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Left Cerebral Cortex Complexity in Patients with Major Depression Disorder: A Small-Sample Pilot Study

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ABSTRACT

Objective: To investigate cerebral cortical complexity (CCC) in patients with first-episode, drug-naive major depressive disorder (MDD) with source-based morphometry (SBM) analyses.
Methods: We used the SBM parameters gyrification index (GI) and fractal dimension (FD) to evaluate CCC in 14 first-episode, drug-naive patients diagnosed with MDD. The severity of depression symptoms was assessed with the 17-item Hamilton Depression Scale (HAMD-17). GI and FD alterations in the MDD group, relative to healthy controls (HCs), were correlated with depression symptom severity with GI/FD.
Results: Increased GIs in the MDD group, relative to HCs, were found mainly in the left postcentral gyrus, whereas GI reductions were found in the left angular gyrus, left lingual gyrus, left superior temporal gyrus, and left insular cortex. Increased FDs in the MDD group, relative to HCs, were located in the superior frontal gyrus. In contrast, decreased FDs were located in the left superior temporal gyrus and left superior frontal gyrus.
Conclusion: Although the group differences in GI and FD values obtained did not withstand family-wise error (FWE) correction, the results show a consistent trend of alterations in left-hemisphere CCC in first-episode, drug-naive patients diagnosed with MDD. These findings support the hypothesis that there is a pattern of subtle neocortical aberrations in early-stage MDD.

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INTRODUCTION

Previous studies have reported localized abnormalities in cortical gray matter structure in patients diagnosed with major depressive disorder (MDD). Structurally, the cerebral cortex is a multi-layered tissue that is folded within a three-dimensional space in the cranial cavity. The structural parameters of cerebral cortex gray matter, including cortical thickness, cortical area, and gyrus folding, have been related to independent genetic and developmental factors.[1-3] Regional alterations in cortical thickness versus alterations in area yield differing changes in volume measurement, and studies applying differing traditional structural analysis methods have reported highly inconsistent volume results. This challenge may be overcome by separating brain-structure parameters into their basic components and using a method of analysis that accounts for the different component parameters.

Voxel-based morphometry (VBM) is a well-established and validated method for investigating gray matter alterations. Meanwhile, source-based morphometry (SBM)[4] is a technique that uses independent component analysis (ICA)[5] to obtain patterns of common gray matter concentration (GMC) variation among subjects. Gray matter concentration deficits clustered within independent spatial regions can be identified by applying SBM to neuropsychiatric studies. This approach has 3 main advantages. First, it involves a multivariate analysis of whole-brain data, and it does not restrict the analysis to a single region of interest. Second, it accounts for spatial dependencies between brain locations, which are not taken into consideration

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by univariate analyses such as VBM.[6] Third, it provides a better interpretation of the location of GMC variations than VBM.[7] SBM has been used to investigate brain differences in various mental disorders, neurological diseases, and symptoms of mental disorders.[8,9] SBM yields 2 important indices used for quantitative assessment of cerebral cortex complexity (CCC). The first, gyrification index (GI), is a ratio of the whole gyral contour length to the outer, exposed cortical surface; it has been reported to be heavily influenced by second-trimester neurodevelopment.[10] The second, fractal dimension (FD), is a quantitative measure of morphological complexity that has been shown to be a good descriptor of the complex shape of cerebral cortex structures in humans.[11-13]

The SBM method has been applied to investigations of structural brain abnormalities in patients with MDD. For example, Wolf and colleagues used SBM to explore structural network alterations induced by electroconvulsive therapy in patients with MDD. They found that depressed patients had increased structural connectivity of the medial temporal lobe network after electroconvulsive therapy. However, structural connectivity strength in the medial temporal lobe network did not correlate with improvements in clinical symptoms.[14] However, Depping et al.[15] reported finding that gray matter volume reductions in the frontostriatal network and prefrontal cortex in patients with MDD correlated with depressive symptoms.[15] The aforementioned findings have provided important clues for further investigating CCC in patients with MDD.

Although previous SBM studies have demonstrated cortical alterations in MDD patients, and cortical alterations have been related to depressive symptoms and possibly to treatment effects, to the best of our knowledge, there are limited SBM data regarding cortical alterations in first-episode, drug-naive patients with MDD. Thus, the aim of the present work, a pilot study, was to use SBM and CCC analyses to investigate MDD-specific features in the brains of patients with early-stage MDD. In contrast to previous studies, here, we focused on CCC alterations in patients with first-episode, drug-naive MDD. Because GI aberrations have been related to neurodevelopmental abnormalities,[16] and FDs provide information about the shape of cortical alterations,[17] we adopted CCC's GI and FD indices. We hypothesized, first, that GI and FD would be altered in first-episode, drug-naive patients diagnosed with MDD, compared with healthy controls (HCs), and second, that these alterations would correlate with MDD symptom severity.

