Changes of grey matter volume in first-episode drug-naive adult major depressive disorder patients with different age-onset

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A B S T R A C T

Objective: Little is known about the pathological mechanism of early adult onset depression (EOD) and later adult onset depression (LOD). We seek to determine whether grey matter volume (GMV) change in EOD and LOD are different, which could also delineate EOD and LOD.
Methods: In present study, 147 first-episode, drug-naive patients with major depressive disorder (MDD), age between 18 and 45, were divided into two groups on the basis of age of MDD onset: the early adult onset group (age 18–29) and the later adult onset group (age 30–44), and a total of 130 gender-, and age-, matched healthy controls (HC) were also divided into two groups which fit for each patient group. Magnetic resonance imaging was conducted on all subjects. The voxel-based morphometry (VBM) approach was employed to analyze the images.
Results: Widespread abnormalities of GMV throughout parietal, temporal, limbic regions, occipital cortex and cerebellum were observed in MDD patients. Compare to young HC, reduced GMV in right fusiform gyrus, right middle temporal gyrus, vermis III and increased GMV in right middle occipital gyrus were seen in the EOD group. In contrast, relative to old HC, decreased GMV in the right hippocampus and increased GMV in the left middle temporal gyrus were observed in the LOD group. Compared to the LOD group, the EOD group had smaller GMV in right posterior cingulate cortex. There was no significant correlation between GMV of the right posterior cingulate cortex and the score of the depression rating scale in patients group.
Conclusions: The GMV of the brain areas that were related to mood regulation was decreased in the first-episode, drug-naive adult patients with MDD. Adult patients with EOD and LOD exhibited different GMV changes relative to each age-matched comparison group, suggesting depressed adult patients with different age-onset might have different pathological mechanism.

1. Introduction

Major depressive disorder (MDD) is an affective disorder with a lifetime prevalence of 16% (Kessler et al., 2003). The etiology of MDD might be related to genetic factors, deficit in monoamine neurotransmitter, dysfunction of hypothalamic-pituitary-adrenal axis (HPA), stress, and nerve growth factor (Belmaker and Agam, 2008). Thus, MDD is considered a heterogeneous and multifactorial disorder, it is great benefit to understand the core pathophysiology according to differentiate patients into homogeneous subgroups and would help guide treatment selection. However, there is still lack of validating indicators to define the heterogeneity of MDD.

The age-onset might be a potential indicator to define the heterogeneity of MDD. There is heterogeneity in depressive symptoms between different age-onset depression (Charlton et al., 2013; Korten et al., 2012; Park et al., 2014), one meta-review also indicating the different age-onset depression might be different subtypes of depression (Harald and Gordon, 2012). Previous studies showed the evidence that early onset MDD has been associated with higher positive family history of depression in first degree relatives (Tozzi et al., 2008; Weissman et al., 1984). Furthermore, the heritability of MDD is about 37% (Sullivan et al., 2000), the heritability of early onset (EO) MDD (<30 years) is higher than that in later onset (LO) MDD (>30 years) (Lyons et al., 1998) (47% vs 10%), this study implicated that EO MDD and LO MDD might have different pathological mechanisms. Moreover, genetic association research found the MDD patients with age younger than 30 years was associated with disease severity and chronicity of depressive symptoms when compared to patients with age older than 30 years (Mondimore et al., 2006). Tozzi et al. reported the patients with onset age after 50 years

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are not associated with family history of MDD (Tozzi et al., 2008). In summary, in comparison to patients with LO MDD, patients with EO MDD might represent a homogeneous subgroup associated with higher family history of depression.

