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## Research Report

## Cortical thickness, cortical and subcortical volume, and white matter integrity in patients with their first episode of major depression

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## ABSTRACT

**Background:** The uncertainty over the true morphological changes in brains with major depressive disorder (MDD) underlines the necessity of comprehensive studies with multimodal structural brain imaging analyses. This study aimed to evaluate the differences in cortical thickness, cortical and subcortical volume, and white matter integrity between first episode, medication-naïve MDD patients and healthy controls.

**Methods:** Subjects with their first episode of MDD whose illness duration had not exceeded 6 months ( $n=20$ ) were enrolled in this study and were compared to age-, sex-, and education level-matched healthy controls ( $n=22$ ). All participants were subjected to T1-weighted structural magnetic resonance imaging (MRI). We used an automated procedure of FreeSurfer and Tract-based spatial statistics (TBSS) to analyze differences in cortical thickness, cortical and subcortical volume, and white matter integrity between two groups.

**Results:** The patients with first episode MDD exhibited significantly reduced cortical volume in the caudal anterior cingulate gyrus ( $P < 0.0015$ ) compared to healthy controls. We also observed altered white matter integrity in the body of the corpus callosum ( $P < 0.01$ ), reduced cortical volume of the caudal middle frontal gyrus and medial orbitofrontal gyrus, and enlarged hippocampal volume in the first episode MDD patients.

**Limitations:** We relied on a relatively small sample size and cortical volume reduction in several brain regions was not replicated in the analysis of cortical thickness.

**Conclusions:** Using multimodal imaging analyses on medication-naïve first episode MDD patients, we demonstrated fundamental structural alteration of brain gray and white matter, such as reduced cortical volume of the caudal ACC and white matter integrity in the body of the corpus callosum.

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## 1. Introduction

Several neurobiological models of major depressive disorder (MDD) have been proposed to explain the underlying mechanism by emphasizing the possible role of dysfunctional limbic–cortical networks in MDD (Phillips et al., 2008). The limbic–cortical dysregulation model conceptualizes the etiology of MDD as disturbances in the network of several brain regions responsible for regulating emotional processing (Phillips et al., 2008). Indeed, cumulative structural neuroimaging studies on MDD have consistently revealed that brain regions related to this model show

altered gray matter volume in MDD patients. These regions include the anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (DLPFC), orbitofrontal cortex (OFC) and amygdala (Bora et al., 2012), (Drevets et al., 2008). However, structural neuroimaging studies of MDD have produced inconsistent findings. These inconsistencies might be attributable to the heterogeneity of MDD patients, such as the influence of chronic or recurrent episodes of MDD (Du et al., 2012), differences in medication status (Koolschijn et al., 2009), and the diversity of applied neuroimaging techniques. Multiple recurrent episodes of MDD also could influence the observed volumetric abnormalities, such as reduction in ACC and hippocampal volume due to the neurotoxic effect of recurrent or chronic MDD (Yucel et al., 2008). Additionally, the neurotrophic effects of antidepressants could impact particular brain regions (Duman and Monteggia, 2006). Avoiding interference of these factors on the results of volumetric studies is particularly difficult

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when studying MDD. To this end, a few studies have attempted to recruit first episode, medication-naïve MDD patients as subjects in order to elucidate trait factors (rather than state factors) underlying structural brain changes in MDD (Du et al., 2012).

Several methods are available to closely measure morphological changes in the brain. The manual volumetric region-of-interest (ROI) method has evolved into the fully automated, whole-brain voxel-based morphometry (VBM) method (Ashburner and Friston, 2000). VBM overcomes several limitations of the ROI approach, including researchers' subjectivity, *a priori* specification of ROIs, and replicability of analysis, and it allows for more powerful and unbiased analytical tools (Du et al., 2012). Beyond whole-brain VBM analysis, automated procedures have been developed more recently that can estimate cortical thickness and white matter integrity. These estimates serve as more accurate indicators of the integrity of cortical cytoarchitecture (Rakic et al., 2004) and white matter tracts (Smith et al., 2006) using magnetic resonance image (MRI) scans. However, recent analyses of cortical thickness in MDD patients have reported somewhat inconsistent results regarding several brain regions, including the ACC and frontal and temporal gyri (Lim et al., 2012). Others have reported negative findings (Koolschijn et al., 2009; Colloby et al., 2011) due to heterogeneities in subjects with respect to illness duration, recurrence, age or medication status. Several studies using diffusion tensor image (DTI) of first episode, medication-naïve, non-geriatric MDD patients reported that MDD patients showed impaired integrity in several white matter regions (Zhu et al., 2011; Guo et al., 2012). However, these studies only conducted a single analysis on white matter tract and did not perform a multimodal approach including analysis on cortical and subcortical volume or cortical thickness.