METHODS

Subjects

Two groups of patients were enrolled in this study, an MDD group and a HC group. The MDD group consisted of 14 right-handed first-episode, drug-naive MDD patients admitted to the outpatient clinic of Tianjin Anding Hospital between January 2017 and December 2017. The HC group consisted of 14 healthy right-handed volunteers who were demographically similar to the MDD group. The mean age, sex ratios, and mean education levels of the groups are reported in Table 1.

In every case, clinical diagnoses were made according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). Structured clinical interviews for DSM-IV Axis I Disorders-Patient Edition were conducted by 2 senior psychiatrists, each with ≥10 years of experience. During the same appointment, the patients' each completed the 17-item Hamilton Depression Scale (HAMD-17). The HAMD (originally published in 1960) was developed in the late 1950s to assess the effectiveness of the first generation of antidepressants. In the past 5 decades, the HAMD has been widely used in MDD studies with adequate discriminant validity for clinical assessment (internal reliability ≥ 0.70, inter-rater reliability ≥ 0.81). The requirements for enrollment in this study as a first-episode drug-naive patient with MDD were as follows: (1) depressive symptoms meeting the DSM-IV criteria of a major depression episode; (2) patient experiencing their first episode ever of depressive symptoms; (3) 17-item HAMD score ≥ 17; (4) no history of manic or hypo-manic symptoms; (5) no family history of bipolar disorder or any other mental disorder. The HCs were evaluated using the same psychiatrists to evaluate the structured clinical interview for DSM-IV Axis I Disorders-Normal Edition and the HAMD-17.

Table 1. Comparison of Social-demographic Characteristics Between MDD Patients and HCs with *t* Tests or χ^2 Tests

Characteristic	MDD Patients	HCs	t/χ^2	*P*	Cohen's *d*
Sex (*n*)	Female (11)	Female (12)	0.028	.868	
	Male (3)	Male (2)			
Age, years	33.91 ± 8.22	33.86 ± 9.10	0.267	.606	0.678
Education, years	13.80 ± 2.94	14.74 ± 2.85	3.378	.068	0.773
HAMD-17 score	27.49 ± 4.82	2.38 ± 0.81	92.747	<.001	0.982
Illness days	21.50 ± 3.25	0	NA	NA	

Sex was analyzed as a categorical variable with the chi-square test; age and education years were analyzed as continuous variables with independent sample *t* tests.

Only patients with a HAMD-17 score ≥ 17 were included in the MDD group. The exclusion criteria for the MDD group were: use of any psychotropic medication (to avoid antidepressant drug effects on structural imaging results); any neuropsychiatric comorbidity (including another mood disorder); mental retardation; alcohol or drug dependence; organic brain lesions; any physical/systemic disease comorbidity; and any magnetic resonance imaging (MRI) counterindication. The exclusion criteria for HCs were: a history of depression or any other mental or affective disorder; alcohol or drug dependence; organic brain disease; any physical, systemic, or neurological disease; a family history of mental illness; and any MRI counterindication. Each participant was informed of the study purpose and process in detail and signed a written informed consent form. The study protocol was approved by the Ethics Committee of Tianjin Anding Hospital, Tianjin, China.

MRI Data Acquisition

Brain images were acquired with a Phillips Achieva 3.0-T MR scanner with an eight-channel phased-array head coil. Before scanning, each patient was asked to remain in a resting state as much as possible, and his or her head was fixed with foam padding to limit head movement. Routine scan sequences were conducted, including axial T1WI, T2WI, and a fluid-attenuated inversion recovery sequence to identify any exclusionary intracranial lesions. The anatomical structure was captured with a T1W-3D-TFE-ref pulse sequence that produces a three-dimensional, high-resolution sagittal T1WI image. The main scan parameters were as follows: repetition time = 7.5 ms, echo time = 3.7 ms, flip angle = 8°, voxel size = 1 mm × 1 mm × 1 mm, field of view = 240 mm × 240 mm, matrix = 232 × 227, number of layers = 150, and layer spacing = 0.

