Alterations in the Occipital Cortex of Drug-Naïve Adults With Major Depressive Disorder: A Surface-Based Analysis of Surface Area and Cortical Thickness

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Objective Advances in surface-based morphometric methods have allowed researchers to separate cortical volume into cortical thickness (CTh) and surface area (SA). Although CTh alterations in major depressive disorder (MDD) have been observed in numerous studies, few studies have described significant SA alterations. Our study aimed to measure patients’ SAs and to compare it with their CTh to examine whether SA exhibits alteration patterns that differ from those of CTh in drug-naïve patients with MDD.

Methods A total of 71 drug-naïve MDD patients and 111 healthy controls underwent structural magnetic resonance imaging, and SA and CTh were analyzed between the groups.

Results We found a smaller SA in the left superior occipital gyrus (L-SOG) in drug-naïve patients with MDD. In the CTh analysis, the bilateral fusiform gyrus, left middle occipital gyrus, left temporal superior gyrus, and right posterior cingulate showed thinner cortices in patients with MDD, while the CTh of the bilateral SOG, right straight gyrus, right posterior cingulate, and left lingual gyrus were increased.

Conclusion Compared with the bilateral occipito-temporal changes in CTh, SA alterations in patients with MDD were confined to the L-SOG. These findings may improve our understanding of the neurobiological mechanisms of SA alteration in relation to MDD.

Keywords Major depressive disorder; Surface area; Cortical thickness; Occipital cortex.

INTRODUCTION

Major depressive disorder (MDD) is one of the most disabling mental illnesses and a major public health concern. According to the recent global burden of disease study in 2017, the depressive disorder has prevailed as one of the leading causes of years lost to disability for the last three decades.¹ However, the neurobiological mechanisms underlying MDD and its effects in the brain are still unclear.

Brain magnetic resonance imaging (MRI) has played a crucial role in clarifying the structural abnormalities in MDD.² Previous studies have traditionally focused on the cortical volume using voxel-based morphometry (VBM). However, VBM is limited in that it cannot distinguish between different cortical morphological properties.³ Advances in neuroimaging data processing have made it possible to divide the cortical volume into cortical thickness (CTh) and surface area (SA) using surface-based morphometry (SBM). These two morphometric parameters have been shown to be independent contributors to volume measurements and have distinct pathophysiological implications, with different genetic etiologies and developmental trajectories.⁴⁻⁷ Based on the hypothesis that neurons within the cerebral cortex are arrayed in columns perpendicular to the cortical surface, CTh represents the number of cells within columns, while SA reflects the number of cortical columns.⁸⁻¹¹

The pattern of change in the CTh of patients with MDD has been reported in numerous studies, and recent meta-analyses provide strong evidence for the regional alteration of CTh in
METHODS

Participants

The study included 71 patients with MDD and 111 healthy controls (HCs). Patients were recruited from the outpatient psychiatric clinic of Korea University Anam Hospital, located in Seoul, Republic of Korea, between February 2010 and December 2017. All MDD diagnoses were determined by board-certified psychiatrists (Ham B) and Han KM) using the Structured Clinical Interview for DSM-IV Axis I Disorders. The patients included in the present study were adults aged 19–65 years. In addition, two psychiatrists assessed the duration of MDD by interviewing patients using the life-chart methodology. The exclusion criteria for this study were as follows: 1) primary or comorbid psychiatric diagnoses on Axis I or Axis II (based on DSM-IV-TR criteria) other than MDD; 2) MDD with psychotic features; 3) history of serious or unstable medical illness; 4) primary neurological illness; and 5) any contraindication for MRI, including pacemakers, metal implants, and claustrophobia. HC participants with no current or past history of psychiatric disorders were recruited using advertisements in the community. HCs were evaluated by two psychiatrists with the same set of exclusion criteria applied to the patient group. The age of healthy participants ranged from 19 to 65 years, and all participants were right-handed, as revealed by the Edinburgh Handedness Test. The severity of depressive symptoms for patients with MDD and HCs was measured using the 17-item Hamilton Depression Rating Scale (HDRS-17) on the day of MRI acquisition. The study protocol was approved by the Institutional Review Board of Korea University Anam Hospital (IRB No. 2009AN0105). All participants provided written informed consent to participate in the study in accordance with the Declaration of Helsinki (revised in 2008).

