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Cortical and subcortical gray matter alterations in first-episode drug-naïve adolescents with major depressive disorder

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Major depressive disorder is a major mental disorder affecting adolescents. Cortical thickness provides a sensitive measure of age-associated changes. Previous studies using cortical thickness analysis reported inconsistent results on brain structural changes in adolescent major depressive disorder. The neuroanatomical substrates of major depressive disorder in adolescents are not fully understood. We aimed to compare the anatomical structures of the brain in first-onset drug-naïve adolescents with major depressive disorder to normal controls. Twenty-seven first-episode drug-naïve adolescents with major depressive disorder and an equal number of age-matched control subjects were scanned on a 3T MRI scanner. Comparisons between those two groups were performed using surface-based morphometry analysis for cortical thickness and volumetric analysis of subcortical gray matter. The correlations between morphometric indexes and clinical measures (Hamilton depression rating scale score or children's depression inventory score) were also calculated. We found that the cortical area is thinner in major depressive disorder patients than in controls, specifically in the left occipital area (precuneus and cuneus, cluster-level family-wise corrected $P < 0.05$). The hippocampus volume was also smaller in major depressive disorder patients than in the control group. No significant correlations were found between morphometric indexes (average cortical thickness extracted from the left precuneus cluster and hippocampal volume) and clinical measures. The left occipital cortical regions may have a role in the pathophysiology of adolescent major depressive disorder, and the involvement of the hippocampus is important for pathogenic changes even in the early stages of major depressive disorder.

NeuroReport 2019, **30:**1172–1178

Keywords: adolescence, cortical thickness, depression, drug-naïve, first-onset

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Received 4 July 2019 **Accepted** 16 August 2019

Introduction

Adolescent major depressive disorder (MDD) is associated with increased risk of suicide and long-term functional impairment into adulthood, and patients do not respond well to evidence-based treatments. Therefore, understanding the neurobiological mechanism underlying adolescent MDD has important clinical implications for early diagnosis and proper treatment.

Morphometric analysis of structural MRI has become a widely used method to unveil the neuroanatomical correlates of pathophysiological changes in MDD. Voxel-based morphometry (VBM) is a fully automated, unbiased, whole-brain analytic technique enabling the detection of regionally specific differences in brain tissue composition between groups. Meta-analyses of VBM studies showed significant gray matter (GM) volume reduction in the prefrontal cortex, including the orbitofrontal cortex and the anterior cingulate cortex, and subcortical GM structures such as the hippocampus, amygdala, and thalamus, in MDD patients compared to healthy controls [1]. Although the main findings are not unanimous across the studies, the brain regions of significant volume alterations are widespread and generally accepted to be related with various neuropsychological activities, resulting in abnormal functioning of neural circuits [2].

Although VBM can assess GM changes, this assessment is limited since it provides a mixed measurement of GM that includes surface area, cortical folding, and cortical thickness. An alternative approach to quantify morphometric changes of cortical GM is to measure cortical thickness, which is a well-validated analytic procedure. It can provide complementary information to VBM on the neuroanatomy of brain disorders, by allowing the regional distribution and quantification of cortical GM changes to be specifically examined, as opposed to VBM, which often combines GM and white matter (WM) within regional volumes.

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Cortical thickness analysis studies performed on adult patients with MDD have shown cortical thinning mainly in the prefrontal cortex, but also in other areas, including the parietal cortex, temporal cortex, and anterior cingulate cortex [3].

MDD in adolescents can be simply viewed as an early-onset subform of the equivalent adult disorder, as it is strongly linked with recurrence in later life. However, important differences also exist between the two disorders, including the prominence of irritability, mood reactivity, fluctuating symptoms, and the clinical efficacy of antidepressants in adolescent MDD. Treatment choices are not the same in adolescents as in adults [4]. Moreover, not only the pathophysiology but also the influence of natural brain development on the course of MDD must be considered, making the situation more complex than in adults. Ducharme *et al*. reported that most brain regions showed a linear monotonic decline of cortical thickness so that cortical thickness might be related with developmental maturation [5]. In adolescence, the brain regions related to the affective network are still developing, and their structure can be influenced by the pathophysiological processes of depression [6]. Cortical thickness may also reflect the major functional and structural changes related to MDD pathophysiology during childhood and adolescence.

