

Fractal dimension of cerebral cortical surface in schizophrenia and obsessive–compulsive disorder

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Abstract

Schizophrenia and obsessive–compulsive disorder (OCD) are assumed to be neurodevelopmental disorders. To examine the cortical patterns in the two disorders, three-dimensional fractal dimension (FD) of skeletonized cerebral cortical surface was estimated from magnetic resonance (MR) images of 50 patients with schizophrenia, 45 patients with OCD and 26 healthy normal controls. The schizophrenic group had a significantly smaller mean FD than OCD group, and the OCD group than normal controls. The FD revealed a significant interaction effect of group-by-hemisphere, and the FD asymmetry index distinguished the schizophrenic group from normal controls. In logistic regression models, the FD and CSF volume correctly classified 95.6% of the schizophrenics from the controls and 88.0% of the patients with OCD from the controls. In the control and schizophrenic groups, the FD was not associated with any of tissue volume measures. In the OCD group, however, the FD was significantly correlated with gray matter tissue volume and intracranial volume (ICV). The results of the present study suggest that three-dimensional FD of cortical surface may be a sensitive indicator for investigation of the structural brain abnormalities in mental disorders, especially those developmentally disturbed. Further studies to explore regional FD changes in mental disorders and clinical implications of the FD including diagnostic value should be performed in the future.

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A great deal of evidence has been accumulated that suggests structural and functional brain abnormalities are involved in schizophrenia and obsessive–compulsive disorder (OCD) [11]. Despite discreteness of the two conditions as the former a psychotic disorder and the latter an anxiety disorder, both are assumed to be neurodevelopmental disorders [17,21] and share some aspects of clinical and pathophysiological characteristics in common; i.e., higher co-occurrence rates than expected and same neural substrates such as the frontostriatal circuit and serotonin and dopamine systems [20]. Interestingly, certain findings on pathophysiology of the two disorders ran in opposite directions, for example, the frontal hypoactivation in schizophrenia [4], but frontal

hyperactivation in OCD [11], though non-specific abnormalities also were found [13]. In previous studies directly comparing schizophrenia with OCD, as candidates for overlapping structural brain abnormalities, volumes of the hippocampus–amygdala complex [13] and the insula [12] were examined.

In the present study, we explored three-dimensional fractal dimension (FD) of cerebral cortical surface in three groups of schizophrenia, OCD and normal controls. FD is an extremely compact measure of shape complexity, condensing all the details into a single numeric value that summarizes the irregularity of an object. Its application into neuroimaging data enabled a quantitative description of the cortical pattern that was difficult to describe otherwise. There have been a few studies that measured FD of brain structures in pathological conditions including schizophrenia [2,16]

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and manic-depressive illness [2], anorexia nervosa [7] and epilepsy [3,5]. Among those studies on schizophrenia, Bullmore et al. [2] used two-dimensional cortical–subcortical boundary and Narr et al. [16] used manual delineation of 12 major sulci to produce FD value. The purpose of this study was to apply a newly developed method for estimating three-dimensional FD of the cortical surface [14] to the examination of the structural brain abnormalities in schizophrenia and OCD. We assumed that the FD in patients would be smaller than that in controls and the schizophrenics would have the smallest FD among the three groups, according to the degree of disturbances in the neurodevelopmental process. While decreased FD was expected in both disorders, some measures such as FD asymmetry were assumed to be expressed differently between the two separate mental disorders.

Fifty patients (34 males and 16 females; mean age \pm S.D.: 26.7 ± 7.0) who met the DSM-IV criteria for OCD and 45 patients (26 males and 19 females; mean age \pm S.D.: 27.0 ± 5.4) for schizophrenia, as diagnosed using Structured Clinical Interview for DSM-IV (SCID-I), were recruited from the inpatient unit and the outpatient clinic at Seoul National University Hospital. Twenty-six healthy controls (16 males and 10 females; mean age \pm S.D.: 24.1 ± 4.8) were recruited from the community through newspaper advertisements and screened by SCID-I. All subjects were right-handed and free of any lifetime history of neurological or significant medical illnesses. There was no significant group difference with respect to gender, age, education years and parental socioeconomic status [8]. The OCD group had an earlier mean onset age (18.0 ± 6.0) ($F = 13.69$; d.f. = 1, 93; $P < 0.001$) and longer mean duration of illness (8.1 ± 6.4) ($F = 9.25$; d.f. = 1, 93; $P = 0.003$) than schizophrenic group (mean onset age: 22.3 ± 5.2 ; mean duration of illness: 4.7 ± 3.9). The severity of obsessive–compulsive symptoms of patients with OCD was 23.9 ± 6.9 measured on the Yale–Brown Obsessive Compulsive Scale [6], and the severity of psychotic symptoms of patients with schizophrenia 74.8 ± 16.9 measured on the Positive and Negative Syndrome Scale [10].

