L, Bratti IM, Bschor T, Bauer M, Viguera AC, *et al.* Prophylaxis latency and outcome in bipolar disorders. *Can J Psychiatry* 2003, 48: 449–457.
- [10] Baldessarini RJ, Tondo L, Baethge CJ, Lepri B, Bratti IM. Effects of treatment latency on response to maintenance treatment in manic-depressive disorders. *Bipolar Disord* 2007, 9: 386–393.
- [11] Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR, *et al.* The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *JAMA* 2003, 289: 3095–3105.
- [12] Houenou J, Frommberger J, Carde S, Glasbrenner M, Diener C, Leboyer M, *et al.* Neuroimaging-based markers of bipolar disorder: evidence from two meta-analyses. *J Affect Disord* 2011, 132: 344–355.
- [13] Phillips ML, Drevets WC, Rauch SL, Lane R. Neurobiology of emotion perception II: Implications for major psychiatric disorders. *Biol Psychiatry* 2003, 54: 515–528.
- [14] Savitz J, Drevets WC. Bipolar and major depressive disorder: neuroimaging the developmental-degenerative divide. *Neurosci Biobehav Rev* 2009, 33: 699–771.
- [15] Strakowski SM, Delbello MP, Adler CM. The functional neuroanatomy of bipolar disorder: a review of neuroimaging findings. *Mol Psychiatry* 2005, 10: 105–116.
- [16] Adler CM, DelBello MP, Jarvis K, Levine A, Adams J, Strakowski SM. Voxel-based study of structural changes in first-episode patients with bipolar disorder. *Biol Psychiatry* 2007, 61: 776–781.
- [17] Nugent AC, Milham MP, Bain EE, Mah L, Cannon DM, Marrett S, *et al.* Cortical abnormalities in bipolar disorder investigated with MRI and voxel-based morphometry. *Neuroimage* 2006, 30: 485–497.
- [18] Fornito A, Malhi GS, Lagopoulos J, Ivanovski B, Wood SJ, Saling MM, *et al.* Anatomical abnormalities of the anterior cingulate and paracingulate cortex in patients with bipolar I disorder. *Psychiatry Res* 2008, 162: 123–132.
- [19] Ochsner KN, Gross JJ. The cognitive control of emotion. *Trends Cogn Sci* 2005, 9: 242–249.
- [20] Arnone D, McIntosh AM, Ebmeier KP, Munafo MR, Anderson IM. Magnetic resonance imaging studies in unipolar depression: systematic review and meta-regression analyses. *Eur Neuropsychopharmacol* 2012, 22: 1–16.
- [21] Bora E, Harrison BJ, Davey CG, Yucel M, Pantelis C. Meta-analysis of volumetric abnormalities in cortico-striatal-pallidal-thalamic circuits in major depressive disorder. *Psychol Med* 2012, 42: 671–681.
- [22] Koolschijn PC, van Haren NE, Lensvelt-Mulders GJ, Hulshoff Pol HE, Kahn RS. Brain volume abnormalities in major depressive disorder: a meta-analysis of magnetic resonance imaging studies. *Hum Brain Mapp* 2009, 30: 3719–3735.
- [23] Bora E, Fornito A, Pantelis C, Yucel M. Gray matter abnormalities in Major Depressive Disorder: a meta-analysis of voxel based morphometry studies. *J Affect Disord* 2012, 138: 9–18.
- [24] Ellison-Wright I, Bullmore E. Anatomy of bipolar disorder and schizophrenia: a meta-analysis. *Schizophr Res* 2010, 117: 1–12.
- [25] Bora E, Fornito A, Yucel M, Pantelis C. Voxelwise meta-analysis of gray matter abnormalities in bipolar disorder. *Biol Psychiatry* 2010, 67: 1097–1105.