For these reasons, there has been an increasing necessity for comprehensive neuroimaging studies investigating brain alterations of MDD patients with new strategies of multimodal structural brain imaging analyses and well controlled study designs for illness chronicity, recurrence, and medication status, in order to elucidate the fundamental morphological changes in the brains of patients with MDD. To the best of our knowledge, this is the first study to combine analyses of cortical thickness, cortical and subcortical volume, and white matter integrity in first episode, medication-naïve MDD patients compared with healthy controls. Our main hypothesis was that patients with first episode MDD would exhibit characteristic gray and white matter abnormalities in the corticolimbic region compared to healthy controls.

## 2. Methods

### 2.1. Participants

A total of 20 patients diagnosed with their first episode MDD whose illness durations did not exceed 6 months were recruited from the outpatient psychiatric clinic of Korea University Anam Hospital located in Seoul, South Korea. Inclusion criteria for the patient group were (1) having their first episode of major depression; (2) currently experiencing a major depressive episode with a score of 10 or greater on the 17-item Hamilton Depression Rating Scale (HDRS); and (3) a duration of major depression not exceeding 6 months. The exclusion criteria were (1) presumptive primary comorbid diagnosis of any other major psychiatric illness, including anxiety disorders and substance abuse or dependence within the last 6 months based on DSM-IV criteria; (2) suffering from serious or unstable medical illness; and (3) primary neurological illness, such as cerebrovascular disease, Parkinson's disease, and epilepsy. Using the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I), trained psychiatrists examined all of the first episode MDD patients. The duration of illness for MDD was

assessed in an interview by using the life-chart methodology. Twenty-two healthy age-, sex-, and education-level matched controls without histories of psychiatric problems were recruited by advertisements from the community. The age of subjects in both groups ranged from 23 to 65 years. All subjects in both groups were right-handed, as revealed by the Edinburgh Handedness Test (Oldfield, 1971). The severity of depressive symptoms was evaluated in both subject groups on the day as the MRI scan by using HDRS. All patients with first episode MDD were drug-naïve at the time of enrollment. In accordance with the Declaration of Helsinki, all subjects gave informed consent to participate in the study, and the study protocol was approved by the ethics committee of the Korea University Anam Hospital.

### 2.2. MRI data acquisition

Three-dimensional structural MRI scans were acquired from a 3.0T Siemens Trio whole-body imaging system (Siemens Medical Systems, Iselin, NJ, USA), using a T1-weighted magnetization-prepared rapid gradient-echo MP-RAGE (1900 ms repetition time, 2.6 ms echo time, 220 mm field of view, 256 × 256 matrix size, 176 coronal slices without gap, 1 × 1 × 1 mm<sup>3</sup> voxels, 16° flip angle, number of excitations=1). Diffusion tensor images (DTI) were acquired using an echo-planar imaging (EPI) sequence with the following parameters: repetition time (TR): 6300 ms; echo time (TE): 84 ms; field of view (FOV): 230 mm; 128 × 128 matrix; 3 mm slice thickness with no gap; voxel size 1.8 × 1.8 × 3.0 mm<sup>3</sup>; diffusion directions=20; number of slices=50; *b*-values: 0 and 600 s/mm<sup>2</sup>; acceleration factor (iPAT-GRAPPA) 2 with 38 reference lines for phase encoding direction and 6/8-phase partial Fourier.