Image acquisition

T1-weighted images were acquired using a 3.0-Tesla Trio™ whole-body imaging system (Siemens Healthcare GmbH, Erlangen, Germany). T1-weighted images were acquired parallel to the anterior-commissure-posterior-commissure line using the 3D T1-weighted magnetization-prepared rapid gradient-echo sequence with the following parameters: repetition time, 1,900 ms; echo time, 2.6 ms; the field of view, 220 mm; matrix size, 256×256; slice thickness, 1 mm; the number of coronal slices, 176 (without gap); voxel size, 0.86×0.86×1 mm³; flip angle, 16° flip angle; and number of excitations, 1.

Image processing

Analysis of CTh and SA was performed on the three-dimensional model of cortical surface reconstructions computed from T1 images using the FreeSurfer 6.0 version (Laboratory for Computational Neuroimaging, Athinoula A. Martinos Center for Biomedical Imaging, Charlestown, MA, USA; http://surfer.nmr.mgh.harvard.edu). The details of the technical aspects of these procedures have been described in previous pub-
lications.23-29 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,26 inflation of the 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.27 The transition of gray/white matter and the pial boundary was indicated by detecting the greatest shift in intensity through surface deformation.

We visually checked the cortical reconstruction of each subject for inaccuracies and manually corrected major topological inaccuracies with vertex edits or control points, and subsequently repeated the processing. The CTh was calculated as the shortest distance between the gray matter/white matter boundary and pial surface at each vertex across the cortical mantle, measured in millimeters (mm). Cortical SA was calculated as the sum of the area of the vertices falling within a given region on the white matter surface. Smoothing with a Gaussian kernel of 20 mm full width at half-maximum was performed on the cortical maps of each subject for the entire cortex analyses.28 In addition to vertex-based reconstruction, FreeSurfer automatically parcellated the cortex into 38 gyral-based regions-of-interest per hemisphere, according to the Destrieux atlas.30 For each of the 76 cortical parcellations in the bilateral hemispheres, FreeSurfer calculates 1) the average CTh (in mm), 2) total cortical SA of the pial (mm²).

**Statistical analysis**

Group differences in the demographic and clinical characteristics of the drug-naïve patients with MDD and HCs were analyzed using an independent t-test for continuous variables (age, TICV, illness duration, and HDRS scores) and chi-square tests for categorical variables (sex and education). All statistical analyses were performed using IBM SPSS Statistics for Windows (version 24.0; IBM Corp., Armonk, NY, USA).

As the main analysis, we compared CTh and SA between drug-naïve patients with MDD and HCs using a one-way analysis of covariance. The extracted values of CTh and SA in 76 cortical parcellations in the bilateral hemispheres were set as dependent variables and the groups (MDD vs. HC group) as independent variables. Age, sex, education level, and total intracranial volume (TICV), which was manually measured as previously described, were included as nuisance covariance in the analysis.31 For multiple comparisons, false discovery rate (FDR) correction, as described by Benjamini and Hochberg,32 was applied to each main analysis.

To determine the relationship between the mean values of CTh or SA and disease burden-related clinical characteristics (illness duration and severity of depression), a two-tailed Pearson's partial correlation analysis (adjusted for age, sex, education level, and TICV) was performed separately for both CTh and SA, which revealed significant differences between the MDD and HC groups in the main analysis.