- [26] Yu K, Cheung C, Leung M, Li Q, Chua S, McAlonan G. Are bipolar disorder and schizophrenia neuroanatomically distinct? An anatomical likelihood meta-analysis. *Front Hum Neurosci* 2010, 4: 189.
- [27] Liu CH, Ma X, Wu X, Zhang Y, Zhou FC, Li F, *et al.* Regional homogeneity of resting-state brain abnormalities in bipolar and unipolar depression. *Prog Neuropsychopharmacol Biol Psychiatry* 2013, 41: 52–59.
- [28] Schermyly I, Fellgiebel A, Wagner S, Yakushev I, Stoeter P, Schmitt R, *et al.* Association between cingulum bundle structure and cognitive performance: an observational study in major depression. *Eur Psychiatry* 2010, 25: 355–360.
- [29] Almeida JR, Akkal D, Hassel S, Travis MJ, Banihashemi L, Kerr N, *et al.* Reduced gray matter volume in ventral prefrontal cortex but not amygdala in bipolar disorder: significant effects of gender and trait anxiety. *Psychiatry Res* 2009, 171: 54–68.
- [30] Ashburner J, Friston KJ. Voxel-based morphometry--the methods. *Neuroimage* 2000, 11: 805–821.
- [31] Tan L, Fan Q, You C, Wang J, Dong Z, Wang X, *et al.* Structural changes in the gray matter of unmedicated patients with obsessive-compulsive disorder: a voxel-based morphometric study. *Neurosci Bull* 2013, 29: 642–648.
- [32] Lyoo IK, Kim MJ, Stoll AL, Demopoulos CM, Parow AM, Dager SR, *et al.* Frontal lobe gray matter density decreases in bipolar I disorder. *Biol Psychiatry* 2004, 55: 648–651.
- [33] Blumberg HP, Krystal JH, Bansal R, Martin A, Dziura J, Durkin K, *et al.* Age, rapid-cycling, and pharmacotherapy

- effects on ventral prefrontal cortex in bipolar disorder: a cross-sectional study. *Biol Psychiatry* 2006, 59: 611–618.
- [34] Fountoulakis KN, Giannakopoulos P, Kovari E, Bouras C. Assessing the role of cingulate cortex in bipolar disorder: neuropathological, structural and functional imaging data. *Brain Res Rev* 2008, 59: 9–21.
- [35] Bremner JD, Vythilingam M, Vermetten E, Nazeer A, Adil J, Khan S, *et al.* Reduced volume of orbitofrontal cortex in major depression. *Biol Psychiatry* 2002, 51: 273–279.
- [36] Tang Y, Wang F, Xie G, Liu J, Li L, Su L, *et al.* Reduced ventral anterior cingulate and amygdala volumes in medication-naïve females with major depressive disorder: A voxel-based morphometric magnetic resonance imaging study. *Psychiatry Res* 2007, 156: 83–86.
- [37] Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, *et al.* The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 1998, 59 Suppl 20: 22–33;quiz 34–57.
- [38] Hamilton M. The assessment of anxiety states by rating. *Br J Med Psychol* 1959, 32: 50–55.
- [39] Bech P, Rafaelsen OJ, Kramp P, Bolwig TG. The mania rating scale: scale construction and inter-observer agreement. *Neuropharmacology* 1978, 17: 430–431.
- [40] Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960, 23: 56–62.
- [41] Ashburner J. A fast diffeomorphic image registration algorithm. *Neuroimage* 2007, 38: 95–113.
- [42] Kong X, Ouyang X, Tao H, Liu H, Li L, Zhao J, *et al.* Complementary diffusion tensor imaging study of the corpus callosum in patients with first-episode and chronic schizophrenia. *J Psychiatry Neurosci* 2011, 36: 120–125.
- [43] Cai Y, Kuang W, Guo T, Yan L, Zhu J, Chen H. Clinical characteristics and cognitive function of unipolar and bipolar depression. *Zhong Nan Da Xue Xue Bao Yi Xue Ban* 2012, 37: 1152–1155.