Three-dimensional T1-weighted spoiled gradient echo magnetic resonance (MR) images were acquired on a 1.5 T GE SIGNA Scanner (GE Medical Systems; Milwaukee, USA). Imaging parameters were as follows: 1.5 mm sagittal slices, echo time 5.5 ms, repetition time 14.4 ms, number of excitations 1, rotation angle 20° , FOV $21 \text{ cm} \times 21 \text{ cm}$ and a matrix 256×256 . The images were resampled to 1.0 mm^3 isocubic voxels, reoriented and realigned parallel to the intercommissural line and along the inter-hemispheric fissure. The data sets were then filtered using anisotropic diffusion methods to improve signal to noise ratio. These pre-processing of images were performed by using ANALYZE software (version 3.0, Mayo Foundation, USA). Images of tissues exterior to the brain were removed by a semi-automated region growing method [15]. Since a conventional region growing method cannot extract the sulcal cerebrospinal fluid (CSF), that was a crucial factor for an analysis of the complexity pattern of cortical surface, from other tissues due to similar

intensities in the T1-weighted MR image, we applied morphological operations consisted of sequential dilatation and erosion to the cerebrum-extracted images in order to restore the sulcal CSF approximately [15]. This semi-automated method produced more accurate segmentation results than other automated skull stripping algorithms in a previous study [15]. The extracted brain images were segmented into gray matter (GM), white matter (WM) and CSF, employing the fuzzy C-means algorithm [23]. Then each tissue images were reconstructed into binary images and volumes of each tissue were calculated. The inter-hemispheric border was defined by measuring sagittal-directional slice volume and determining two slices whose volume were minimal in the vicinity of midsagittal plane. Binary volume data corresponded to the union of the part of GM and CSF were skeletonized slice-by-slice in the sagittal direction, and then, skeletonized slices were integrated into three-dimensional skeleton volume which represented cortical folding pattern. The skeletonization method used in this study removes the voxels located at boundaries of objects, but does not allow objects to break apart in order to preserve the Euler number, a topological invariant [15]. The FD of the three-dimensional skeletonized volume was calculated using the box-counting method. In this method, the shape of interest was initially mapped onto a rectangular grid or lattice, the edges of each box in the grid being of equal length (r), and the number of grid boxes occupied by one or more voxels of the image (N_r) was counted. The image was mapped repeatedly onto a series of rectangular grids of increasing box size, and the number of occupied boxes in each grid was counted. The FD was then derived from the following relationship: $N_r \propto 1/r^{\text{FD}}$ (see reference [14] for a complete description of the methods and figures).

Statistical analyses were conducted using SPSS software (version 10.0) and the significance level was set at $P < 0.05$. We performed analysis of covariance (ANCOVA) with the group (schizophrenic group, OCD group and control group) as between-subjects factor, the brain FD and tissue volumes as dependent variables and age as a covariate. To explore the hemispheric difference in the FD, repeated measures ANCOVA was performed additionally, with the group as between-subjects factor, the hemisphere (right and left) as within-subjects factor and age as a covariate. Then, the asymmetry index of FD was produced by the following equation; $(\text{left hemisphere FD} - \text{right hemisphere FD}) / (\text{left hemisphere FD} + \text{right hemisphere FD}) \times 2$, and was compared between groups. The accuracy of the group classification by the FD and volume measures was estimated by employing logistic regression models. The relationship of the FD with brain tissue volumes and symptom severity was investigated by calculating Pearson correlation coefficients. Bonferroni correction for multiple comparisons was used when needed.