Recently, structural magnetic resonance imaging (MRI) study have sought to identify the brain regions involved in the pathogenesis of MDD which might be helpful in defining different subtype of depression (Zhou et al., 2011). Voxel-based morphometry (VBM) is an automated method for analyzing neuromorphological MRI data. It has been widely used to detect subtle changes in brain structure in MDD (Lai, 2013). VBM studies have reported that the grey matter volume (GMV) of frontal cortex, cingulate, hippocampus, amygdala and putamen were reduced in depressed patients (Du et al., 2012; Grieve et al., 2013; Lai, 2013). There was a study suggested the age of onset was an important factor that influenced the GMV change in different brain regions in non-affective psychosis (Tordesillas-Gutierrez et al., 2015), suggesting that the GMV changes might be a candidate method to differentiate EO and LO MDD, but there is still a lack of VBM study that is conducted to detect the grey matter volume abnormalities in first episode depression with different onset age.

Considering the role of different age onset in the pathology of MDD, we hypothesized that GMV abnormalities in different brain region might be observed respectively in early adult onset depression (EOD) and later adult onset depression (LOD), and these structural abnormalities might characterize EOD and LOD correspondingly. A previous study suggested that the median age at onset of MDD is 32 years (Kessler et al., 2005), and the median age was often used as the cutoff point in mixed age samples (Benazzi, 2004). To test our hypotheses, we defined the first episode of depression occurred before age 30 years as early adult onset depression which based on our previous study (Cheng et al., 2014). In that study, we found specific abnormalities of the brain circuitry in EOD vs LOD by using 30 years as the cutoff age. Moreover, 30 years was also the median age at onset of our sample. The antidepressant treatment could cause regional GMV changes in MDD, so the drug-naive patients could better elucidate grey matter volume changes that are directly related to disease itself. We investigated abnormalities of GMV in drug-naive, first-episode MDD patients aged 18–45 years old (the age of onset was 18–44), to exclude the interferences of vascular disease.

2. Materials and methods

2.1. Subjects

2.1.1. Depression group

All patients were recruited from the outpatient clinic or inpatient wards of Department of Psychiatry, the First Affiliated Hospital of Kunming Medical University. The inclusion criteria were as follows: ① The diagnosis of MDD was independently made by two experienced psychiatrists in accordance with the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV, American Psychiatry Association, 1994), ② first episode without a history of antidepressants treatment, ③ be aged between 18 and 45 years, ④ the total score of 17-item Hamilton Depression Rating Scale (HDRS) was not <17, ⑤ right handedness, ⑥ the patients or their legal guardian signed the informed consent form. The exclusion criteria included the following items: ① having a history of Axis I psychiatric disorders. ② having a history of neurological illnesses or other severe diseases, ③ having a history of brain injury or obvious psychiatric symptoms, ④ with substance abuse, ⑤ having received electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS) or systematical psychotherapy, ⑥ pregnant or nursing women and ⑦ having physical limitations prohibiting them undergoing MRI scans. Finally, 147 patients met the criteria and underwent MRI scans.

2.1.2. Healthy controls (HCs)

130 gender-, and age-, matched healthy controls were recruited by an advertisement in the local community and school, and excluded: ① with a family history of psychiatry, ② with a psychiatry disorder, ③ with a severe physical disease and/or neurological disease, ④ with substance abuse, ⑤ with a history of brain injury, ⑥ pregnant or nursing women, or ⑦ inability to undergo a MRI scan.

This research was approved by the Institutional Review Board of Kunming Medical University, Yunnan Province, P.R. China.

2.2. Methods

2.2.1. Clinical materials and subgroups

All participants were collected data on age, gender, education level and the duration of depression. The depressive symptoms were assessed by an experienced psychiatrist using the 17-item Hamilton Depression Rating Scale (HDRS, Hamilton 1960). Based on previous research, we divided all patients into two subgroups: the early adult onset depression (18–29 years), the later adult onset depression (30–44 years), and HC were also divided into two subgroups (young HC and old HC) matching for each patient subgroup.