Some studies investigated cortical thickness in adolescents with MDD and showed inconsistent results about brain structural changes in adolescent MDD [7]. In a meta-analysis of structural neuroimaging studies on MDD, it was associated with volume changes in the frontal lobe, orbitofrontal cortex, and gyrus rectus [8]. In addition, a meta-analysis of structural connectivity in the WM revealed that the involved brain regions also include the occipital lobe [9]. As for subcortical structures, the lateral ventricles, basal ganglia, thalamus, hippocampus, and amygdala have been reported to show volume changes [8,10]. To our knowledge, relatively few studies on brain structure in pediatric affective disorders using cortical thickness analysis have been reported. In this study, we aimed to explore cortical thickness and subcortical GM abnormalities of MDD-related structures identified in previous studies, in a homogeneous group of adolescent MDD patients. To ensure the homogeneity of clinical characteristics, and to minimize the effects of potential confounding factors, we prospectively recruited adolescent, first-episode, drug-naïve patients with MDD. We predicted that patients would have structural GM abnormalities of the cortical regions involved in emotional processing (e.g. medial prefrontal cortex and occipital cortex). We also hypothesized that there would be smaller hippocampal and amygdala volumes in the subcortical regions in MDD patients. We predicted that these anatomical changes would also be reflected in the disease status of the patients, as assessed by their clinical variables (i.e. disease duration and depression scale score).

Materials and methods

Participants

Patients and control subjects between 13 and 18 years of age were included in the study only if they (1) had no current or previous psychiatric disorder (for the MDD group: no other major comorbid psychiatric illnesses, including bipolar disorder and psychotic disorder) and (2) had undergone a full-scale intelligence quotient assessment and obtained an intelligence quotient (IQ) score above 85. Demographic features (e.g. age, gender, and years of education) were collected at baseline. After obtaining informed consent from all participants, they underwent a comprehensive diagnostic assessment. The Korean version of the Kiddies-SADS-Present and Lifetime Version was applied to confirm the diagnosis in all participants [11].

Patients diagnosed with a first episode of MDD as determined using the Diagnosis and Statistical Manual for Mental Disorders-5 criteria, were prospectively recruited from the Child and Adolescent Psychiatry Clinic of the University Hospital. Healthy volunteers matched for age, gender, and education years were prospectively recruited to serve as controls.

Depressive symptoms were scored by the Hamilton depression rating scale (HDRS) and children's depression inventory (CDI) in all patients and controls.

Data acquisition

Participants were scanned on a 3T MR scanner (Siemens Skyra, Erlangen, Germany) with a 64-channel phased-array head coil. For identification of structural abnormalities, axial fluid-attenuated inversion recovery images were acquired with the following parameters: repetition time (TR) = 9000 ms, echo time (TE) = 77 ms, Inversion Time = 2500 ms, matrix = 256 × 166, field of view (FOV) = 145 × 220 mm, slice thickness = 5 mm. For volumetric analysis, a high-resolution 3D magnetization-prepared rapid gradient-echo sequence was acquired using the following parameters: 192 continuous sagittal slices, TR = 2300 ms, TE = 2.32 ms, matrix = 256 × 256, FOV = 230 × 230 mm, voxel size = 0.9 mm^3. Diffusion tensor imaging and resting-state functional MR images were also acquired simultaneously but were not included in the current study. The MR images were visually inspected for structural abnormalities and artifacts from head motion or dental instruments. One control subject and 4 patients were excluded from the analysis due to structural abnormalities (i.e. ventriculomegaly, focal cortical encephalomalacia) or poor image quality from excessive head motion.