**RESULTS**

**Demographic and genotypic characteristics**

We compared age, sex, education level, TICV, illness duration, and HDRS scores of drug-naïve patients with MDD and HCs. The results are presented in Table 1. The drug-naïve MDD and HC groups did not differ significantly in terms of age, sex, education level, and TICV. A significant difference was observed for the HDRS scores between diagnostic groups, with the mean (standard deviation) HDRS scores being 18.28 (4.99) and 1.53 (1.85) for patients and HCs, respectively (p<0.001). The mean duration of illness in the patient group was 25.79±37.46 months.

**Table 1.** Demographic and clinical characteristics of drug-naïve patients with major depressive disorder (MDD) and healthy controls (HCs)

|                      | Drug-naive MDD patients (N=71) | HCs (N=111) | Significance (p-value) |
|----------------------|---------------------------------|-------------|------------------------|
| Age (years)          | 40.97±12.43                     | 39.11±13.51 | 0.350                  |
| Sex (male/female)    | 17/54                           | 38/73       | 0.133                  |
| Education level      |                                 |             | 0.78                   |
| Elementary and middle school | 15                              | 16          |                        |
| High school or college/university | 53                             | 83          |                        |
| Above graduate school | 3                               | 12          |                        |
| TICV (cm³)           | 1426.35±116.08                  | 1452.26±167.03 | 0.0219               |
| Illness duration (months) | 25.79±37.46                   | -           | N/A                    |
| HDRS score           | 18.28±4.99                      | 1.53±1.85   | <0.0001*               |

Significance was evaluated using a two-sample t-test. *denotes significance. TICV, total intracranial volume; HDRS, Hamilton Depression Rating Scale
Analysis of the differences in CTh between patients with MDD and HCs

The mean CTh values of the cortical regions in the MDD and HC groups with their respective significant differences are shown in Table 2. Both significantly decreased and increased CTh values were observed in patients with MDD compared with those of HCs (at a statistical level of p<0.05, FDR-corrected). The cortical regions with decreased thickness were the left and right fusiform gyri (left: F=8.621, \( p_{\text{corr}}=0.035 \); right: F=8.456, \( p_{\text{corr}}=0.035 \)), left middle occipital gyrus (F=8.847, \( p_{\text{corr}}=0.035 \)), right posterior-ventral part of cingulate gyrus (F=8.817, \( p_{\text{corr}}=0.035 \)), and left temporal plane of the superior temporal gyrus (F=9.087, \( p_{\text{corr}}=0.035 \)). Cortices with increased thickness in the patient group included the left and right superior occipital gyri (left: F=22.311, \( p_{\text{corr}}=0.00038 \); right: F=12.132, \( p_{\text{corr}}=0.024 \)), left lingual gyrus (F=10.175, \( p_{\text{corr}}=0.035 \)), right middle-posterior cingulate gyrus (F=8.124, \( p_{\text{corr}}=0.037 \)), and right straight gyrus (F=8.5, \( p_{\text{corr}}=0.035 \)). Correlation analysis performed for regions with a significant change in CTh did not reveal a significant correlation between changes in CTh and illness duration or HDRS scores (Table 3).

Analysis of the difference in SA between patients with MDD and HCs

As shown in Table 4, the mean SA of the left superior occipital gyrus (L-SOG) of drug-naïve patients with MDD was significantly smaller than that of HCs (F=14.87, \( p_{\text{corr}}=0.012 \)). Correlation analysis performed for the SA of the L-SOG did not