2.2.2. Image acquisition

MRI scanning was performed by a skilled radiological technician on a Philips Achieva 3.0-T MRI scanner. Restraining foam pads were used to minimize head motion. Normal T1 and T2-weighted MRI scans were first performed to exclude obvious structural abnormalities. The parameters were as follows: time of repetition (TR)/time of echoing (TE) = 2500/80 ms, slice thickness = 6 mm, field of vision (FOV) = AP (250 mm) × RL (193 mm) × FH (142 mm), matrix size = 128 × 128, flip angle = 90°, slices = 16, gap = 2 mm, scan duration time = 45 s.

The three-dimensional volumetric structural MRI scan sequence was then acquired using a fast spoiled gradient recalled acquisition (FSPGR). The parameters were as follows: TR/TE = 7.38/3.4 ms, slice thickness = 1.2 mm, FOV = 250 mm × 250 mm, matrix size = 256 × 256, flip angle = 90°, slices = 230 with no gap, scan duration time = 6 min 53 s. All of the sections were acquired parallel to the anterior-posterior commissure line.

2.3. Voxel-based morphometry

All primary DICOM images were converted into NIfTI format using the MRIconvert software (http://lcni.uoregon.edu/downloads/mriconvert/mriconvert-and-mcverter). All the structural data were analyzed using the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm) in the statistic parametric mapping software package (SPM8, http://www.fil.ion.ucl.ac.uk/spm) running in the Matlab 2012a (MathWorks, Natick, MA, USA). The default parameters were used to analysis the data. The data were automatically segmented into grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF). After Jacobian modulation, the GM images were smoothed with 8-mm full width at half maximum (FWHM) Gaussian kernel. Then the smoothed GM images were performed the voxel-based comparison of the grey matter volume.

2.4. Statistical analysis

Statistical analyses were performed using the Statistical package for the Social Sciences (SPSS 17.0 for Windows). The distributions of age and years of education of the four groups were compared by using one-way analysis of variance (ANOVA), and the chi-square test was used to compare the gender distribution. Two sample t-tests were performed to compare the illness duration, HDRS score between the two patients subgroups. The significance threshold was set to p < 0.05.

A 2 × 2 full factorial model were performed in SPM8, assessing the effects of age-onset (EO vs LO) and diagnosis (MDD vs HC) using age,

gender, education level and whole brain GMV as covariates. Then post hoc pairwise comparisons were used to compare differences in GMV between each pair of subgroups by using the covariates which mentioned above. Multiple comparisons were corrected by using the Monte Carlo simulation-based Alphasim program, which is implemented in the REST toolbox (http://restfmri.net/forum/REST_V1.8). The multiple comparisons to a significant level of p < 0.05 by combining the individual voxel p < 0.001 and cluster size > 148 voxels (using the global grey matter mask, FWHM = 8 mm, cluster connection radius = 5 mm and 1000 iterations). And the results were further confirmed by using small volume correction (SVC) in SPM8. All results were visualized using xjview8.0 software (http://www.alivelearn.net/xjview8/).

To investigate the relationship between abnormal GMV and clinical features, brain regions with abnormal GMV were identified as regions of interest. Mean values of GMV were extracted using the REX toolbox (http://gablab.mit.edu/downloads/rex.m). Pearson partial correlation explored the correlation between these abnormal values of GMV and HDRS score in each patients subgroup in SPSS, controlling for age and whole brain GMV in SPSS.

3. Results

3.1. Demographic data

Seventy-two patients with EOD, seventy-five patients with LOD, seventy-two young HC, and fifty-eight old HC were included in this study. The demographic information, illness duration, HDRS score were presented in Table 1. There was no significant difference in age, gender between MDD and HC, as well as between EOD, LOD relative to each age-matched comparison group. However, since the control subjects had

Table 1
The demographics and clinical characteristics of the sample.