Surface-based morphometry analysis

Data preprocessing, cortical surface extraction, and statistical analyses were carried out using the Computational Anatomy Toolbox (CAT12; http://dbm.neuro.uni-jena.de/cat/), an extension toolkit of the Statistical Parametric Mapping software package (SPM12;

http://www.fil.ion.ucl.ac.uk/spm/) running in MATLAB (R2014a; MathWorks, Natick, Massachusetts, USA). CAT12 provides a fully automated processing pipeline for surface-based morphometry, including a recent but well-established algorithm for cortical surface extraction [12]. This method allows computing multiple morphometric parameters, including cortical thickness and gyrification index, based on the absolute mean curvature approach [13].

For MRI data preprocessing, we used the default parameters described in the CAT12 manual. Briefly, high-resolution T1-weighted MR images underwent tissue segmentation to estimate WM distance. Local maxima were then projected to other GM voxels by using a neighbor relationship described by the WM distance. These values are equal to the cortical thickness. This projection-based method also includes partial volume correction, sulcal blurring, and sulcal asymmetries without sulcus reconstruction. Topological correction is performed through a spherical harmonics-based approach. For inter-participant analysis, an algorithm for spherical mapping of the cortical surface was included [14]. An adapted volume-based diffeomorphic DARTEL algorithm was applied to the surface for spherical registration. For group comparison, the cortical thickness maps of the left and right hemispheres were re-parameterized into a common coordinate system and smoothed with a 15 mm full-width half-maximum Gaussian kernel. Group comparisons of cortical thickness between patients and controls were assessed using a two-sample *t*-test correcting for age, sex, and IQ. Statistical parametric maps were thresholded at a voxel-level height threshold of $P < 0.001$ and a cluster-level extent threshold of $P < 0.05$, corrected for multiple comparisons using family-wise error.

Volumetric analysis of subcortical gray matter

Image preprocessing and volumetric measurements were performed using the FMRIB's Software Library (FSL 5.0.9, https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/) on the basis of volume definitions of the three-dimensional Montreal Neurological Institute (MNI) 152 standard space. Automated segmentation of subcortical GM was carried out using FIRST (FMRIB's Integrated Registration and Segmentation) using a Bayesian probabilistic approach [15]. Briefly, registration in FIRST comprises an affine transformation (12 degrees of freedom) of the raw, volumetric T1-weighted images to the MNI 152 standard space. After subcortical registration, subcortical masks were applied to locate the subcortical structures, followed by segmentation based on shape models and voxel intensities. All segmentations were visually inspected for accuracy. Absolute volumes of the bilateral accumbens, amygdala, hippocampus, caudate, pallidum, putamen, and thalamus were measured in cubic millimeters. To reduce the effects of inter-individual variability in head size, a volumetric scaling factor was obtained for each subject with the SIENAX tool (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/SIENA) from the corresponding volumetric T1-weighted image. Thus, the normalized volume for each GM was obtained by multiplying the measured volume from FIRST by the volumetric scaling factor from SIENAX. Data were first tested for normality of distribution and homogeneity of variance using the Kolmogorov–Smirnov and Levene tests, respectively. Differences in normalized volumes of the 14 GM structures between patients and controls were assessed by analysis of covariance correcting for age, gender, and IQ score. Possible relationships were explored between the normalized volumes of 14 GM structures and depression scale scores using Pearson correlations. A *P*-value less than 0.05 was considered significant. We did not perform a post-hoc Bonferroni correction as we thought it was not essential and could be deleterious to significant statistical inference [16]. Statistical analyses were performed with the Statistical Package for Social Sciences (SPSS, Version 21.0; IBM, Armonk, New York, USA).

Results

Demographic and clinical characteristics of the 27 MDD patients and the 27 controls are detailed in Table 1. Patients and controls did not differ in age, gender, or education years (all $P > 0.05$). MDD patients had higher HDRS and CDI scores, and lower IQ score, than controls (all $P < 0.001$).