As shown in Table 1, three groups differed in FD of cerebral cortical surface and in volumes of GM and CSF. Post hoc analyses revealed that the schizophrenic patients had

Table 1

Fractal dimension of cerebral cortical surface and brain tissue volume in controls and patients groups

Groups	Healthy controls (N = 26)	OCD patients (N = 50)	Schizophrenics (N = 45)	F ^a	d.f.	P
Fractal dimension						
Whole brain	2.418 ± 0.017	2.392 ± 0.021	2.367 ± 0.031	34.34**	2, 117	<0.001
Left hemisphere	2.413 ± 0.022	2.383 ± 0.024	2.354 ± 0.032	37.35**	2, 117	<0.001
Right hemisphere	2.423 ± 0.015	2.401 ± 0.021	2.379 ± 0.033	23.71**	2, 117	<0.001
Tissue volume (cm ³)						
Gray matter	765.9 ± 90.0	731.9 ± 78.4	693.3 ± 68.9	5.97***	2, 117	0.003
White matter	426.2 ± 47.8	423.8 ± 42.1	409.1 ± 43.1	1.82	2, 117	0.164
CSF	204.4 ± 58.7	264.9 ± 43.7	309.3 ± 59.6	30.26**	2, 117	<0.001
Intracranial volume	1396.6 ± 129.7	1420.6 ± 123.1	1411.7 ± 115.9	0.66	2, 117	0.521

^a ANCOVA with age as a covariate.** Measures in schizophrenics < in OCD < in controls, post hoc with Bonferroni correction ($P < 0.05/3$).*** Measures in schizophrenics < in OCD = in controls, post hoc with Bonferroni correction ($P < 0.05/3$).

significantly ($P < 0.05/3$) smaller whole brain FD than the patients with OCD ($F = 24.59$; d.f. = 1, 117; $P < 0.001$), and that FD in the OCD patients was significantly smaller than that in the controls ($F = 17.28$; d.f. = 1, 117; $P < 0.001$). The 95% confidence interval for mean FD was 2.357–2.376 for the schizophrenic patients, 2.386–2.398 for the OCD group, and 2.411–2.425 for the controls (Fig. 1). FD revealed a significant interaction effect of group-by-hemisphere ($F = 4.915$; d.f. = 2, 117; $P = 0.009$). There also was found a significant group effect in the FD asymmetry index ($F = 5.078$; d.f. = 2, 117; $P = 0.008$). In post hoc analyses, the difference of the measure was significant ($P < 0.05/3$) only between the schizophrenic patients and the controls ($F = 9.642$; d.f. = 1, 117; $P = 0.002$). Neither FD nor FD asymmetry index was significantly correlated with clinical symptom severity. The CSF volume had the same pattern with FD across groups (Fig. 1). The schizophrenic group had smaller CSF volume than the OCD group ($F = 16.14$; d.f. = 1, 117; $P < 0.001$) and the controls ($F = 60.01$; d.f. = 1, 117; $P < 0.001$). And the OCD group had smaller CSF volume than the controls ($F = 20.67$; d.f. = 1, 117; $P < 0.001$). On the other hand, the GM volume differed only in the schizophrenic patients. The schizophrenic group had smaller GM volume

than the OCD group ($F = 6.03$; d.f. = 1, 117; $P = 0.016$) and the controls ($F = 10.63$; d.f. = 1, 117; $P = 0.001$).

When the two groups, controls and schizophrenics, were considered as a dependent variable, the whole brain FD (Wald $\chi^2 = 16.27$, d.f. = 1, $P < 0.001$) alone correctly classified 80.8% of the controls and 86.7% of the schizophrenics in a logistic regression model. Adding the CSF volume, a tissue volume measure that best discriminated groups, as an independent variable, these prediction rates raised up to 92.3% for the controls and 95.6% for the schizophrenics (whole brain FD: Wald $\chi^2 = 7.73$, d.f. = 1, $P = 0.005$, CSF volume: Wald $\chi^2 = 5.78$, d.f. = 1, $P = 0.016$). Regarding OCD group, the rates of correct classification by the whole brain FD (Wald $\chi^2 = 16.53$, d.f. = 1, $P < 0.001$) alone were 50.0% for the controls and 86.0% for the patients. These rates raised up to 69.2% for the controls and 88.0% for the OCD patients, when the whole brain FD (Wald $\chi^2 = 12.58$, d.f. = 1, $P < 0.001$) and the CSF volume (Wald $\chi^2 = 10.60$, d.f. = 1, $P = 0.001$) were simultaneously put into the independent variables.

