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Cortical Complexity Analysis of Patients with Bipolar Disorder Using Three-Dimensional Gyrification Index

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Abstract—**Bipolar disorder (BD) is a common affective disorder. In morphometric brain imaging studies, BD subjects have atrophic gray matter, especially in the prefrontal area. These structural abnormalities could involve the change of cortical shape. Gyrification index (GI) is a useful metric to measure the degree of cortical complexity. This work aims to compare the cortical development between bipolar patients and healthy controls using GI. No significant difference was detected between two groups. However, we found asymmetry pattern of cortical complexity was increased in limbic lobe on bipolar patients. Significant negative correlation was also observed between rating scores and asymmetry coefficients in frontal lobe.**

I. Introduction

CORTICAL complexity, which relates to the development of brain, represents the frequency of folding and degree of gyral convolution (gyrification) on the cortex. The change of cortical complexity has been reported in many studies of psychiatric disorder. For examples, reduced cortical complexity was found in schizophrenia patients [1] and obsessive-compulsive disorder (OCD) patients were also revealed structural abnormalities [2].

Brain morphometry in affective disorders have been studied for several years. Neuroscientists and psychiatrists are interested in the relationships between structural changes in brain and cognitive, emotional, or behavioral problems of psychiatric disorders. With the rapid development of neuroimaging techniques, the developing pattern in regions of interest can be precisely localized and malformed structures can be detected.

Bipolar disorder (BD) is one of the common mood disorders characterized by recurrent episodes of manic and depressive mood states interposed by remission periods. From previous brain morphometric studies, anatomical differences, such as reduced cortical volume [3], changed tissue concentration [4], or cortical thinning [5][6] were observed in bipolar patients in comparison with healthy subjects, especially in the anterior limbic network. These changes may correlate with the change of cortical shapes and therefore the abnormal development in associated cortical regions on patients. Im et al. found that the degree of cortical complexity is correlated with cortical thickness and folding area [7]. Fornito et al. [8] found bilateral reduction of the cortical folding patterns in the anterior cingulate and paracingulate regions. These studies motivated us to examine the degree of cortical complexity in local brain partitions from structural magnetic resonance (MR) images to assess whether cortical folding patterns were changed on the bipolar patients.

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II. Materials and Methods

A. Participants

24 bipolar patients (male/female=10/14, age mean±S.D. = 36±11 years, age range = 20-55 years) were recruited from the outpatient clinic of the Psychiatric Department, Taipei Veterans General Hospital, and evaluated by the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) criteria. Patients' duration of illness was 9±7 years, with 5±3 depressive episodes and 4±3 manic episodes. 24 age- and gender-matched healthy controls were also included in this study. All participants have filled written institutional review board (IRB) consent forms.

B. Data Acquisition

All structural images were obtained using a 1.5 Tesla MR scanner (General Electric, Milwaukee, Wisconsin, USA) by three-dimensional fast spoiled gradient recalled (3D-FSPGR) T1 sequence (TR/TE/TI=8.54/1.84/400 ms, FOV=26cm, matrix size=256×256, slice thickness=1.5mm, NEX=1, flip angle=15°) to acquire 124 axial slices with in-plane resolution 1.02×1.02 mm^2.

C. Image Preprocessing Procedures

The acquired anisotropic images were resampled into isotropic resolution of 1.02 mm. To extract regions of interest, the Anatomical Automatic Labeling (AAL) 116 atlas [9] was used in the Individual Brain Atlases using Statistical Parametric Mapping (IBASPM) software [10], which performed nonlinear registration and gray matter segmentation through SPM5 [11] subroutines to label gross

cortical structures. All extracted regions were then grouped into several partitions as in [9], i.e. frontal, parietal, temporal, occipital, limbic lobes, and cerebellum, according to the labels in the AAL atlas. The limbic lobe encompasses the cingulate gyrus, paracingulate gyrus, hippocampus, parahippocampal gyrus, and temporal pole.

D. Cortical Complexity and Asymmetry Coefficient

Once the interested regions were defined, a metric was employed to describe the degree of folding for each region. Gyrification index (GI), proposed by Zilles et al. [12], has become one of the popular measures to this end. The conventional method computes the value of GI in each slice as the ratio of the length of complete contour (the original cortical contour) to that of outer contour (the superficially exposed cortical contour). Although this 2D GI is capable of detecting abnormal folding patterns in neurological disorder, i.e. dyslexia [13], there may be a bias when different two-dimensional cuts were measured. For example, folding along sagittal direction may not be exactly detected from coronal or axial view. To alleviate this problem, a general three-dimensional (3-D) GI is adopted in this study.

The estimation of 3-D GI followed the procedures described in [14], where GI values were computed as the ratio of the surface area of each brain partition to that of its convex hull. For each extracted object in binarized images, the 3-D convex hull was constructed by filling local concavities in a 5×5×5 neighborhood iteratively as proposed by Borgefors et al. [15]. In each iteration the border voxels were first identified (defined as background voxels having at least one 6-neighbourhood object voxel), followed by counting the number of its 18-neighbourhood object voxel in the x-, y-, and z-plane, respectively. The three values were used to check whether the current border voxel should be changed from a background voxel to an object voxel by the following criteria. Among the three values, at least one of them was greater than four, or one of them was equal to four and had at least one 8-neighbor in the same plane with the value greater than two. After each iteration, several voxels were filled and the object shape became more and more convex. Note that the number of iterations in this algorithm was fixed to 10 to prevent from creating an overly convex surface.