Variables (mean ± SD)	HC	MDD	t(F)/χ2	p-Value
Gender (male/female)	49/81	50/97	0.524	0.533[a]
Age (years)	30.09 ± 7.03	30.58 ± 7.41	0.548	0.571[b]
Years of education	15.22 ± 3.96	12.10 ± 4.21	−6.325	0.000[b]
HDRS score	0.45 ± 0.67	23.83 ± 4.84	54.491	0.000[b]
Whole brain GMV (cm³)	615.29 ± 61.15	601.95 ± 58.23	−1.858	0.065[b]

Variables (mean ± SD)	Young HC	Old HC	EOD	LOD	t(F)/χ2	p-Value
Gender (male/female)	31/41	18/40	32/40	18/57	9.113	0.028[c]
Age (years)	24.57 ± 2.33	36.93 ± 4.36	24.03 ± 3.03	36.87 ± 4.21	\	0.000[d]
Age onset (years)	\	\	23.33 ± 3.08	36.20 ± 4.34	\	0.000[b]
Illness duration (months)	\	\	9.02 ± 7.30	7.98 ± 7.66	0.844	0.400[b]
Years of education	16.40 ± 2.52	13.76 ± 4.86	13.68 ± 3.22	10.59 ± 4.51	4.767	0.000[e]
HDRS score	0.42 ± 0.62	0.50 ± 0.73	23.39 ± 4.49	24.29 ± 5.18	−1.275	0.204[c]
Whole brain GMV (cm³)	632.79 ± 60.36	593.55 ± 55.29	621.80 ± 55.31	582.90 ± 54.82	12.238	0.000[g]

MDD = major depressive disorder; EOD = early adult onset depression; LOD = later adult onset depression; HC = healthy control; HDRS = Hamilton Rating Scale for Depression.

[a] The p-value for gender distribution in the two groups was obtained by chi-square test.
[b] The p-values were obtained by two sample t-test.
[c] The p-values for gender distribution among the four groups was obtained by chi-square test p = 1.000 (young HC vs EOD), p = 0.433 (old HC vs LOD).
[c] The p-values were obtained by two sample t-test.
[d] The p-values were obtained by one-way analysis of variance tests. Post hoc t-test: p = 0.360 (EOD vs young HC), p = 0.917 (LOD vs older HC).
[e] The p-values were obtained by one-way analysis of variance tests. Post hoc t-test: p = 0.000 (EOD vs young HC), p = 0.000 (LOD vs older HC), p = 0.000 (EOD vs LOD).
[g] The p-values were obtained by one-way analysis of variance tests. Post hoc t-test: p = 0.244 (EOD vs Young HC), p = 0.282 (LOD vs older HC).

higher educational level and whole brain GMV than depressed patients, years of education and whole brain GMV were used as covariates in the analysis. There was no significant difference in terms of illness duration, HDRS score between the two patients groups.

3.2. Abnormal GMV among groups

Fig. 1 showed the 2 × 2 full factorial analysis of GMV among the four groups. Significant group differences of GMV were found in right hippocampus, right angular gyrus, right precuneus, right middle temporal gyrus, right middle occipital cortex, vermins III, left cerebellum VIII and left cerebellum X (Table 2, Fig. 1.A).

3.3. Abnormal GMV in EOD patients versus young HC

Compared with young HC, patients with EOD showed significantly decreased GMV in the right middle temporal gyrus, right fusiform, vermins III. Increased GMV in the right middle occipital gyrus was observed in EOD group (Table 2, Fig. 1.B).

3.4. Abnormal GMV in LOD patients versus old HC

Compared with old HC, patients with LOD had significant GMV reduction in right hippocampus. The GMV of left middle temporal gyrus was increased in LOD group (Table 2, Fig. 1.C).

3.5. Abnormal GMV in patients with EOD versus patients with LOD

Relative to patients with LOD, patients with EOD displayed significantly decreased GMV in the right posterior cingulate cortex. There was no significant GMV increased in EOD compared to LOD (Table 2, Fig. 1.D).

3.6. The correlation of the GMV and HDRS score

One brain region (right posterior cingulate cortex) demonstrated GMV difference between EOD and LOD. We use the REX toolbox to extract the mean values of GMV in the right posterior cingulate in both patient group. GMV in right posterior cingulate did not significantly correlate with symptom severity (HDRS) in both EOD group (r = −0.072, p = 0.554) and LOD group (r = 0.100, p = 0.401), after controlling for age and whole brain GMV.