| Cortical regions | MDD | HC | F-value | \( p_{\text{corr}} \) |
|------------------|-----|----|---------|-----------------|
| Lt. fusiform gyrus | 2.646±0.379 | 2.795±0.283 | 8.621 | 0.035* |
| Rt. fusiform gyrus | 2.663±0.331 | 2.792±0.247 | 8.456 | 0.035* |
| Lt. middle occipital gyrus | 2.499±0.22 | 2.59±0.19 | 8.847 | 0.035* |
| Rt. ventral part of the posterior cingulate gyrus | 2.456±0.374 | 2.629±0.332 | 8.817 | 0.035* |
| Lt. temporal plane of the superior temporal gyrus | 3.180±0.357 | 3.335±0.322 | 9.087 | 0.035* |
| Lt. superior occipital gyrus | 2.317±0.275 | 2.144±0.202 | 22.311 | 0.00038* |
| Rt. superior occipital gyrus | 2.297±0.276 | 2.176±0.195 | 12.132 | 0.024 |
| Lt. lingual gyrus | 2.085±0.423 | 1.953±0.227 | 10.175 | 0.035* |
| Rt. middle part of the posterior cingulate gyrus | 2.686±0.181 | 2.612±0.162 | 8.124 | 0.037* |
| Rt. straight gyrus | 2.743±0.348 | 2.627±0.275 | 8.5000 | 0.035* |

\( p<0.05 \) FDR-corrected. *denotes significance. Lt., left; Rt., right

| Cortical regions | Illness duration | HDRS |
|------------------|------------------|------|
|                  | R    | \( p_{\text{corr}} \) | R    | \( p_{\text{corr}} \) |
| MDD<HC            |      |                  |      |                  |
| Lt. fusiform gyrus | -0.11422 | 0.82945 | -0.11657 | 0.54709 |
| Rt. fusiform gyrus | -0.01064 | 0.93512 | -0.13365 | 0.54709 |
| Lt. middle occipital gyrus | 0.06856 | 0.85657 | -0.05932 | 0.72194 |
| Rt. posterior-ventral part of the cingulate gyrus | -0.01808 | 0.82945 | -0.09676 | 0.57276 |
| Lt. temporal plane of the superior temporal gyrus | -0.15113 | 0.82945 | -0.12464 | 0.54709 |
| MDD>HC            |      |                  |      |                  |
| Lt. superior occipital gyrus | 0.09289 | 0.82945 | -0.01547 | 0.90579 |
| Rt. superior occipital gyrus | 0.08849 | 0.82945 | -0.13497 | 0.54709 |
| Lt. lingual gyrus | 0.10703 | 0.82945 | -0.1137 | 0.54709 |
| Rt. middle-posterior part of cingulate gyrus | 0.14985 | 0.93512 | -0.20272 | 0.54709 |
| Rt. straight gyrus | -0.04283 | 0.92886 | -0.17116 | 0.54709 |

\( p<0.05 \) FDR-corrected. HC, healthy controls; Lt., left; Rt., right
reveal a significant correlation between changes in SA and illness duration or HDRS scores (Table 5).

Analysis of the correlation between CTh and SA in an altered region

Since patients with MDD exhibited significant alterations in both the CTh and SA of their L-SOG, we conducted an additional two-tailed Pearson’s partial correlation analysis to determine the relationship between CTh and SA in this region. We performed the correlation analysis separately for patients with MDD and HC. Age, sex, education level, and TICV were controlled as covariates. As shown in Supplementary Table 1 (in the online-only Data Supplement), there was a significant positive correlation between the SA and CTh of L-SOG in the patient group (R=0.277, p=0.023). In the HC group, CTh and SA of the L-SOG exhibited significant inverse correlations (R=-0.271, p=0.005).

DISCUSSION

We examined cortical abnormalities in drug-naïve patients with MDD by simultaneously investigating CTh and SA. Our major finding was that in drug-naïve patients with MDD, CTh was altered to a broad extent, mostly affecting the bilateral occipitotemporal area, and SA was reduced in the L-SOG. To our knowledge, this is the first report of significant occipital SA alterations in drug-naïve adults with MDD.