After the binarized partitioned areas and their convex versions were obtained, we estimated the corresponding surface area for calculating GI. To estimate the surface area from volumetric data, we adopted the method proposed by Lindblad [16] using a summation of the local area contributions. The frequency of occurrence for each 2×2×2 configuration of voxels, as used in the marching cubes algorithm [17], was counted, and multiplied by the corresponding surface area weight, derived by Lindblad [16], resulting the surface area for each binarized volumetric region. Then 3-D GI was computed as the ratio of two surface areas, original surface and its derived convex one. In addition, the asymmetry pattern of cortical complexity was assessed by asymmetry coefficient (AC), which was defined similarly as in [18] by $AC=(R-L)/(R+L)$, where R and L were the 3-D GI values in right and left cortical regions, respectively.

E. Statistics

Group difference in the cortical complexity of each brain partition was examined by two-sample t-test based on the 3-D GI values and asymmetry coefficients. The correlation between disease severity and the degree of cortical complexity is of special interest for clinical interpretation. Behavior tests are used to evaluate patients' mental condition, representing the morbidness to some extent. Therefore we explored the relationship between the rating scores and 3-D GI values by calculating the Pearson's correlation coefficient. Four rating scales were used here: MADRS (Montgomery Asberg Depression Rating Scale), HAMD-17 (Hamilton Depression-17), HARS (Hospital Anxiety Rating Scale), and YMRS (Young Mania Rating Scale). In addition, the effect of specific clinical variables on cortical complexity was investigated. We put duration of illness, number of depressive episodes, number of manic episodes, and number of total episodes into the correlation analysis as well. Since the diagnostic information of one of the patients was unavailable, only 23 bipolar patients' data were used in the correlation analysis. Statistical significance was set at $P < 0.05$ with two-tailed tests.

III. Results

The statistical tests for bipolar-normal difference of cortical complexity and asymmetry coefficient are listed in Table I and II, respectively. No brain partitions revealed significant difference between bipolar patients and healthy controls for 3-D GI. The asymmetry of cortical complexity, however, manifested significant changes in limbic lobe (P=0.023). Also, both difference of 3-D GI between two groups in right frontal lobe (P=0.072) and asymmetry of cortical complexity in frontal lobe (P=0.079) exhibited trends of significance. Corresponding areas in the cortex are shown in Fig. 1.

For correlation analysis, we observed negative correlation between asymmetry coefficients and two scores of rating scales (HAMD-17: r=−0.489, P=0.018; HARS: r=−0.485, P=0.019) in frontal lobe. Interestingly, the other two scores showed the trends for significance as shown in Fig. 2 (MADRS: r=−0.391, P=0.065; YMRS: r=−0.334, P=0.119). In the right limbic lobe, the duration of illness are negatively correlated (r=−0.436, P=0.038) with GI values (see Fig. 3).

IV. Discussion

In this study, we adopted the 3-D GI, an extended definition from its original 2-D form, to describe the quantity of variation of regional cortical convolution. This metric is employed to take the complex nature of cortical surface into account, which cannot be readily measured in a single plane due to the bending and evolving of cortical surface along different directions. Previous studies related to the structural

abnormalities on bipolar disorder mostly focused on the volume changes, and few on the change of cortical folding. In this paper, we investigated the partial shape change and altered cortical complexity on bipolar patients. Our results showed that hardly any difference can be detected at lobar scale. However, the trend for significance shown in the right frontal lobe (Table I), which has been reported as areas with significant gray matter density difference in [19], gave us a hint to probe into the sucal or gyral level to study the tinier malformation in the future.

The asymmetry coefficient was found to show significant difference between patients and controls due to an inconsistent bilateral development in limbic lobe, i.e. complexity in the patients decreased in the left side, whereas in the right side it increased (Table II). In other lobes, there were only slight decreases consistently in the opposite sides, or complexity did not change between two groups.

Asymmetry coefficients were significantly correlated with rating scores in frontal lobe, whereas no significant correlation was detected in limbic lobe. This inconsistency illustrated that there may be a complicated mechanism behind, which should be beyond our proposition, to relate the symptom to brain morphological change. Several confounding factors could contribute to the structural change and how the disorder acts on the cortical shape is left as an open question.

Our findings suggested the usefulness of 3-D GI value and asymmetry coefficient as imaging biomarkers for bipolar disorder. The decreasing pattern of asymmetry in frontal lobe connected to the illness severity as illustrated in Fig. 2. Also, the longer a patient suffered, the lower cortical complexity presented in the right limbic lobe (see Fig. 3). These abnormal developments of cortical complexity can be adopted as indicators for diagnosis and of interest to clinicians.