Structural MRI Data Processing

In this process, gray-white matter segmentation and cortical reconstruction were performed in CAT12 software equipped with the cortical parcellation software FreeSurfer and the Destrieux Atlas (aparc.a2009s). Pre-processing steps included head motion correction and the averaging of the volume data for multiple T1WI, removal of the non-brain structures, gray-white matter segmentation, and spatial normalization using a Gaussian kernel with a full-width at half-maximum of 8 mm. Source-based morphometry analysis was carried out using the GIFT toolbox (http://icatb.sourceforge.net). The minimum description length principle, which was used to estimate the number of independent components (ICs), indicated that there were 6 reliable ICs. We performed ICA using a neural network algorithm (Infomax) that attempts to minimize the mutual information of the network outputs to identify naturally grouping and maximally independent sources. ICA was repeated 20 times in ICASSO (http://research.ics.aalto.fi/ica/icasso/), and the resulting components were clustered to ensure the consistency and reliability of the results. The reliability is quantified using a quality index Iq, ranging from 0 to 1 and reflecting the difference between intra-cluster and extra-cluster similarity. All 6 components extracted from the GM images were found to be associated with an Iq > 0.97 that indicated a highly stable ICA decomposition. SBM converts each gray-matter volume into a vector. As a result, we obtained a matrix wherein the 28 rows represent the 28 subjects (the first 14 rows represent HCs and the next 14 rows represent MDD patients), and each column indicates a voxel. This matrix was decomposed into 2 matrices by ICA. The first matrix was named "mixing matrix" and it is composed of a subject per row and an IC per column. Therefore, the mixing matrix indicates how much a subject expresses a given component. For this reason, values in the mixing matrix are called "loading coefficients." The second matrix was named "source matrix," and it specifies the relation between the ICs and the voxels. As for the gray-matter volume component visualization, the source matrix was reshaped back to a three-dimensional image, and scaled to unit standard deviations (Z maps) with a threshold at Z > 2.5.[4-7] We used the mixing matrix to verify whether the components were differently expressed between the patients and the controls. A two-sample t-test, without assuming equal variances (F-test revealed unequal variances), was used to test whether all the ICs were similarly expressed by either group.[4-7] Similarly, we used the loading coefficients in the mixing matrix to test a linear relation between HAMD scores and the level of components' expression. All of the results were subjected to a threshold of $P < .05$ corrected for FWE, with age, gender, education years, and illness duration defined as covariates to perform multiple comparisons.[8,9]

Statistical Analysis

A chi-square test was used to compare differences in the sex of study participants between the 2 groups. Independent sample *t* tests were used to compare differences in age, education years, and HAMD-17 scores between the 2 groups. We used the mixing matrix to verify whether the components were differently expressed between MDD patients and HCs. A two-sample t-test, without assuming equal variances (F-test revealed unequal variances), was used to test whether all of the ICs were similarly expressed by the groups. Similarly, we used the loading coefficients in the mixing matrix to test the linearity of the relationship between HAMD-17 scores and the level of components' expression. All of the results were subjected to a threshold of $P < .05$ corrected for FWE, with gender, age, illness duration, and education years considered as covariates. A two-sample t-test was used to compare GI and FD differences between the MDD and HC groups.

RESULTS

There were no significant differences in sex composition, age, or education years between the 2 groups (all $P > .05$).

Table 2. Regions with Altered GI Values in MDD Patients Compared to HCs as Indicated by *t* Tests

Atlas Region	Cluster Size	Value	Cohen's *d*
G_pariet_inf-Angular	96	−3.4	0.801
G_oc-temp_med-Lingual	91	−4.0	0.700
G_temp_sup-Plan_tempo Lat_Fis-post	64	−3.5	0.855
G_Ins_lg_and_S_cent_ins G_insular_short	58	−3.4	0.911
G_post central	61	3.4	0.988

P < .001 and cluster size ≥50, without FWE correction.

Table 3. Regions with Differing FD Between MDD Patients and HCs as Determined by *t* Tests

Atlas Region	Cluster Size	Value	Cohen's *d*
G_temp_sup-Lateral S_temporal_sup	126	−3.4	0.777
G_front_sup	76	3.4	0.833

P < .001 and cluster size ≥50, without FWE correction.

HAMD-17 scores differed significantly between the 2 groups (*P* < .05) (Table 1). Although the HC group's HAMD-17 scores indicated that they had some depressive symptoms, the severity of those symptoms was below the threshold for a subtle severity of depression (HAMD ≥ 7) applied in previous studies as a criterion for HC enrollment.[6-9]

As reported in Table 2, compared to HCs, the MDD patients had a greater GI in the G_postcentral region in the left cerebral cortex and lesser GI values in the G_pariet_inf-Angular, G_oc-temp_med-Lingual, G_temp_sup-Plan_tempo, Lat_Fis-post, G_Ins_lg_and_S_cent_ins, and G_insular_short regions in the left cerebral cortex (double threshold of ≥50 clump size, and uncorrected *P* < .001). Compared to HCs, MDD patients had a higher FD in the G_front_sup region in the left cerebral cortex and lower FDs in G_temp_sup-Lateral and S_temporal_sup regions in the left hemisphere (Table 3). The brain regions in which GI and FD values differed between the 2 groups were localized to the left cerebral hemisphere. The indicators were mostly reduced in the MDD group relative to HCs. Projections onto the pial surface of areas that were buried in sulci are shown in Figures 1 and 2. The aforementioned group differences disappeared after FWE correction. No significant correlations of GI/FD data with clinical symptoms were demonstrated.