Cortical thickness

The cortical regions with CTh alterations were similar to those observed in previous studies that analyzed CTh in drug-naïve patients with MDD,13,16,28,33,34 although we observed limited alteration of the occipitotemporal regions in our study. In contrast to previous studies, we could not replicate the commonly observed alterations in the prefrontal cortex.15,34,36 The results of our study showed that patients with MDD had a thinner cortex in the bilateral fusiform gyrus, left middle occipital gyrus (MOG), left superior temporal gyrus (STG), and right ventral posterior cingulate cortex (PCC). In contrast, cortical thickening was observed in the bilateral SOG, left lingual gyrus, right middle part of the PCC, and right straight gyrus in patients with MDD. Affected cortical regions are associated with visual perception and the default mode network. Several studies on MDD have observed cortical thinning in the fusiform gyrus,12,14,37 which plays a key role in distinguishing high-level visual information in face perception.38,39 Significant cortical alterations in the lingual gyrus, which is part of the visual association cortex, have also been observed in several studies on MDD.12,40,41 In the lateral occipital region, the medial, superior, and inferior occipital gyrus are also mostly part of the visual association cortex and are observed to be vulnerable to depression.12,16,41-43 The STG is also associated with face processing and attention to emotion, and plays an important role in social and emotional processing.44-46 Such findings suggest that changes in the occipitotemporal region may manifest as clinical symptoms of MDD, such as an impairment in social perception. The PCC is a core node in the default mode network, which is associated with cognitive control and self-referential thinking47 and is frequently disrupted in patients with MDD.12,13,48,49 Additionally, the PCC is a region that is functionally connected to the occipital region and is deactivated when the lateral occipital cortex is activated.50

The reason for the complex pattern of regional hypertrophic and atrophic cortical changes in our study is unclear. However, the results of previous studies on patients with untreated MDD have often indicated both regional increases and decreases in CTh.15,48 A possible explanation for the pathophysiology of cortical thickening is that it is caused by cellular changes resulting from reactive gliosis or neurogenesis in the early course of MDD to recover from insult.31,52 In contrast, cortical thinning may occur due to neurotoxic and/or gliotoxins processes.53,54 The heterogeneous pattern of functional dysconnectivity and differing symptom combinations within the MDD group may have contributed to this divergent pattern. Factors that determine the type of change in the CTh need to be examined in future research.
Surface area

Although both CTh and SA indicated cortical changes in the occipital lobe, SA showed a finer result, restricted to the L-SOG. This is one of the few studies to report a significant reduction of SA in drug-naïve patients with MDD to the best of our knowledge. This is the first report of SA reduction in the SOG in MDD. Nevertheless, SA reduction in the occipital gyrus has been reported in several subgroups of MDD. A recent SBM study revealed that patients with current episodes of MDD showed increased SA in the left precuneus and right pericalcarine gyrus compared to remitted MDD. Moreover, one twin study demonstrated widespread SA reduction in an occipitotemporal cluster in subjects with high anxiety–depression score. Our finding is partly supported by previous research that showed larger SA in the left lateral occipital cortex and postcentral area in MDD patients with a history of suicide attempt(s) compared to non-attempters. However, our sample of drug-naïve patients with MDD showed a reduction, not an enlargement of the SA.

In our study, the average L-SOG SA decreased while the average CTh in the same region increased. This inverse change has been observed in both HC and patient groups in several studies. According to the “balloon model” hypothesis, the cortex is stretched out tangentially to the pial surface as a result of white matter myelin growth like a balloon, resulting in a larger SA and lower CTh. The results of the correlation analysis between the patient and HC groups revealed that HCs exhibited a significant inverse correlation between CTh and SA, supporting the balloon model hypothesis (R=-0.271, p=0.005). However, a positive correlation was found within the patient group (R=0.277, p=0.023). We speculate that the reduction of SA caused by a disease entity cannot be solely caused by the concomitant process of cortical thickening. Different patterns of correlation between the two parameters in healthy subjects and the patient group need to be analyzed in future studies.