V. Conclusion

The change of cortical complexity in bipolar patients was studied. We estimated the degree of local cortical folding in each lobe by 3-D GI and assessed the difference between bipolar and control groups. Although no brain partitions revealed significant difference, we noticed the inconsistent bilateral development in limbic lobe, leading to the emergence of asymmetry pattern. Trends for significant difference were also observed in the frontal lobe. This study verified the structural abnormalities in frontal and limbic areas from shape-based metric and provided us additional information to study the neuropathology of bipolar disorder.

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TABLE I
CORTICAL COMPLEXITY ESTIMATED BY GYRIFICATION INDEX IN BIPOLAR PATIENTS AND HEALTHY CONTROLS

Brain Partition		Bipolar Patients	Healthy Controls	*P* Value
Frontal Lobe	Left	1.793 (0.073)	1.768 (0.059)	0.260
	Right	1.817 (0.065)	1.780 (0.069)	0.095*
Parietal Lobe	Left	1.895 (0.086)	1.886 (0.079)	0.729
	Right	1.860 (0.087)	1.846 (0.093)	0.611
Temporal Lobe	Left	1.786 (0.098)	1.805 (0.071)	0.500
	Right	1.828 (0.097)	1.826 (0.086)	0.971
Occipital Lobe	Left	1.768 (0.095)	1.730 (0.070)	0.176
	Right	1.670 (0.101)	1.624 (0.092)	0.152
Limbic Lobe	Left	1.345 (0.052)	1.363 (0.041)	0.238
	Right	1.330 (0.036)	1.325 (0.034)	0.651
Cerebellum	Left	1.597 (0.067)	1.607 (0.097)	0.697
	Right	1.570 (0.072)	1.574 (0.069)	0.852

GI values are listed as means, and the values in parentheses are standard deviations.
*P<0.1, indicating a trend for significance.

TABLE II
ASYMMETRY COEFFICIENTS CALCULATED FROM GI IN BIPOLAR PATIENTS AND HEALTHY CONTROLS

Brain Partition	Bipolar Patients	Healthy Controls	*P* Value
Frontal Lobe	0.007086 (0.010241)	0.002225 (0.008379)	0.079*
Parietal Lobe	-0.008293 (0.013541)	-0.013827 (0.016848)	0.216
Temporal Lobe	0.008894 (0.015209)	0.004701 (0.014596)	0.335
Occipital Lobe	-0.028008 (0.013859)	-0.030227 (0.016542)	0.617
Limbic Lobe	-0.003522 (0.016174)	-0.012899 (0.010682)	0.023**
Cerebellum	-0.011502 (0.017995)	-0.011698 (0.016680)	0.969

AC values are listed as means, and the values in parentheses are standard deviations.
*P<0.1, indicating a trend for significance.
**P<0.05, showing the significance.

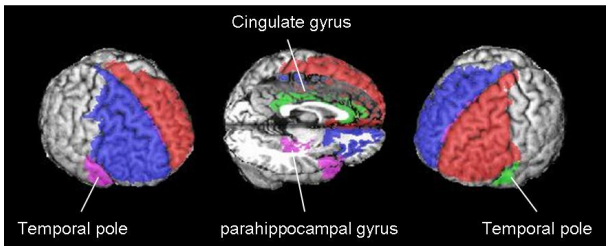

Fig. 1. Cortical areas exhibited significant difference and trends for significance. The left and right frontal lobes are in red and blue, respectively. The left and right limbic lobes are in green and magenta, respectively. Several regions of limbic lobe are indicated.

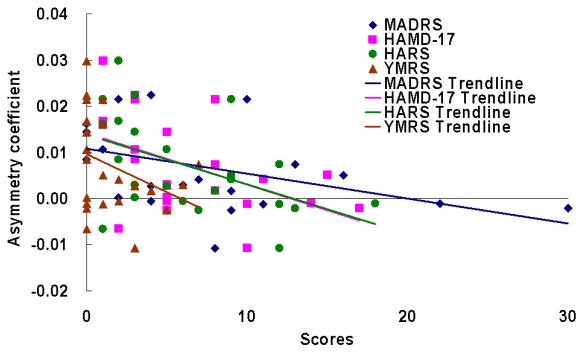

Fig. 2. The correlation plot of four rating scores, MADRS, HAMD-17, HARS, and YMRS, versus asymmetry coefficients of frontal lobe.

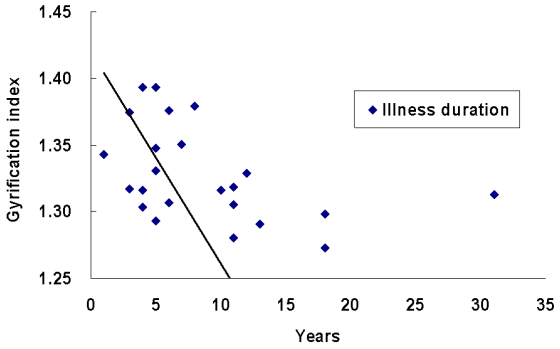

Fig. 3. The correlation plot of illness duration versus gyrification index of right limbic lobe.