4. Discussion

MDD is a multifactorial disorder with clinically heterogeneous features. First of all, findings of the present study were consistent with previous study results in that the MDD patients had significant GMV reduction in hippocampus (Schmaal et al., 2016) and temporal lobe (Bora et al., 2012a). These brain regions are important part of the limbic-cortical-striatal-pallidal-thalamic (LCSPT) circuit (Sheline et al., 2010). A wealthy number of studies demonstrated abnormalities of the LCSPT circuit in MDD (Bora et al., 2012b), which indicated that deficits in these brain regions might be the anatomical basis for abnormal function of the LCSPT circuit, and may play an important role in the pathogenesis of MDD.

The most important finding in the present study was that patients with EOD or LOD exhibited different GMV abnormalities when compared to each matched HC subgroup. A different form of GMV changes was also observed when compared the EOD subgroup to the LOD subgroup. The finding supported the postulation of distinct heritability of patients with EOD versus LOD reported in genetic studies. Our finding was also in line with the ENIGMA study recently, and further supported the smaller hippocampus volume in MDD might moderated by age of onset (Schmaal et al., 2016). Moreover, the findings lent credit to our
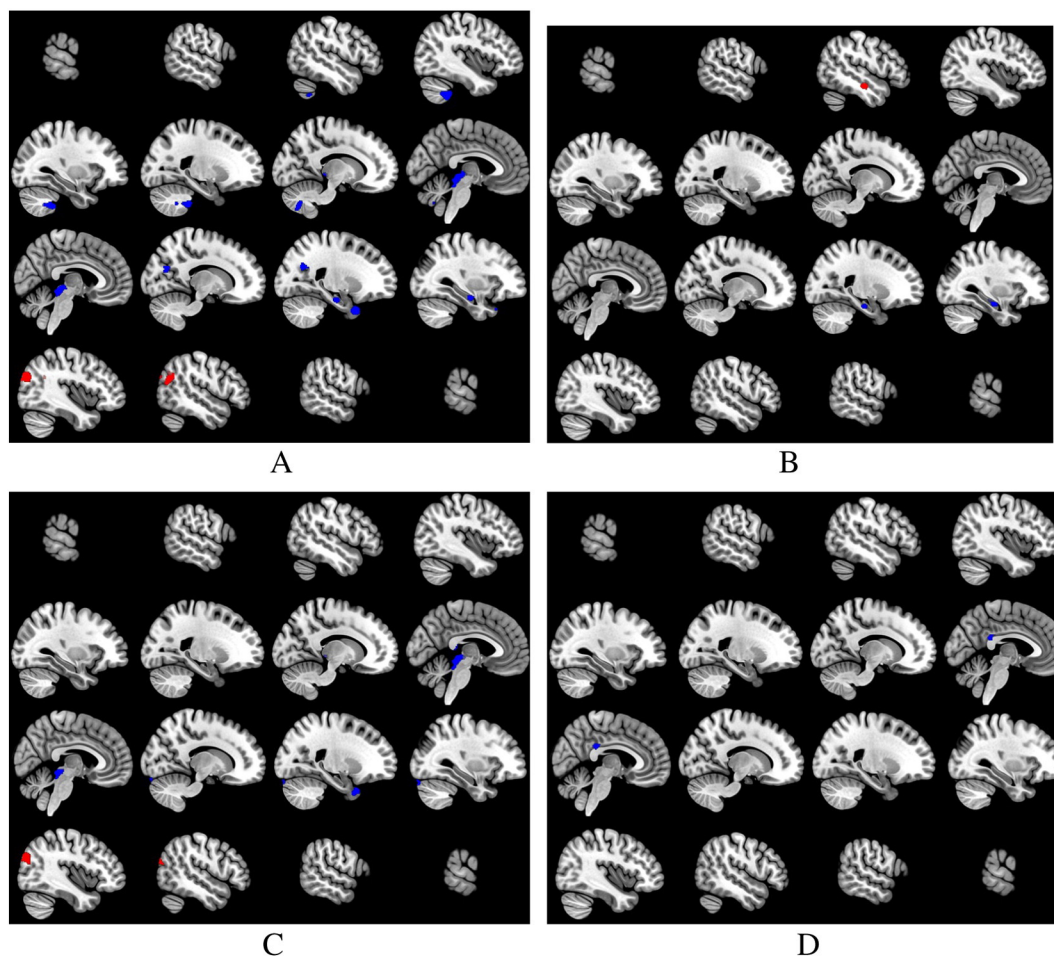
Fig. 1. (A). Statistical maps showing the results of GMV deficits in patients with EOD or LOD compared with HC. (B). Brain region showing the GMV deficits in patients with EOD compared with young HC. (C). Brain region showing the GMV deficits in patients with LOD compared with old HC. (D). Brain region showing the GMV differences between patients with EOD and patients with LOD. Red color: significant increased GMV. Blue color: significant decreased GMV. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

