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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.

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-naive 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, $1 \times 1 \times 1$ mm^3 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 $1.8 \times 1.8 \times 3.0$ mm^3; diffusion directions = 20; number of slices = 50; *b*-values: 0 and 600 s/mm^2; 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 full width at half-maximum was performed on the cortical maps of each subject for the entire cortex analyses.