### 2.3. Cortical thickness analysis

Cortical thickness analyses were performed on the three-dimensional model of cortical surface reconstructions computed from T1 images using the FreeSurfer 5.0 software package (Massachusetts General Hospital, Boston, U.S., <http://surfer.nmr.mgh.harvard.edu>). The details of technical aspects in these procedures have been described in the previous publication (Fischl and Dale, 2000). Briefly, the implanted processing stream involved motion correction of volumetric T1-weighted images, removal of non-brain tissue using a hybrid watershed/surface deformation procedure, automated Talairach transformation of each subject's native brain, segmentation of the gray matter–white matter volumetric structures (Fischl et al., 2004), inflation of cortical surface to an average spherical surface to locate both the pial surface and the gray matter–white matter boundary, intensity normalization, and automated topology correction (Segonne et al., 2007). Transition of gray/white matter and pial boundary was indicated by detecting the greatest shift in intensity through surface deformation. The entire cortex of each subject was then visually confirmed for accuracies in segmentation. The entire cerebral cortex was parcellated into 33 anatomical structures (Fischl et al., 2004). The computed cortical thickness was defined as the shortest distance between the pial surface and the gray matter–white matter boundary at each given point across the cortex. The cortical maps were generated by computing mean cortical thickness for each subject at each vertex, right and left hemispheres separately, and mapping these data to the surface of an average brain template enabling visualization of data across the entire cortical surface (Fischl and Dale, 2000). Smoothing with a Gaussian kernel of 10 mm of each subject at half-maximum was performed on the cortical maps of full width for the entire cortex analyses.

## 2.4. Cortical and subcortical volume analysis

The cortical and subcortical volumes were calculated by the automated procedure for volumetric measures of the brain structures implemented in FreeSurfer. The procedures regarding segmentation and assignment of a neuroanatomical label to each voxel based on probabilistic information automatically estimated from a manually labeled training set were previously described (Fischl et al., 2004). We obtained cortical volumes of 33 parcellated regions in the entire cortex of each hemisphere, and 6 subcortical structural volumes (hippocampus, amygdala, caudate, thalamus, pallidum, and putamen) were extracted from a total of 27 subcortical structures of each hemisphere.

## 2.5. White matter analysis

All diffusion tensor images were processed using software tools from the Functional MRI of the Brain (FMRIB) software library (FSL version 4.1.9, Oxford, U.K., <http://www.fmrib.ox.ac.uk/fsl/>) for pre-processing of raw DTI data (Smith et al., 2004). A voxel-wise statistical analysis of the fractional anisotropy (FA) data was performed using Tract-based spatial statistics (TBSS) version 1.2 (Smith et al., 2006). First, the head movement and eddy current distortions of raw data from each subject were corrected. Then, we used a brain extraction tool (BET) to generate a single binarized brain mask in diffusion space, with 1 s inside the brain and 0 s outside the brain ( $b=0$ ). After these steps, the diffusion tensor models were fitted for each voxel within the brain mask, and then the FA images were created. Non-linear alignment of each subjects' FA images into 1 mm × 1 mm × 1 mm Montreal Neurologic Institute standard space was performed using a FMRIB58 FA template. After non-linearly transformed FA images were applied to the each subjects' original FA images to generate the averaged FA image, a mean FA skeleton image embodying the center of all tracts derived from the white matter of the whole subjects was created. The FA threshold of 0.20 or higher was set to include the major white matter tracts, and to exclude unnecessary peripheral tracts.

## 2.6. Statistical analyses

Group differences in demographic and clinical characteristics of the first episode MDD patients and healthy controls were analyzed using the Mann–Whitney test for continuous variables (age, education and HDRS scores) and chi-square tests for categorical variables (sex).

### 2.6.1. Cortical thickness

We used a general linear model (GLM) to estimate differences in cortical thickness between the subjects with first episode MDD and healthy controls at each vertex of the surface, controlling for age, sex, and intracranial volume (ICV) as covariates, and separately testing the right and left hemispheres. For multiple comparisons correction, family-wise error correction  $P < 0.05$  using the Monte Carlo Null-Z simulation with 10,000 permutations was applied. This approach is implemented in FreeSurfer and is based on the AlphaSim algorithm (Ward, 2000).

### 2.6.2. Cortical and subcortical volume

Automatically derived outcomes of cortical and subcortical volumes from FreeSurfer were analyzed using a GLM with individual volumes as dependent variables, group as an independent variable, and age, sex and ICV as covariates. Bonferroni's correction for multiple comparisons was applied with a significance level of  $P < 0.0015$  ( $P < 0.05/33$  number of comparisons in each

hemisphere) to cortical volume analysis of 33 regions and a significance level of  $P < 0.008$  ( $P < 0.05/6$  number of comparisons in each hemisphere) to analysis of 6 subcortical structural volumes. Both corrected and uncorrected probability values are presented in this study. The statistical analyses were performed using SPSS version 12.0 (SPSS Inc., Chicago, IL, USA).