- [44] Strakowski SM, Eliassen JC, Lamy M, Cerullo MA, Allendorfer JB, Madore M, *et al.* Functional magnetic resonance imaging brain activation in bipolar mania: evidence for disruption of the ventrolateral prefrontal-amygdala emotional pathway. *Biol Psychiatry* 2011, 69: 381–388.
- [45] Foland-Ross LC, Bookheimer SY, Lieberman MD, Sugar CA, Townsend JD, Fischer J, *et al.* Normal amygdala activation but deficient ventrolateral prefrontal activation in adults with bipolar disorder during euthymia. *Neuroimage* 2012, 59: 738–744.
- [46] Lopez-Larson MP, DelBello MP, Zimmerman ME, Schwiers ML, Strakowski SM. Regional prefrontal gray and white matter abnormalities in bipolar disorder. *Biol Psychiatry* 2002, 52: 93–100.
- [47] Grieve SM, Korgaonkar MS, Koslow SH, Gordon E, Williams LM. Widespread reductions in gray matter volume in depression. *Neuroimage Clin* 2013, 3: 332–339.
- [48] Delvecchio G, Fossati P, Boyer P, Brambilla P, Falkai P, Gruber O, *et al.* Common and distinct neural correlates of emotional processing in Bipolar Disorder and Major Depressive Disorder: a voxel-based meta-analysis of functional magnetic resonance imaging studies. *Eur Neuropsychopharmacol* 2012, 22: 100–113.
- [49] Phan KL, Wager T, Taylor SF, Liberzon I. Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. *Neuroimage* 2002, 16: 331–348.
- [50] Phillips ML, Drevets WC, Rauch SL, Lane R. Neurobiology of emotion perception I: The neural basis of normal emotion perception. *Biol Psychiatry* 2003, 54: 504–514.
- [51] Allman JM, Hakeem A, Erwin JM, Nimchinsky E, Hof P. The anterior cingulate cortex. The evolution of an interface between emotion and cognition. *Ann N Y Acad Sci* 2001, 935: 107–117.
- [52] Benes FM, Vincent SL, Todtenkopf M. The density of pyramidal and nonpyramidal neurons in anterior cingulate cortex of schizophrenic and bipolar subjects. *Biol Psychiatry* 2001, 50: 395–406.
- [53] Sassi RB, Brambilla P, Hatch JP, Nicoletti MA, Mallinger AG, Frank E, *et al.* Reduced left anterior cingulate volumes in untreated bipolar patients. *Biol Psychiatry* 2004, 56: 467–475.
- [54] Lochhead RA, Parsey RV, Oquendo MA, Mann JJ. Regional brain gray matter volume differences in patients with bipolar disorder as assessed by optimized voxel-based morphometry. *Biol Psychiatry* 2004, 55: 1154–1162.
- [55] Bearden CE, Thompson PM, Dalwani M, Hayashi KM, Lee AD, Nicoletti M, *et al.* Greater cortical gray matter density in lithium-treated patients with bipolar disorder. *Biol Psychiatry* 2007, 62: 7–16.
- [56] Frodl T, Jager M, Born C, Ritter S, Kraft E, Zetsche T, *et al.* Anterior cingulate cortex does not differ between patients with major depression and healthy controls, but relatively large anterior cingulate cortex predicts a good clinical course. *Psychiatry Res* 2008, 163: 76–83.
- [57] Lai CH. Gray matter volume in major depressive disorder: a meta-analysis of voxel-based morphometry studies. *Psychiatry Res* 2013, 211: 37–46.
- [58] Guo Y, Zhang Z, Zhou B, Wang P, Yao H, Yuan M, *et al.* Grey-matter volume as a potential feature for the classification of Alzheimer's disease and mild cognitive impairment: an exploratory study. *Neurosci Bull* 2014, 30: 477–489.