Unipolar Depression and Bipolar Depression Manifest Different Brain Abnormalities: A Voxel-based Morphometry Study

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ABSTRACT

Background: Patients with bipolar depression is often misdiagnosed to be as unipolar depression due to the phenotype similarity of these two diseases. We hypothesize that patients with these two diseases may demonstrate difference in terms of gray matter volume.

Methods: Structural magnetic resonance imaging (MRI) data were acquired from 64 subjects, including 17 unipolar depression patients, 19 bipolar depression patients and 28 healthy controls. Image preprocess were conducted using Voxel-based morphometry (VBM). Then the gray matter volume changes were compared among different groups.

Results: Compared to healthy controls, both Unipolar and bipolar patients demonstrated significantly decreased gray matter volume in the right anterior cerebellum lobe. Moreover, we observed significant right superior temporal gyrus volume decrease in unipolar patients compared to both healthy controls and bipolar subjects.

Conclusion: Our results indicated that volume changes in anterior cerebellum lobe could be used for the diagnosis of both unipolar and bipolar depressions. Additionally, the right superior temporal gyrus volume variations may differ in unipolar and bipolar patients and thereby could be used as a marker for differentiating these two diseases.

Key Words: Unipolar Depression; Bipolar Depression; Gray Matter Volume

INTRODUCTION

Depressed mood, lack of interest and loss of pleasure are the core symptoms in the patients with unipolar depression and bipolar depression. Because there is no biomarker of distinguishing the unipolar and bipolar depressions, the misdiagnosed situation often occurs during the clinical practice of unipolar and bipolar depression

disorders. To accurately identify and diagnose the unipolar and bipolar depressions becomes a big challenge in cross-diagnosis study of affective disorder. The brain dysfunction is usually followed by the damage of brain structure. The identification of the damaged brain structure can provide the abnormal neuroanatomical models of diseases.(1)

At present, there are not so many brain morphologic MRI studies on the direct comparison between the unipolar depression and bipolar depressions. The studies showed that the gray matter volume of hippocampus and amygdala and the white matter volume of hippocampus and cerebellum in the bipolar depression group both decreased; however, the gray matter volume of anterior cingulate in the unipolar depression group decreased.(2) Another study showed that gray matter volume of right inferior frontal gyus in both patients with unipolar and bipolar depressions decreased and the gray matter volume of dorsal cingulate in patients with bipolar depression decreased.(3)

These studies provided the neuroimaging evidences for brain structure difference of both unipolar and bipolar depressions, and there existed the difference of inferior frontal gyrus, hippocampus, amygdala, cingulate gyrus and cerebellum of brain volume in the patients with unipolar and bipolar depressions, but the results were also different. Moreover, the biomarkers for brain morphology in both unipolar and bipolar depressions were unclear yet, and in addition, the influence of drug factors was not controlled in these studies. The studies showed that the long-term use of antidepressant medications and affective stabilizers and other treatment methods would affect the change of local brain structures.(4,5) For example, the lithium salt and antidepressant medications may lead to the change of gray matter volume of hippocampus, amygdala, cerebellum, etc. (6-8)

In order to minimize the impact of the medications on the brain volume, the patients with unipolar and bipolar depressions within two weeks after drug-introduction treatment were compared to the healthy controls without significant difference of age, gender and education degree in this study for purpose of providing the reference for diagnosis and treatment of unipolar and bipolar depressions.

SUBJECTS AND METHODS

1. Subjects

64 cases (19 patients with unipolar depression, 17 patients with bipolar depression and 28 healthy controls) were recruited in this study, and all subjects were originated from the psychiatric clinics and wards of the Second Xiangya Hospital from February 2012 to February 2015. All subjects (Ss) were informed of the risks and benefits before the trials and they signed the informed consent. This study was approved by Medical Research Ethics Committee of the Second Xiangya Hospital of Central South University.

1.1 Unipolar Depression Disorder

Inclusion Criteria: ① comply with the diagnosis criteria of major depression of the Diagnostic and Statistical Manual of Mental Disorders, DSM-IV(9) and more than twice attacks of depressive episodes; ② 18-45 years old; ③ educational level ≥9 years; ④ total score of Hamilton's Rating Scale for Depression, HRSD (17 items) is over 17 scores;(10) ⑤ total score of Young manic rating scale (YMRS) is less than 6 scores;(11) ⑥ dextromanuality, Han nationality; ⑦ able to understand the experimental contents and sign the Informed Consent.

Exclusion Criteria: ① patients suffered from any other diseases of DSM-IV axis I or axis II; ② patients with a history of alcohol or substance abuse; ③ patients suffered from neurological disorders, loss of consciousness or severe physical illness or who are pregnant; ④ patients with a history of electric shock treatment; ⑤ patients contraindicated against the MRI tests and patients with brain abnormalities in the inspection of MRI.