### 2.6.3. White matter

The FSL Randomize procedure (version 2.1) was used in voxel-wise cross-subject statistics, and these were applied to skeletonized data for each subjects of both groups. The FA comparisons were performed using 5000 permutations with threshold-free cluster enhancement (TFCE) methods (Smith and Nichols, 2009). The definitions of significance level as (i)  $P < 0.01$  uncorrected for multiple comparisons or (ii) family-wise error (FWE)-corrected  $P < 0.05$  were applied to group comparison between the first episode MDD patients and healthy controls. Significant regions with more than 50 voxels were reported in this study. We identified anatomical localization of significant white matter clusters with the aid of human white matter anatomy (Mori et al., 2008).

## 3. Results

### 3.1. Demographic and clinical characteristics

Age, sex, years of education, duration of illness, and HDRS scores of 20 patients with their first episode of MDD and 20 healthy controls are shown in Table 1. The first episode MDD group and healthy control group did not differ significantly in terms of age, sex, and years of education. The mean duration of illness in the patients with first episode MDD was  $4.40 \pm 1.35$  months.

### 3.2. Cortical thickness analysis

There were no significant differences between subjects with the first episode MDD and healthy controls in terms of cortical thickness across the entire cortical mantle in both cerebral hemispheres.

### 3.3. Cortical and subcortical volume analysis

Cortical volume reductions of the left caudal ACC, right medial OFC, and left caudal middle frontal cortex were detected in the first episode MDD group, compared to healthy controls (at statistical level of  $P < 0.05$ , uncorrected). Only the difference in left caudal ACC volume remained significant after Bonferroni

**Table 1**  
Demographic and clinical characteristics of first episode major depressive disorder patients and healthy controls.

Characteristic	First episode MDD ( $n=20$ )	Healthy controls ( $n=22$ )	<i>P</i> -value
Age (Years)	42.70 ± 12.43	43.73 ± 12.25	0.810
Sex (Male/Female)	5/15	7/15	0.625
Education (Years)	13.06 ± 2.46	14.00 ± 3.20	0.237
Duration of illness (Months)	4.40 ± 1.35		
HDRS scores	19.05 ± 6.74	2.30 ± 2.32	< 0.001

Data are mean ± standard deviation, except sex distribution.

The *P* value for sex distribution was obtained by chi-square test.

The *P* values for comparison in age, education years, and HDRS scores were obtained using the Mann–Whitney test.

MDD, major depressive disorder; HDRS, Hamilton Depression Rating Scale.

**Table 2**

Regional cortical and subcortical volume differences between first episode major depressive disorder group and healthy controls based on FreeSurfer analyses.

Cortical and subcortical regions	Volume (mm <sup>3</sup> ), Mean $\pm$ S.D.		General linear model (GLM)	
	First episode MDD	Healthy controls	F	P-value
<b>Left hemisphere</b>				
Caudal anterior cingulate gyrus	1597.30 $\pm$ 318.61	2015.23 $\pm$ 453.37	12.76	0.001 <sup>a</sup>
Lingual gyrus	6567.7 $\pm$ 1106.15	6150.36 $\pm$ 1031.97	4.60	0.039
Parahippocampal gyrus	2247.45 $\pm$ 329.74	2096.5 $\pm$ 288.62	4.49	0.041
Caudal middle frontal gyrus	6112.65 $\pm$ 1021.54	6897.72 $\pm$ 1124.35	4.22	0.047
Hippocampus	4126.25 $\pm$ 318.72	3941.68 $\pm$ 415.59	5.25	0.028
<b>Right hemisphere</b>				
Pericalcarine gyrus	2304.55 $\pm$ 383.94	2106.05 $\pm$ 299.71	5.60	0.023
Medial orbitofrontal gyrus	4971.85 $\pm$ 549.57	5313.36 $\pm$ 480.42	4.72	0.036
Hippocampus	4367.55 $\pm$ 409.11	4194.91 $\pm$ 427.46	4.39	0.043

MDD, major depressive disorder; S.D., standard deviation.

The general linear model (GLM) was adjusted for age, sex, and intracranial volume (ICV) as covariates. Only data with a significant difference between groups are reported.