There are plausible explanations for why the L-SOG is specifically vulnerable to SA reduction. First, this could be due to low gamma-aminobutyric acid (GABA) concentration in the occipital cortex, which is commonly observed in MDD. The occipital lobe exhibits a high expression of GABA and genes that modulate GABAergic transmission such as BDNF and GAD67, which are subject to epigenetic changes in MDD. A positive correlation between the GABA concentration and SA size of the primary visual cortex was observed, supporting our hypothesis that alteration of GABAergic neurotransmission in MDD might lead to SA reduction. Second, the L-SOG has the potential to be an important node in the visual network. Biophysical limitations during SA alteration can cause network disruption. The SOG is functionally connected to other regions of the occipital lobe and PCC, comprising the lateral visual cortical network. The adjacent L-MOG has shown decreased activity in several MDD studies and left inferior longitudinal fasciculus, a white matter tract that connects the SOG to the limbic system, showed disrupted integrity in drug-naïve MDD. Third, the SA of the L-SOG could be more susceptible to genetic factors related to MDD. SA has higher heritability than CTh and the occipital cortex has been reported to be the region with the highest heritability among the cerebral cortex, especially in relation to MDD. This implies that SA alteration in the L-SOG could be a genetically determined feature that contributes to the etiology of MDD.

Correlations with illness duration and symptom severity

We did not detect a significant correlation between cortical alteration and illness duration or the HDRS score. This is consistent with the findings of the ENIGMA consortium, implying that cortical measurements do not directly represent the clinical state. However, a few studies have reported SA differences according to remission state of MDD or in relation to the anxiety–depression score. Therefore, further studies are needed to clarify this issue.

Limitation

Our study had some limitations. First, the cross-sectional design of this study meant that we could not determine whether cortical alteration is a causative or secondary phenomenon. Longitudinal data are required to understand causal relationships. Second, our analysis was restricted to cortical regions, and measurements of subcortical regions such as the thalamus, hippocampus, amygdala, and striatum were not included. As both cortical and subcortical regions are reportedly involved in MDD, analyzing both the cortical and subcortical areas separately may lead to more precise results. Third, we could not replicate the previously reported alterations in the prefrontal cortex of patients with MDD. This may be due to the heterogeneity of the sample or limitations of the atlas-based method. Considering that most of the studies that reported significant changes in CTh in prefrontal regions used vertex-based analyses and compared CTh values at each vertex, our method of comparing the mean values of the functionally predefined regions may have averaged out the complex pattern of deformity within the region. Furthermore, relatively small sample size may contribute to null finding regarding the prefrontal cortex. In future studies, combining the use of vertex-based comparison and atlas-based comparison would strengthen the evidence gathered. Integration of anatomical data with functional imaging data or genetic studies in the future may shed light on the neural mechanisms underlying SA alterations in the occipital cortex.
In conclusion, our results indicated that drug-naive patients with MDD had a smaller L-SOG SA. Along with the results of the CTh analysis, we found that patients with MDD are predisposed to alterations in the occipital area. Furthermore, the physiological, functional, and genetic traits of the occipital cortex may explain why SA alterations are more likely to occur in the L-SOG. Further studies are required to determine the role of SA in MDD.

Supplementary Materials
The online-only Data Supplement is available with this article at https://doi.org/10.30773/pi.2021.0099.

Availability of Data and Material
All data generated or analyzed during the study are included in this published article (and its supplementary information files).

Conflicts of Interest
Kyu-Man Han, a contributing editor of the Psychiatry Investigation, was not involved in the editorial evaluation or decision to publish this article. All remaining authors have declared no conflicts of interest.

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**Supplementary Table 1.** Correlation between the cortical surface area and the cortical thickness among patients with drug-naive major depressive disorder (MDD) and healthy controls (HC)

| Cortical region                  | R    | p-value |
|----------------------------------|------|---------|
| MDD                              |      |         |
| Left superior occipital gyrus    | 0.277| 0.023*  |
| HC                               |      |         |
| Left superior occipital gyrus    | -0.271| 0.005*  |

p<0.05. *denotes significance