1.2 Bipolar Depression Disorder

Inclusion Criteria: ① comply with the diagnosis criteria of bipolar depression episodes of the Diagnostic and Statistical Manual of Mental Disorders, DSM-IV (9); ② 18-45 years old; ③ educational level ≥9 years; ④ total score of Hamilton's Rating Scale for Depression, HRSD (17 items) is over 17 scores;(10) ⑤ total score of Young manic rating scale is less than 6 scores;(11) ⑥ dextromanuality, Han nationality; ⑦ able to understand the experimental contents and sign the Informed Consent.

Exclusion Criteria: ① patients suffered from any other diseases of DSM-IV axis I or axis II; ② patients with a history of alcohol or substance abuse; ③ patients suffered from neurological disorders, loss of consciousness or severe physical illness or who are pregnant; ④ patients with a history of electric shock treatment; ⑤ patients contraindicated against the MRI tests and patients with brain abnormalities in the

inspection of MRI.

1.3 Healthy Control

Inclusion Criteria: ① 18-45 years old; ② educational level ≥9 years; ③ dextromanuality, Han nationality; ④ gender matched with the patient; ⑤ no mental illness history for individual or family; ⑥ able to understand the experimental contents and sign the Informed Consent.

Exclusion Criteria: ① patients with a history of alcohol or substance abuse; ② patients with a history of mental illness for individual or family; ③ patients suffered from neurological disorders, loss of consciousness or severe physical illness or who are pregnant; ④ patients with a history of electric shock treatment; ⑤ patients contraindicated against the MRI tests and patients with brain abnormalities in the inspection of MRI.

2. Clinical Assessment and MRI Data Acquisition

2.1 Clinical Assessment

DSM-IV-TR Axis I disorder clinical interview (for patients) (namely, SCID-I/P) (12) was used to assess the condition of the patients; DSM-IV-TR Axis I disorder clinical interview (not for patients) (namely, SCID-NP) (13) was used to screen the normal controls; the oldfield inventory (14) was used to assess the handedness; demography and clinical basic data of the subjects were collected, including, age, gender, educational level, onset age and disease course; the HADS and YMRS were used to assess respectively the depression and manic symptoms of the patients with affective disorders in the last week.

2.2 Acquisition of MRI Data

The acquisition of MRI data was completed in the MRI room of the Second Xiangya Hospital of Central South University. The 3.0T magnetic resonance imaging system (Achieva, Philips, The Netherlands) was used to complete the scanning in the standardized head coil. The subject lied on his/her back and closed eyes, and the supportive foam pad was used to limit the movement of the head. The subject was instructed to keep the whole body motionless and relax, but he/she could not fall asleep. The structure MRI data used the sequence of T1W-3D-TFE. The whole brain structure image of a high resolution was scanned from the sagittal plane. Scanning parameters included repetition time (7.5 ms), echo time (3.7 ms), flip angle (8 degrees), field of view (24 × 24 cm), matrix (256 × 200), slice thickness (2 mm), gap (1 mm) and 180 slices.

3. Data Processing and Statistical Analysis

MRI data were analyzed based on MATLAB 7.1 and the data packages of SPM8 (http://www.fil.ion.ucl.ac.uk/spm) and VBM8 software were used to process the brain structure images. The “unified partitioning method” of voxel-based morphometry (VBM) was used to pre-process the 3D structure MRI data, including the standardization, partitioning, adjustment and translation. EPI template was used for the standardization to obtain the adjusted brain gray matter, white matter and cerebrospinal fluid images, which represent the volumes of three tissue types respectively. Isotropic 8mm (full-width at half-maximum) Gaussian kernel was used to translate the images. The brain gray matter volume, brain white matter volume and cerebrospinal fluid volume of each subject was calculated. The total intracranial volume was the sum of the three volumes. The total intracranial volume served as coviarate and the statistical model of covariance (analysis of covariance, ANCOVA) was used to detect the difference of brain gray matter volumes of the three groups. The threshold value of significant difference of brain gray matter volume was set as $P<0.001$ (uncorrected), and $k>100$. Software Rest was used to obtain the absolute values of cerebral areas of three groups of subjects with significant difference of brain gray matter volumes. Based on SPSS20, Post-hoc (LSD) was used to compare the difference of brain gray matter volumes among the three groups. Pearson’s correlation analysis method was used to test and check the correlation between patient demographic, clinical symptoms and cerebral area with significant difference of brain gray matter volumes ($P<0.05$).