The pattern of average cortical thickness of the patients was similar to that of controls (Fig. 1). The global average cortical thickness was not different between patients (2.94 ± 0.09 mm) and controls (2.94 ± 0.07 mm, $P = 0.959$), but MDD patients exhibited a single cluster of significant cortical thinning in the left precuneus (MNI coordinates = −11/−68/33, peak z-value = 3.55, cluster extent = 608 voxels, cluster-level family-wise error corrected $P = 0.033$) (Fig. 2). No region of significant cortical thickening was found in patients relative to controls at the same statistical threshold. The average cortical thickness extracted from the left precuneus cluster failed to show significant correlations with the HDRS or the CDI score (both $P > 0.05$).

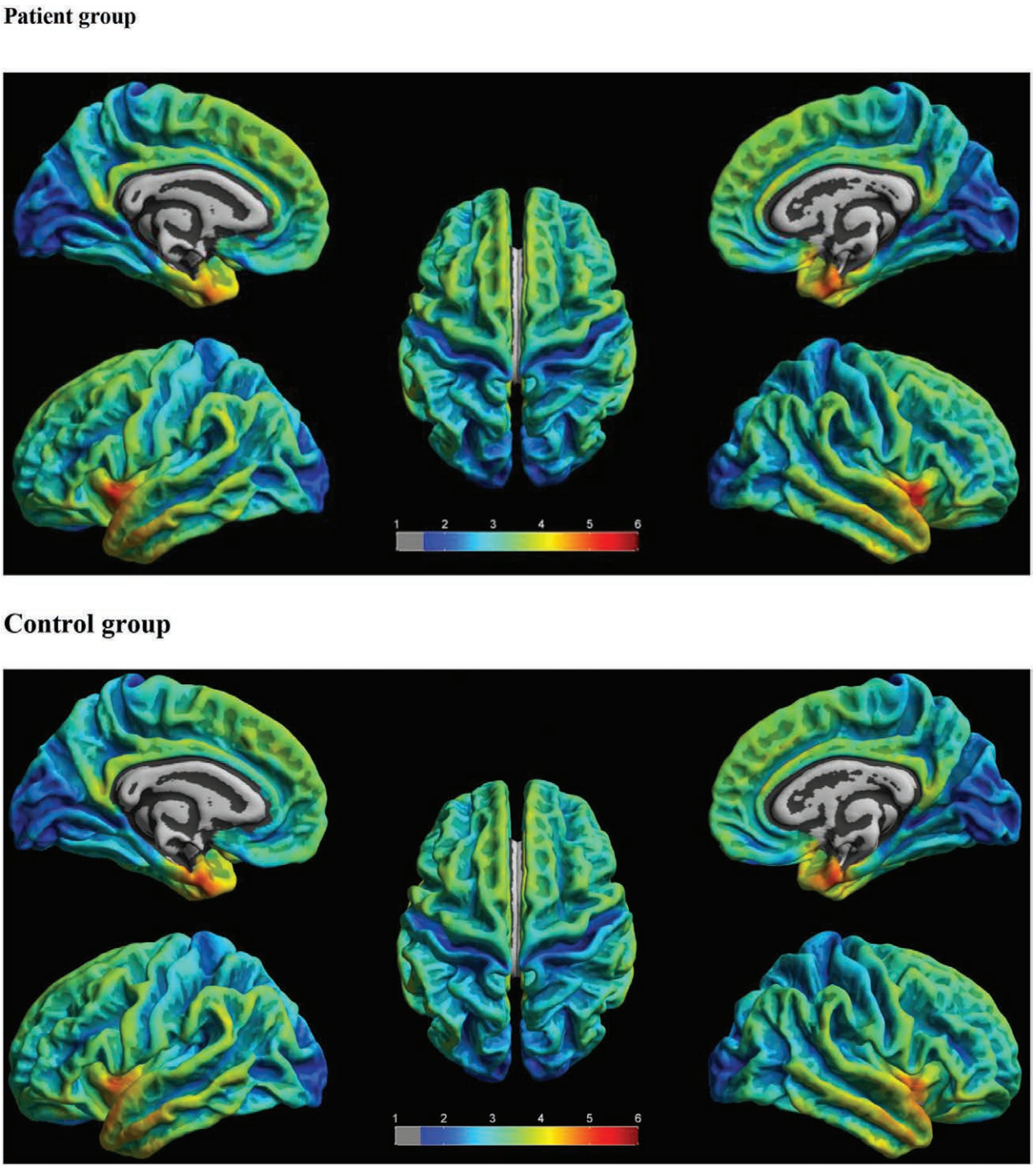
Normalized volumes for the 14 subcortical GM structures and statistical results are summarized in Table 2. Compared to controls, patients had significant volume