previous study that specific abnormalities of the brain circuitry in patients with EOD and LOD were delineated by an age of onset of 30 years.

Patients with LOD showed significant GMV reduction in the right hippocampus, which was in line with a previous finding that late-onset depression is associated with smaller hippocampus volume while early-onset did not exhibit such an association (Lloyd et al., 2004). Numerous structural neuroimaging studies on patients with MDD have shown the hippocampus is a core region in the limbic system, and play a distinct role in the pathologic mechanism of MDD, the hippocampus volume reduction in MDD was repeatedly reported and further confirmed by meta analyses (Videbech and Ravnkilde, 2004). One possible explanation for hippocampus atrophy in MDD suggested that hippocampus atrophy is due to prolonged exposure to stress-induced biochemical abnormalities mediated via the HPA-axis (Sheline, 2011). Because of the widely distribution of glucocorticoid receptors in the hippocampus, stress induced elevated glucocorticoid level in patients with MDD could result in GMV reduction in the hippocampus (Belmaker and Agam, 2008; Frodl and O'Keane, 2013). However, L. Schmaal et al. found that the hippocampus volume was likely to decreased in early-onset (<21 years) depression patients, whereas hippocampus volume reductions was not observed in patients with later age of onset (>21 years) MDD (Schmaal et al., 2016). But they only found hippocampus volume reduction in recurrent patients rather than first episode patients, and 57% of early onset patients had a recurrent episode in their sample (Schmaal et al., 2016). The hippocampus volume was negatively correlated with illness duration and the number of

episode (McKinnon et al., 2009). Thus, they speculated the smaller hippocampus volume in early onset depression reflect a longer illness duration and/or greater number of episodes in patients with early onset MDD. In our study, all patients were at first episode and with short illness duration, so the morphological hippocampus alterations weren't observed in EOD patients in our study. On the other hand, the hippocampus volumes were negatively correlated stressful life events before the onset of depression (Kronmuller et al., 2008). Furthermore, the patients with later onset of depression exhibited higher prevalence of stressful life events preceding onset compared to patients with early age of onset (Bukh et al., 2011). Additionally, Eker and Gonul reported that depressed patient with mean age older than 40 years are more likely to demonstrated smaller hippocampus volumes (Eker and Gonul, 2010). Taken together, it is more likely to observed hippocampus atrophy in LOD and the pathophysiological mechanism of LOD may be mediated by environmental factors such as stress.

On the other hand, in patients with EOD, the primary GMV reductions were located in occipitotemporal gyrus. Our finding of reduced GMV in right fusiform and right middle temporal gyrus partly concurred with previous studies (Peng et al., 2011; Wang et al., 2012). The GMV and amplitude of low frequency fluctuation (ALFF) decreased in right fusiform gyrus has been observed in first episode, treatment-naive patients with MDD (Wang et al., 2012). And GMV decreased in the bilateral middle temporal gyrus in first-episode MDD were also found in previous study (Peng et al., 2011). There was an evidence suggested the fusiform gyrus connects with middle temporal gyrus (Wu et al.,

Table 2
Regions of GMV deficits in patients with MDD or EOD or LOD compared with HC.