<sup>a</sup> Regions that remained significant after Bonferroni correction are marked with an asterisk. Bonferroni correction within each hemisphere was applied: 33 regions of the cortex, corrected  $P=(0.05/33)=0.0015$ ; 6 regions of the subcortex, corrected  $P=(0.05/6)=0.008$ .

correction of  $P < 0.0015$ . The bilateral hippocampi, right pericalcarine gyrus, left lingual gyrus, and left parahippocampal gyrus in the first episode MDD patients had an enlarged volume at the significance level of  $P < 0.05$  (uncorrected), compared to healthy controls. Regional cortical and subcortical volumes with significant differences between the first episode MDD group and healthy control group are shown in Table 2.

#### 3.4. White matter analysis

In a voxel-wise analysis of brain white matter tracts, the body of the corpus callosum was the only brain region revealed to have reduced FA in MDD patients compared to healthy controls (The same result was obtained on statistical threshold of uncorrected  $P < 0.01$  or FWE-corrected  $P < 0.05$ ), as shown in Table 2 and Fig. 1.

#### 3.5. Correlation analysis

As a post-hoc analysis, two-tailed Pearson partial correlation analysis controlling for age, gender, and ICV was performed between the parameters of left caudal ACC and the body of the corpus callosum in the both group and the clinical variables including the duration of illness and HDRS score. The statistical threshold was  $P < 0.05$  Table 3.

There was a significant inverse correlation between the volume of left caudal ACC and HDRS score ( $r = -0.404$ ,  $P = 0.014$ ). The FA value in the body of the corpus callosum was also inversely correlated with HDRS score on significant statistical level ( $r = -0.417$ ,  $P = 0.034$ ). However, the duration of illness was not correlated with the left caudal ACC volume or FA in the body of the corpus callosum.

## 4. Discussion

To our knowledge, this is the first study to elucidate the structural brain alterations present in first episode, medication-naïve MDD patients by simultaneously measuring cortical thickness, cortical and subcortical volume, and white matter integrity. Adoption of multimodality in the brain imaging analyses enabled us to perform more comprehensive examinations. Furthermore, the relatively short duration of illness (4.4 months) in our MDD patients compared with those of the recent VBM studies (Du et al., 2012), facilitated a closer analysis of trait-dependent abnormalities in the brain of the depressive patients.

**Table 3**

Areas with reduced fractional anisotropy in patients with their first episode of major depressive disorder compared with healthy controls.

White matter tract	X	Y	Z	Z-max	Voxels
Body of corpus callosum	2	3	24	0.995	64

Only areas with significantly reduced fractional anisotropy are presented. ( $P < 0.01$ , uncorrected), X, Y, and Z are Montreal Neurological Institute (MNI) coordinates.

Experiment/  
VBM Analysis

Our main findings are that the patients with first episode MDD have significantly reduced cortical volume of the caudal ACC and altered white matter integrity in the body of the corpus callosum compared to healthy controls. The reduced caudal ACC volume reported in this study is supported by previous studies based on the VBM method (Bora et al., 2012; Du et al., 2012). ACC abnormalities in MDD have been revealed in post-mortem studies, altered glucose metabolism and its correlation with symptom severity in MDD patients (Lai, 2012). Numerous pieces of evidence have suggested that the ACC plays a critical role in emotional regulation (Phillips et al., 2008), and several structural and functional brain imaging studies have indicated that the ACC is highly related to impairments in emotional processing in MDD (Lai, 2012). Cumulative reports have shown that MDD is associated with dysregulated inter-connections within limbic-cortical structures, especially the ACC and amygdala (Matthews et al., 2008). This dysregulation suggests that MDD patients may receive decreased inhibitory feedback from the caudal ACC to the amygdala. Based on the limbic-cortical dysregulation model characterized by hyperactivity of an emotion processing circuit and hypoactivity of a functionally connected control network (Phillips et al., 2008), we postulate that our result of caudal ACC volume reduction in the first episode of MDD might be a etiological trait factor of depression. Volume reduction in this region could lead to impaired inhibitory feedback from the caudal ACC to the amygdala and eventually trigger a cascade of emotional dysregulation in MDD. There were some limitations in our study that prevented us from clarifying whether caudal ACC volume reduction is a premorbid risk factor for developing MDD, or whether it is an initial structural change induced in the early phase of MDD. We concluded that this finding is a trait factor of MDD based on a comprehensive review of numerous brain imaging studies regarding MDD and its neurobiological basis. In accordance with our conclusion, all of the three recently published meta-analyses on whole-brain VBM studies in MDD identified that volume reduction in the ACC was the most robust finding among





**Fig. 1.** White matter structures with significantly reduced fractional anisotropy (FA) in first episode major depressive disorder (MDD) patients in the body of the corpus callosum ( $P < 0.01$ , uncorrected). The maps of FA show axial and sagittal views. The background image is the standard MNI 152 brain template. Green voxels represent the white matter skeleton of FA. Red–yellow voxels represent brain regions with reduced FA in patients with first episode MDD compared with healthy controls. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

the brain regions reported (Bora et al., 2012; Lai, 2012; Du et al., 2012). Our result reaffirms the alteration of ACC volume that has been consistently reported by numerous structural neuroimaging studies on MDD.