DISCUSSION

To the best of our knowledge, the present pilot study is the first to examine GI and FD results to evaluate CCC based on SBM in first-episode, drug-naive patients with MDD. In this study, we found increased GI values mainly in the left postcentral gyrus, together with decreased GI values in the left angular gyrus, left lingual gyrus, left superior temporal gyrus, and left insular cortex of MDD patients, compared to HCs. Meanwhile, relative to the HCs, our MDD group had increased FD values in the superior frontal gyrus, and decreased FD values in the left superior temporal gyrus and left superior frontal gyrus. There is a clear left-sided laterality preponderance of the group differences in GI and FD values observed in this study. Although individual regional findings did not withstand FWE correction, altogether, they suggest that left-sided CCC alterations are present in first-episode, drug-naive patients with MDD. Furthermore, our data support the hypothesis[18-21] that there is a subtle pattern of cortical aberrations in early-stage MDD, and provide clues for further investigation into the mechanism underlying cortical structural changes in MDD.

Although our results lost their significance after FWE correction, it is noteworthy that our findings are consistent with previous reports of various frontal and temporal cortical thickness alterations, including increased cortical folding of the left postcentral gyrus and structural alterations affecting the insular cortex, in first-episode, drug-naive patients diagnosed with MDD.[18-20] Potential

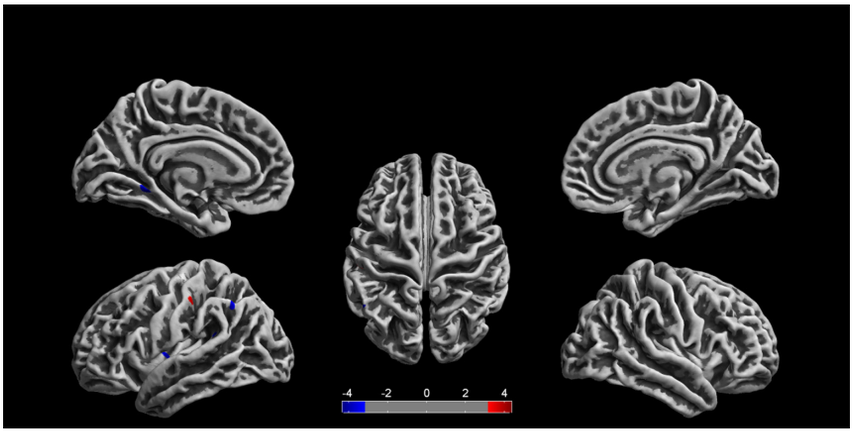

Figure 1. A visual summary of locations and magnitudes of GI differences between MDD patients and HCs.

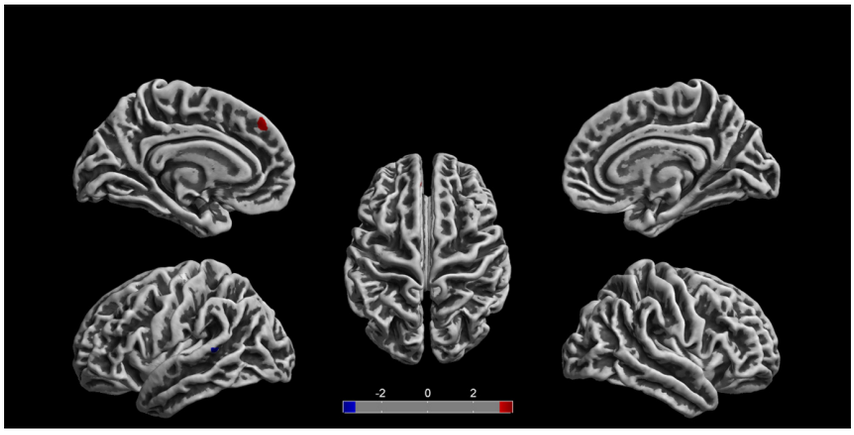

Figure 2. A visual summary of locations and magnitudes of FD differences between MDD patients and HCs.

reasons as to why our findings did not withstand FWE correction are discussed in the limitations section below.