Brain region	Side	Cluster size (voxels)	MNI coordinates (mm)			Z-score	p value
			x	y	z		
MDD < HC							
Precuneus	R	294	24	−61.5	27	−3.8024	<0.05
Hippocampus	R	218	30	−13.5	−19.5	−3.8924	<0.05
Middle temporal	R	332	19.5	13.5	−34.5	−4.2466	<0.05
Vermis III	/	1094	−1.5	−37.5	−12	−4.2080	<0.05
Cerebellum VIII	L	274	−9	−66	−43.5	−3.4930	<0.05
Cerebellum X	L	1050	−22.5	−33	−43.5	−4.3892	<0.05
MDD > HC							
Angular	R	247	49.5	−64.5	24	3.7857	<0.05
Middle occipital	R	427	42	−84	28.5	4.0753	<0.05
EOD < young HC							
Fusiform	R	394	30	−93	−24	−4.3597	<0.05
Middle temporal	R	250	16.5	9	−39	−4.1465	<0.05
Vermis III	/	1006	−6	−34.5	10.5	−4.0078	<0.05
EOD > young HC							
Middle occipital	R	446	42	−84	28.5	3.8176	<0.05
LOD < old HC							
Hippocampus	R	191	25.5	−16.5	−22.5	−3.7108	<0.05
LOD > old HC							
Middle temporal	L	154	−45	−16.5	−16.5	4.3138	<0.05
EOD < LOD							
Posterior cingulate	R	206	7.5	−36	28.5	−3.5553	<0.05

x, y, z are the coordinates of primary peak locations in the MNI space; Z is the statistical value of peak voxel showing GMV differences among the EOD, LOD subgroups and healthy subjects. EOD = early adult onset depression; LOD = later adult onset depression; HC = healthy controls. p < 0.05, Alphasim corrected.

2016), further study found the resting-state activities of these two regions and together with posterior cingulate cortex, right angular gyrus and right parahippocampus gyrus may be related to cognitive processing (Lau et al., 2016). Moreover, The fusiform gyrus is a part of visual recognition network, which is assumed to play an important role in processing facial stimuli (Dichter et al., 2009). The middle temporal gyrus has been linked to successful decision making in the presence of stimulus conflict (Wendelken et al., 2009). Therefore, GMV deficit in fusiform and middle temporal gyrus may be the anatomical basis for cognitive dysfunction, such as emotional dysregulation and impaired decision making, in early adult onset depression.

Moreover, in the present study we found decreased GMV in the right posterior cingulate cortex (PCC) in patients with EOD compared to those with LOD. The PCC is a key region in default mode network (DMN) at resting state (Greicius et al., 2003; Uddin et al., 2009), and is associated with the memory retrieval (Maddock et al., 2001). A large amount of previous studies have demonstrated that the patients with MDD showed dysfunctions in the DMN (Mulders et al., 2015). Bluhm et al. chose the precuneus/posterior cingulate cortex (P/PCC) as the seed region to analyze the DMN connectivity in early depression (<35 years), they found depressed subjects displayed decreased connectivity between the P/PCC and the bilateral caudate (Bluhm et al., 2009), suggesting deficits in the DMN connectivity with the caudate might be an early manifestation of MDD, and highlighting the importance of the P/PCC in the pathophysiology of the early stage of depression. Our findings indicated the deficit in PCC might be the anatomical basis for abnormal function of DMN connectivity. Moreover, patients with early onset age were in association with family history of depression (Tozzi et al., 2008). The adolescents who were at high familial risk for developing clinical depression had different DMN connectivity relative to those who were at low familial risk for depression (Frost