The FA in the body of the corpus callosum was decreased in patients with first episode MDD compared to healthy controls. Decreased FA in the corpus callosum has been reported in patients with first episode MDD, geriatric depression, and chronic recurrent MDD (Murphy and Frodl, 2011). Interestingly, this change has also been observed in healthy adolescents at familial risk for MDD (Huang et al., 2011). The corpus callosum is the largest myelinated inter-hemispheric structure, and lesions to this structure are known to alter inter-hemispheric integration related to cognition, perception, learning, volitional processes, and emotional regulation (Kieseppa et al., 2010). It has been suggested that MDD patients show greater inter-hemispheric asymmetries in brain activity and hypoactivity in the left hemisphere (Gazzaniga, 2000; Maeda et al., 2000). It is possible that disturbed inter-hemispheric information transfer in MDD patients may have contributed to our findings. Specifically, reduced white matter integrity of the corpus callosum in our first episode MDD patients might induce functionally impaired callosal transfer and negatively influence the normal process of hemispheric specialization, which may subsequently lead to deficits in memory, executive functioning, and emotional regulation, and these changes may predispose individuals to more severe depressive symptoms (Tham et al., 2011; Murphy and Frodl, 2011). Based on the above-mentioned neurobiological role of the corpus callosum and consistent reports of reduced FA in the corpus callosum regardless of illness duration or chronicity of MDD, we postulate that the impaired integrity of the corpus callosum tract might be implicated in the etiology of MDD as a trait factor.

Interestingly, our novel finding of reduced caudal ACC volume and FA in the body of the corpus callosum might be involved in the disturbance of inter-hemispheric structural or functional connectivity between the ACC in both hemispheres. Rusch et al. (2010) investigated the inter-hemispheric structural connectivity of several brain regions in borderline personality disorder using diffusion tensor-based fiber tracking method and found decreased inter-hemispheric structural connectivity between both ACCs in fiber tracts that pass through the anterior part of corpus callosum and connect both caudal ACCs. A previous functional MRI study also reported altered functional connectivity of the dorsal ACC in women with impaired cognitive processing of emotions (Margulies et al., 2007). Correlation between altered integrity of corpus callosum and inter-connectivity of both ACCs was indicated by another study that demonstrated reduced FA of the corpus callosum and decreased inter-hemispheric functional connectivity

of both ACCs in migraine patients (Yuan et al., 2012). Therefore, we hypothesize that the impaired integrity of the corpus callosum observed in our study might contribute to dysfunctional inter-hemispheric networks of both ACCs. Impaired inter-hemispheric communication may in turn promote structural alterations of these brain regions and eventually lead to dysfunctional emotional processing in MDD patients. This hypothesis needs to be tested by future studies simultaneously evaluating the integrity of the corpus callosum, inter-hemispheric connectivity of the ACC, and structural changes of the ACC in MDD patients.

We also observed reduced cortical volume in the caudal middle frontal gyrus and the medial OFC in first episode MDD patients, but these differences did not reach statistical significance after Bonferroni correction. Nevertheless, these findings are supported by a recent VBM study on first episode MDD patients that reported reduced gray matter density in these brain regions (Bora et al., 2012). The caudal middle frontal gyrus, which corresponds to the DLPFC, belongs to the ventral compartment of the limbic–cortical dysregulation model and is known to be mainly involved in modulation of emotional responses and attentional and cognitive features of depression (Phillips et al., 2008). In accordance with our results, two meta-analyses of VBM studies on MDD reported that gray matter volume in the middle frontal gyrus was reduced significantly compared to healthy controls (Bora et al., 2012; Du et al., 2012). The medial OFC is known to exert a major influence in the medial orbitofrontal circuit, which originates in medial OFC of Brodmann area 11 and sequentially projects to medial aspects of the accumbens to medial ventral portions of the pallidum and back to the medial OFC via the medial magnocellular division of the mediodorsal thalamic nucleus (Haber, 2003). Lesions in this circuit appear to disrupt the integration of limbic–cortical regions, resulting in behavioral disinhibition and prominent emotional dysregulation (Bonelli and Cummings, 2007). Several tiers of evidence support the dysfunction of a medial orbitofrontal circuit in MDD, and previous neuroimaging studies on MDD using ROI methods and VBM analysis also support our result (Phillips et al., 2008).