RESULTS

1 Demographic and Clinical Symptoms

The demographic and clinical symptoms of bipolar depression group, unipolar depression group and healthy control group are shown in Table. There is no significant difference among the age, gender, and educational level of the three groups; there is also no significant difference for total score of HADS, total score of YMRS, onset age and disease course among the patients with unipolar and bipolar depressions.

Table 1 Demographic and Clinical Symptoms of Bipolar Depression Group, Unipolar Depression Group and Healthy Control Group (M±SD)

Variable	Bipolar Depression M(SD)	Unipolar Depression M(SD)	Healthy Control M(SD)	F/t/x2	P
Age(year)	25.18(5.92)	27.89(5.95)	25.00(5.82)	1.573a	0.216
Gender (male/female)	7/10	10/9	14/14	0.520b	0.771
Education years (year)	13.32(2.88)	12.21(2.97)	13.10(2.08)	0.992a	0.377
Disease course (month)	47.78(46.09)	42.63(46.88)		0.330c	0.743
Onset age(year)	21.36(4.06)	24.37(5.91)		-1.763 c	0.087
HRSD	22(4.78)	22.16(4.18)		-0.106c	0.916
YMRS	1.71(1.69)	2.05(1.72)		-0.610c	0.546

Notes: a. ANAVO Test; b. Chi-square test; c. t test; HRSD: Hamilton Rating Scale for Depression; YMRS: Young Manic Rating Scale.

2. Voxel-based Morphologic Analysis

The comparison results of three groups of brain gray matter volumes of the subjects showed that there was a significant difference of gray matter volumes in right lobus anterior cerebelli and right superior temporal gyrus. The coordinate value and value Z of the cerebral areas with significant difference of brain gray matter volumes are shown in Table 2. The bipolar and unipolar depression disorders showed the significant decrease of gray matter volumes of right lobus anterior cerebelli through the further comparison with the healthy control, and the unipolar depression disorder showed the significant decrease of gray matter volumes of right superior temporal gyrus through the comparison with other two groups of subjects (Table 3, see attached figures).

Table 2 Cerebral Areas with Significant Difference of Gray matter Volumes for Bipolar Depression Group, Unipolar Depression Group and Healthy Control Group

Brain Area	Voxel Number	F	Z	P	MNI Coordinate		
					x	y	z
Right superior temporal gyrus	114	14.30	4.31	<0.001	42	-39	10
Right lobus anterior cerebelli	135	8.69	3.30	<0.001	24	-39	-33

Note: MNI - Montreal Neurological Institute

Table 3 Comparison of Cerebral Areas with Significant Difference of Gray matter Volumes for Bipolar Depression Group, Unipolar Depression Group and Healthy Control Group

Brain Area	Brain Gray Matter Volume (M±SD)			P		
	BD	UD	HC	BD-HC	UD-HC	BD-UD
Right lobus anterior cerebelli	0.264(±0.05)	0.276(±0.04)	0.293(±0.05)	0.000*	0.000*	0.404
Right superior temporal gyrus	0.430(±0.06)	0.383(±0.05)	0.424(±0.06)	0.236	0.000*	0.009*

Note: BD – Bipolar depression; UD – unipolar depression; HC – Healthy Control

Note: Fig. A and Fig. B: P<0.001 (uncorrected), and cluster>100, color strip represents Value F; Fig. C and

Fig. D: *P<0.05.

Attached Figures: Fig. A: Right Lobus Anterior Cerebelli of Three Groups of Subjects with Significant Difference of Gray matter Volumes; Fig. B: Right Superior Temporal Gyrus of Three Groups of Subjects with Significant Difference of Gray matter Volumes; Fig. C: Post-hoc Comparison Result of Right Lobus Anterior Cerebelli among Three Groups of Subjects; Fig. D: Post-hoc Comparison Result of Right Superior Temporal Gyrus among Three Groups of Subjects.

3. Correlation Analysis between Gray matter Volume and Clinical Features of Right Lobus Anterior Cerebelli and Right Superior Temporal Gyrus of Subjects with Unipolar Depression and Bipolar Depression.

The gray matter volume of right lobus anterior cerebelli of subjects with bipolar depression is significantly negatively correlated with the total score of HRSD, see Table 4.