Table 1 Demographic and clinical data

	MDD patients	Controls	*P*-value
No. of subjects	27	27	
Sex (female:male)	18:9	22:5	0.176
Age (years)	15.5 ± 1.7	16.0 ± 1.0	0.217
Education (years)	9.9 ± 1.9	10.0 ± 0.9	0.715
Intelligence quotient	102.0 ± 12.4	123.4 ± 12.9	< 0.001
HDRS	20.7 ± 3.7	0.1 ± 0.4	< 0.001
CDI	27.0 ± 9.0	5.5 ± 4.7	< 0.001

CDI, children's depression inventory; HDRS, Hamilton depression rating scale; MDD, Major depressive disorder.

Fig. 1



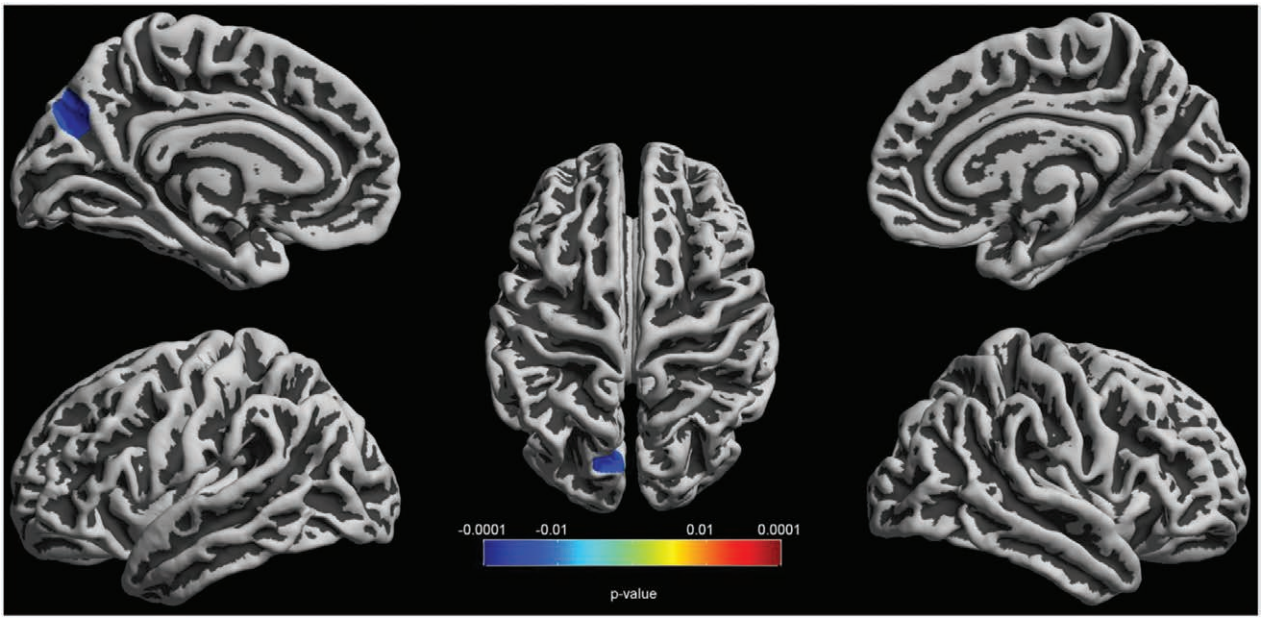
Cortical thickness in participants in the patient and control groups (top and bottom panels, respectively).

reductions in the left and right hippocampus ($F_{1,49}$ = 5.847, P = 0.019; $F_{1,49}$ = 5.283, P = 0.026, respectively). There were no significant differences in normalized volumes of the bilateral accumbens, amygdala, caudate, pallidum, putamen, and thalamus between controls and patients (all $P > 0.05$). No significant correlations were found between hippocampal volumes and HDRS or CDI score (all $P > 0.05$).

