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

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ABSTRACT

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,