Table 4 Correlated Analysis between Demographic and Clinical Features and Gray matter Volume of Right Lobus Anterior Cerebelli and Right Superior Temporal Gyrus of Subjects with Unipolar Depression and Bipolar Depression

Group	Variable	Right Superior Temporal Gyrus		Right Lobus Anterior Cerebelli	
		r	P	r	p
BD	Age	-0.285	0.267	0.244	0.346
	Gender	0.305	0.234	-0.206	0.127
	Education Age(Year)	0.242	0.349	-0.466	0.059
	Onset Age (year)	-0.376	0.137	0.173	0.507
	Disease Course	-0.081	0.757	0.205	0.43
	HRSD	-0.173	0.507	-0.523	0.031
UD	Age	-0.126	0.608	-0.375	0.114
	Gender	-0.264	0.274	-0.145	0.555
	Education Age(Year)	-0.028	0.908	-0.368	0.121
	Onset Age (year)	-0.379	0.11	-0.215	0.378
	Disease Course (Month)	0.378	0.11	-0.118	0.63
	HRSD	0.213	0.382	-0.227	0.35

DISCUSSION

The results of this study showed that the gray matter volume of right superior temporal gyrus of subjects with unipolar depression significantly decreased compared to the healthy control, and there was no significant difference for the subjects with bipolar depression. It was also reported in the past that the gray matter volume of right superior temporal gyrus of subjects with unipolar depression significantly decreased, (15) and there was no significant difference for the subjects with bipolar depression.(16) The superior temporal gyrus mainly contains the cerebral areas of hearing and auditory associated cortex, involving in the auditory system and speech disorders, and the superior temporal gyrus is connected with the medial frontal lobe and dorsal frontal lobe, which plays an important role in constituting the behavior state related to the affective disorders. (17-19) The studies showed that the superior temporal gyrus constituted the brain default network with medial prefrontal lobes, front/rear cingulate, entorhinal area and para-hippocampus. The activities enhanced in the task state and weakened in resting state. The decrease of gray matter volume of superior temporal gyrus might lead to the dysfunction of default network of the unipolar depression, and the dysfunction of default network was however associated with the abnormal functions such as situational memory, self-related thinking, emotional processing, etc.(19-22) The significant decrease of gray matter volume in right superior temporal gyrus of the subjects with unipolar depression indicated that it might be associated with the auditory system and speech disorder dysfunction and default network dysfunction of the subject with the unipolar depression, and displayed that there existed a difference of gray matter volume of right superior temporal gyrus between the subjects with unipolar depression and bipolar depression, which may be associated with

different depression states. The studies showed that the gray matter volumes of right lobus anterior cerebelli of the subjects with unipolar and bipolar depression significantly decreased, which was also reported in the previous studies of brain structure.

Compared to the healthy controls, the results showed the decrease of gray matter volume in cerebellum structure of the patients with unipolar depression or bipolar depression;(23,24) The brain function studies also showed that the activation of cerebellum function of patients with the depressions reduced, but it could be improved after the antidepressant treatment;(25) However, at the molecular level, some evidences indicate that the neurotrophic factor signals expressed in cerebellum granule cells and molecular layer have reduced, which may potentially form the synaptic plasticity of affective disorder.(26) These results supported the abnormal reduction of cerebellum gray matter volume of the patients with the depressions. Lobus anterior cerebelli was the primary sensorimotor area, and it was responsible for coordinating the movement and motor learning. It was associated with the movement control and the sensorimotor integration. (27,28) Andreasen et al. reported the neural circuit of cortex-thalamic-cerebral - cortical circuit to form the classic sensorimotor circuit. The movement defect was associated with the different development of the Lobus anterior cerebelli (29) and the cerebellum was correlated with the inferior colliculus to promote the combination with a wide range of neural circuits of emotions and autonomic functions in addition to the sensorimotor control.(30) The significant decrease of gray matter volume of right lobus anterior cerebelli in the patients with unipolar and bipolar depressions might be associated with the atrophy of gray matter volume of lobus anterior cerebelli in the unipolar and bipolar depressions. It might lead to the reduction of sensorimotor and control ability of the patients and result in the depressive symptoms such as, emotional depression, lack of interest, loss of pleasure, etc. The decrease of gray matter volume of right lobus anterior cerebelli occurred in the patients both with unipolar and bipolar depression, which has reflected the common characteristics of the unipolar depression and bipolar depression. The difference of gray matter volumes of unipolar and bipolar depressions in the right superior temporal gyrus reflects the characteristics of different disease states, which may help distinguishing the two diseases. The decrease of gray matter volumes of right lobus anterior cerebelli in patients with unipolar and bipolar depressions may reflect the trait characteristics of depression disorders and result in the reduction of sensorimotor and control ability related to the depressive symptoms. The correlated analyses showed that the gray matter volume of right lobus anterior cerebelli of subjects with bipolar depression was significantly negatively correlated with the total score of HRSD. This indicates that the decrease of gray matter volume of right lobus anterior cerebelli of subjects with bipolar depression may be associated with the increased severity of depression. As for the patients with unipolar depression, there was no correlation with the gray matter volume of right lobus anterior cerebelli or right superior temporal gyrus. It was possibly associated with the sample quantity and other factors and shall be further verified in the studies in the future.

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