Discussion

We examined cortical and subcortical GM abnormalities in a homogeneous group of adolescents, first-episode,

Fig. 2



Comparison of cortical thickness–left hemisphere: thinner in MDD patients than in controls, cluster-level family-wise-corrected $P < 0.05$. MDD, major depressive disorder.

Table 2 Brain compartment volumes and normalized volumes for the subcortical gray matter structures

	MDD patients	Controls	Cohen's d	*P*-value
Total gray matter (cm^3)	781.9 ± 71.0	785.9 ± 62.2	0.06	0.825
Total white matter (cm^3)	427.9 ± 44.8	428.3 ± 43.1	0.01	0.974
Cerebrospinal fluid (cm^3)	243.8 ± 45.6	244.4 ± 43.8	0.01	0.964
L accumbens (mm^3)	749.9 ± 130.5	746.9 ± 142.5	0.02	0.494
R accumbens (mm^3)	593.3 ± 98.6	586.2 ± 130.3	0.06	0.396
L amygdala (mm^3)	1878.2 ± 264.6	1906.5 ± 279.8	0.10	0.985
R amygdala (mm^3)	1786.7 ± 324.0	1899.6 ± 252.9	0.39	0.180
L hippocampus (mm^3)	5094.7 ± 483.7	5299.7 ± 408.2	0.46	0.019
R hippocampus (mm^3)	5209.2 ± 421.8	5498.6 ± 369.8	0.73	0.026
L caudate (mm^3)	5080.9 ± 495.1	5069.3 ± 484.1	0.02	0.947
R caudate (mm^3)	5225.0 ± 590.3	5226.9 ± 521.9	0.00	0.996
L pallidum (mm^3)	2424.8 ± 192.8	2419.9 ± 167.7	0.03	0.838
R pallidum (mm^3)	2444.8 ± 145.1	2447.4 ± 131.8	0.02	0.952
L putamen (mm^3)	7065.4 ± 549.2	7074.0 ± 500.6	0.02	0.689
R putamen (mm^3)	6962.4 ± 586.9	7097.7 ± 590.7	0.23	0.890
L thalamus (mm^3)	11 348.0 ± 621.7	11 385.9 ± 503.6	0.07	0.747
R thalamus (mm^3)	11 133.4 ± 590.0	11 156.0 ± 555.8	0.04	0.399

Cohen's d indicates the effect size of the difference between groups.
MDD, major depressive disorder.

drug-naïve MDD patients. We observed that, compared to matched controls, adolescent MDD patients showed a reduction in cortical thickness in the left cuneus/precuneus and a reduction in hippocampal volume. The posterior medial cortex regions, including precuneus and cuneus, have been related to adult MDD. As far as we know, changes of cortical thickness in the posterior occipital cortex in adolescent MDD have not been reported.

Few studies have investigated cortical thickness changes in adolescent MDD. MDD has multivariate structure of abnormalities, and researchers thinks that MDD is associated with widespread neurobiological difficulties in areas distributed across the brain and involves alterations in structural brain networks [17]. And, the results of the structural studies in these areas for adolescent MDD are not consistent. The right and left rostral middle frontal gyri and the left caudal anterior cingulate cortex in MDD adolescents were thicker than in controls [18]. Falluca *et al.* reported that the pericalcarine gyrus, the postcentral gyrus, and the superior parietal gyrus in the right hemisphere, and the supramarginal gyrus in the left hemisphere were thinner in pediatric patients with MDD

than in healthy controls [19]. Recently, Schmaal *et al.* reported cortical abnormalities in adults and adolescents with MDD, based on brain scans from 20 cohorts worldwide. Compared to matched controls, adolescents with MDD showed no difference in cortical thickness [7]. The inconsistent findings between these studies could not be entirely explained but might be partly attributed to genetic heterogeneity and differences in sample size, MRI parameters, analytic approach, statistical threshold, and selection of covariates. Clinical complexities and confounders within the patient population, such as duration of illness, number of episodes, and medications may also account for such inconsistencies.