Bellgowan et al., 2015), suggesting the DMN connectivity might be influenced by genetic factors. Considered the heritability of early onset MDD is higher than that in later onset MDD (Lyons et al., 1998), it is speculated the abnormality of PCC within DMN in EOD group might be caused by genetic factors. Additionally, the total HDRS score between the EOD and LOD subgroup did not differ significantly. Nevertheless, the correlation between HDRS score and right posterior cingulate GMV was not statistically significant, which may imply that GMV decreases in the right PCC was independent of depressive symptom severity. This suggests that the right PCC may be an appropriate brain region for differentiating patients with EOD and LOD.

In our study, GMV abnormalities in the cerebellum were also found in patients with MDD. The cerebellum and the cerebral are tightly connected, the fibers of the superior function areas of cerebral project to cerebellum and feed back to the same areas (Dolan, 1998). The primary function of the cerebellum is controlling and adjusting movement, and maintaining body balance. New data suggested that it also plays an important role in the initial processing of emotional information and sensory information (Smith et al., 2002), which is related the process of emotion regulation. Furthermore, there was evidence showed the cerebellum grey matter reduction in the first episode patients with MDD (Peng et al., 2011). Taken together, it is likely that the cerebellum impairment is involved in the pathophysiology of major depressive disorder.

Interestingly, our data exhibited that relative to HC, the right middle occipital gyrus (MOG) volumes were increased in patients with MDD. And the MOG were also found to be increased in patients with EOD compare to young HC. The study on GMV of occipital gyrus increased in MDD patients were limited, but Yan et al. found the GMV of left inferior occipital gyrus (IOG) were increased in aged healthy participants with apathy (Yan et al., 2015). They speculated that the increased GMV of IOG might be compensations that enable effective behavior execution in aged participants. Moreover, there was a study found the GMV of right middle occipital gyrus was one of trait-related region in nonrefractory depression (Zeng et al., 2015). Therefore, the GMV increased in right MOG in present study may be morphological compensations for the reduction GMV in other brain region, and it may be the trait-related region in our sample.

On the other hand, previous study found the fractional amplitude of low-frequency fluctuation (fALFF) was decreased in many brain regions including right angular gyrus and left middle temporal gyrus in first-episode, treatment naive patient with MDD (Shen et al., 2014), suggesting this two regions might be involved with the pathophysiology of MDD. A variety of cognitive deficits were observed in patients with MDD (Li et al., 2010; Turner et al., 2012). The angular gyrus belonged to DMN (Tomasi and Volkow, 2011) and associated with memory retrieval (Criss et al., 2013). The temporal gyrus is associated with working memory and cued attention (Corbetta and Shulman, 2002; Fox et al., 2006). Therefore, we speculated that the GMV of right angular gyrus and left middle temporal gyrus were increased in MDD patients in present study may be one of the underlying neural patterns for these clinical symptoms.

In brief, we used the VBM method to analyze the grey matter image of first episode, drug-naive adult patients with EOD or LOD in the present study. We found that the GMV of brain areas that were related to mood regulation was decreased in the first-episode, drug-naive adult patients with MDD. Patients with EOD and LOD exhibited different GMV changes relative to each age-matched comparison group, suggesting patients with different age-onset might have different pathological mechanism.

The limitations of the present study should be noted. First, there is no consensus on age of onset to define EO and LO MDD. The cut-off age in the present study was based on our previous research results. Second, since the present study is a cross-sectional study, we cannot excluded the possibility that some of our patient subjects who manifested as having depressive episode could be later diagnosed as with bipolar

disorder. Further follow-up study may be necessary to clarify the impact of prolonged and recurrent depressive episodes on brain structure in the future. Third, the deficits brain regions might be the anatomical basis for abnormal function of cognitive or emotion processing in MDD. To further investigate the core pathophysiology mechanism in MDD, multi-mode MRI analysis should be performed in future.

Conflict of interest

The authors have no conflicts of interest to disclose.

Acknowledgments

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