Abnormalities of gray matter properties, such as cortical thickness, have been described in patients with untreated MDD.[20] However, few studies have reported indexes of CCC, such as GI and FD. Generally, cortical folding is thought to reflect cortical connections[21] and the optimized internal structure of the cortex that allows the brain to accommodate more axonal connections in as little volume as possible.[22] Hence, GI analyses provide a quantitative methodology for examining cerebral cortical folding patterns that may help to elucidate the pathological features of MDD.

It is appropriate to use FD data as indicators of the complexity of cortical structure because the brain has been shown to have fractal properties.[23] The FD reflects the complexity of objects with fractal properties such that a higher FD signifies a greater complexity of the studied object. Regarding CCC, FD values describe morphological differences in cortical gyri between brains with typical development and brains affected by a disease or neurodevelopmental disorder. Compared to voxel-based cerebral cortex analyses, surface-based cortical analyses better reflect cortical folding and provide enhanced structural detail.[24]

Importantly, after the first episode of MDD, the frontal and temporal lobes have been shown to play pivotal roles in mood modulation; and mood disorders such as MDD and bipolar disorder have been linked to structural and functional brain disturbances.[25-36] Depressed patients have been shown by multiple research groups to have decreased numbers of neurons and glial cells in the frontal and temporal lobes in an early stage of the disorder.[25-36] Furthermore, in a meta-analysis of VBM studies, Du et al.[25] found frontal-lobe structural alterations in patients with MDD.[37] The frontal[25-28] and temporal[29-36] lobes have been demonstrated to have structural alterations in patients with MDD, and depression-risk genes may influence these frontal and temporal structural alterations. Although our final analyses yielded only trends of aberrant CCC in first-episode, drug-naive patients with MDD, they also provide convergent evidence supporting the frontal and temporal pathological structural aberrance hypothesis of MDD from another perspective.

A notable phenomenon observed in this pilot study was that the GI and FD alterations observed in patients with MDD correlated significantly with clinical HAMD-17 symptom severity scores. These correlations suggest that GI and FD alterations may be trait features of MDD, rather than being related to symptom severity. This postulation is consistent with the neurodevelopment hypothesis of mental disorders.[13,38-41]

Limitations

This study had 2 notable limitations. Firstly, because our originally significant findings did not withstand FWE correction, these CCC index findings are described as trends. The loss of significance could be due to insufficient statistical power. A sample size of 14 patients with MDD is relatively small for a structural MRI study. It might also be that the gender ratios in our groups introduced some noise that reduced the clarity of the pattern of results. Additionally, the subtlety of the structural alterations present in patients with newly emergent symptoms of MDD was likely a factor in the loss of significance with FWE correction. Indeed, most studies examining MDD-related structural alterations in the brain enroll patients who are further out from their initial diagnoses than our patient sample. Given these factors, we will register more significant numbers of participants for future research to clarify these results. A second limitation of the present study was that because the patients were enrolled shortly following their first episode of MDD, there remains a possibility that some of the patients might, ultimately, be determined to have bipolar disorder with an initial presentation of a depressive episode. In future research of CCC in early-stage MDD, we will include a long-term cohort study to obtain subsequent confirmation of pure

MDD and exclude any patients later found to have bipolar disorder.

CONCLUSION

In the present small-sample pilot study (14 patients and 14 HCs), we found that, relative to HCs, first-episode, drug-naive MDD patients had GI and FD alterations mainly in the left cerebral cortex, though these 2 indices did not fully overlap. Although our findings did not withstand FWE correction, the results did reveal at least a trend of alterations in the CCC of the left hemisphere in this patient population. Our findings support the hypothesis that the cerebral cortex has subtle alterations characteristic of early-stage MDD, and provide data that can be useful for planning investigations into the mechanisms underlying cortical structural changes associated with the emergence of MDD.

Ethics Committee Approval: Ethics committee approval was received from the Wenzhou Seventh Peoples Hospital Ethics Committee (IRB:2016-11).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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Author Contributions: Concept - J.L., X.C., C.L., M.C.; Design - L.W., H.T.; Supervision - D.J., X.L., G.L., J.L.; Resource - C.C., D.J.; Materials - L.W., G.L.; Data Collection and/or Processing - L.W., G.L., W.T.; Analysis and/or Interpretation - C.Z., G.L.; Literature Search - C.C., D.J.; Materials -L.W., G.L.; Writing - L.W., G.L., J.L.; Critical Reviews - C.Z., J.L.

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