Fallucca *et al.* reported that the cortical thickness in the cuneus of MDD patients with was not different from that in healthy controls [19]. However, there are also some different study results. Ducharme *et al.* reported that anxious/depressed scores in the child behavior checklist were positively associated with precuneus and posterior cingulate cortical thickness in healthy young adults [20]. Cortical thinning was observed in the left hemisphere, including the precuneus and cuneus, even in subjects at increased familial risk for major depression in another study [21]. This result is compatible with our results in adolescents, showing that drug-naïve MDD adolescents have thinner cortical thickness in the cuneus/precuneus even at the first episode.

There are also some studies about the inclusion of occipital regions in MDD. A whole-brain voxel-based meta-analysis of diffusion tensor imaging in patients with MDD identified consistent locations of decreased fractional anisotropy including the occipital lobe [9]. Qiu *et al.* recruited medication-naive adult patients with first-episode depression and healthy controls and tried to characterize MDD using a multiparametric classification approach based on high-resolution structural images. They reported that regions including the lateral occipital gyrus contributed to the identification of patients with MDD in the cortical thickness discrimination map [22]. In another study using different research methods such as regional cerebral blood flow single photon emission computed tomography on drug-naïve children with a diagnosis of MDD, occipital brain perfusion deficits were observed [23]. Therefore, we can conclude that the left occipital cortical regions shown in our study results may have a role in the pathophysiology of adolescent MDD and that the direction of the changes might depend on the specific clinical characteristics.

Regarding subcortical structure volumes, some studies reported significant changes in adolescents. MDD adolescents showed increased pituitary gland volumes [24], increased adrenal gland volumes [25], decreased amygdala volumes [26], and reductions in the left, right, or both [27] hippocampal volumes. In summary, the findings of comparisons between MDD and controls in adolescents are rather controversial and inconclusive, and these inconsistencies come from variable scanning and analysis methods, as well as clinical variation in medication [7]. The hippocampus is known to have a role in stress, learning, and more specific cognitive processes such as rumination [28]. Accordingly, we may expect its involvement in depression. Some researchers did not report differences in hippocampal volume between adolescents and healthy controls [26]. However, other researchers reported smaller hippocampal volumes in depressed adolescents and even in those at risk [27]. Our results are in line with those previous reports: Hippocampal volume reduction was shown even in first-episode, drug-naïve MDD adolescents. This suggests that the hippocampus is important for pathogenetic alterations even in the early stages of MDD.

Our study has some potential limitations. First, this has relatively small sample size. Second, as our sample included only the patients who visited university hospital, the generalizability can be limited. Last, the normalized volume was obtained by multiplying the measured volume from FIRST by the volumetric scaling factor from SIENAX to control for different brain sizes and intracranial volume. As brain size increases, increased speed of information transfer by the cortical fiber system is also required, and there is an increase in cerebral WM volume. Consequently, brain compartmental measures do not increase linearly with brain size, and the relationship between these parameters is not proportional. Accordingly, our normalization technique could have biased our analyses in an unpredictable manner [29].

Conclusions

The major strength of our study is the inclusion of first-ever, drug-naïve patients. We examined and compared cortical thickness and volumes of subcortical structures between MDD adolescents and healthy controls. The participants are unique in that all of them were naïve to psychotropic drugs. These results implicate that the adolescent brain still has the potential to change structurally due to depression, even in the first episode. In further studies, we will need to keep pursuing the alteration of brain structures in the various stages of depression, since the adolescent brain is still undergoing a maturation cycle and is vulnerable to the pathophysiological influences of MDD.

Acknowledgements

This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (grant number NRF-2014R1A1A2054904 and NRF-2017R1D1A1B03028672).

Conflicts of interest

There are no conflicts of interest.

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