In the post-hoc analysis of correlation analysis, the volume of left caudal ACC and the FA value in the body of the corpus callosum were inversely correlated with HDRS score. This result suggests that level of regional cortical volume reduction in left caudal ACC and impairment in integrity of the body of the corpus callosum correlated with depressive symptom severity. Our result is also supported by previous literatures on this issue (Du et al., 2012; Murphy and Frodl, 2011).

Interestingly, in our analysis, bilateral hippocampal volumes were increased in patients with first episode MDD compared to healthy controls, although these findings were not significant after Bonferroni correction. Numerous structural neuroimaging studies

on MDD have been performed to elucidate alterations of hippocampal volume, but they have produced inconsistent results (Cole et al., 2011). Most studies on MDD reported reduced volume of the hippocampus, while several structural neuroimaging studies on first episode MDD report no significant differences in hippocampal volume between MDD patients and healthy controls or inconsistent findings based on the laterality of hemispheres (McKinnon et al., 2009; Cole et al., 2011). In addition, Frodl et al. reported a larger right hippocampal gray matter volume in first episode female MDD patients compared to female healthy controls using the ROI method (Frodl et al., 2002), which supports our results. Therefore, we cautiously suggest that this issue should be further investigated by future studies.

Although many strong points in our study, there were several limitations. Firstly, we relied on a relatively small sample size to detect robust findings associated with structural brain alteration in first episode MDD patients. While our sample size (a total of 42 subjects) was similar to those of recent brain imaging studies on first episode MDD patients (Du et al., 2012), we think that future studies including a larger sample size might be helpful in demonstrating more confident results. A recent study on sample size estimation of cortical thickness analysis suggested that 60 subjects in each group are required to reliably detect cortical thickness changes of 0.25 mm over 95% of the entire cortical surface with surface-based smoothing of 10 mm FWHM (Pardoe et al., 2012). However, there is still no consensus on sample size estimation in volume analysis derived from cortical modeling procedure performed by FreeSurfer. Therefore, the statistical power of cortical volume analyses in our study would benefit from additional evidences from further studies on this issue.

Second, our result of cortical volume reduction in several brain regions was not replicated in the analysis of cortical thickness. Contrary to our results, Peterson et al. (2009) reported cortical thinning across the lateral surface of the right cerebral hemisphere in biological descendants of MDD patients determined to be a “high risk group.” However, this study differed from ours in the brain imaging analysis techniques used, the homogeneity of subjects in regard to the proportion of MDD patients, comorbidity of anxiety disorder, age, medication status, and duration of illness (Peterson et al., 2009). Although there have been limited number of studies detailing cortical thickness in MDD patients, we carefully presumed that the very early phase of MDD could affect cortical volume change, but not cortical thickness in our MDD patients. Based on this presumption, cortical volume changes might be detected as more initial subtle brain changes rather than cortical thickness changes in our MDD patients. Further studies on first episode MDD patients using simultaneous analyses of cortical thickness and volume are required to understand the true relationship between cortical thickness and volume.

## 5. Conclusion

We observed volume alterations in the caudal ACC, caudal middle frontal gyrus, medial OFC, and both hippocampi, along with reduced integrity of the corpus callosum in first episode MDD patients compared to healthy controls. The regional brain alterations revealed by our analyses reaffirm the results of recent brain imaging studies on first episode MDD patients. Additionally, the primary results of both reduced caudal ACC volume and FA in the body of the corpus callosum could be a novel finding demonstrating the correlation of structural alteration in inter-hemispheric connectivity between both ACC with MDD. Our multimodal brain imaging analyses on first episode, medication-naïve MDD patients might explain the neurobiological mechanism of MDD more fundamentally by elucidating the trait factors of initial structural

changes in the brain of MDD patients. Future longitudinal studies on MDD will help to investigate the mechanistic hypotheses motivated by our results.

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### Conflict of interest

Nothing declared.

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