In the controls, neither the whole brain FD nor the FD asymmetry index was correlated with any of tissue volumes. In the OCD group, however, the whole brain FD was significantly ($P < 0.05/8$) correlated with GM volume ($r = 0.540$, $P < 0.001$) and intracranial volume (ICV) ($r = 0.472$, $P = 0.001$), and the FD asymmetry index with GM volume ($r = 0.434$, $P = 0.002$), WM volume ($r = 0.424$, $P = 0.002$), and ICV ($r = 0.499$, $P < 0.001$). On the other hand, correlations between the whole brain FD and any of tissue volumes failed to reach significance level in the schizophrenic group. In this group, the FD asymmetry index was significantly correlated with ICV ($r = 0.493$, $P = 0.001$) and CSF volume ($r = 0.423$, $P = 0.004$). The correlations between the FD asymmetry index and GM volumes ($r = 0.384$, $P = 0.009$) was insignificant after Bonferroni correction in the schizophrenic patients.

We found a reduction of the cerebral FD in patients with schizophrenia and patients with OCD compared with healthy controls. To our knowledge, this is the first study reporting highly sensitive cerebral FD for mental disorders. In a previous study, Bullmore et al. [2] described a reduction of FD in schizophrenic patients and an increase of FD

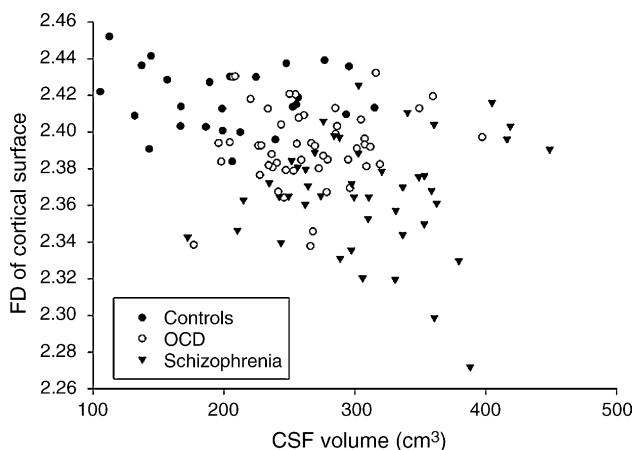


Fig. 1. Distribution of the FD of cortical surface and the CSF volumes in patients and controls ($N = 121$).

in manic-depressive patients. The group effect in their study, however, was quite modest with a limited power to distinguish patients from controls. In the current study, the overlap of FD between the patients and the controls was considerably small, and the rate of group prediction by FD was remarkably high. The FD and the CSF volume correctly distinguished 43 of 45 (95.6%) schizophrenics from controls.

The methods applied in the current study to measure the cerebral FD are distinguishable from those previously applied in several aspects. First, we used cortical–CSF interface to produce a value describing the structural complexity of the cerebrum, while GM–WM interface was used in previous studies [2,3,5]. Second, three-dimensional whole brain images with high spatial resolution were analyzed in this study. Third, the segmentation of brain tissues was performed by a semi-automated algorithm to combine the accuracy of manual methods with the reliability of automated methods [15]. Cortical complexity reflects the pattern of sulcal bifurcations and is thought to reveal potential differences of gyral geometry that become manifest during neurodevelopment or disease process [16,19]. As suggested by Bullmore et al. [2], for mental disorders, the cortical–CSF interface may be a more sensitive MR image feature for fractal analysis than the cortical–subcortical interface, because the former reflects gyral and sulcal geometry more directly than bears developmentally disturbed cortical formation. Our results indicate that FD of the three-dimensional cerebral cortical surface yielded through a more accurate pre-processing method of MR image with a high spatial resolution can provide a more sensitive brain measure for mental disorders.

There is no single neuropathological marker for schizophrenia or OCD. The two disorders are now assumed to manifest by dysfunctions in widely distributed neural circuitries [1,9]. Therefore, it seems rational that when sensitive features are to be found, markers encompassing wide brain regions should be investigated. This may partially explain the reason why the ventricular enlargement is the most robust finding of MR imaging studies in schizophrenia. The findings in the current study suggest that the brain FD may be useful as such a marker.

The patients with schizophrenia had a significant reduction of the brain FD compared with controls and OCD patients, which further confirms structural brain abnormalities in schizophrenia [18,22]. It should be noted that the brain FD reflecting cortical complexity or pattern did not correlate with any of tissue volume measures in controls and schizophrenics. As an indicator different from a volumetric measure, the FD may provide a more appropriate window for searching structural abnormalities in some brain regions, for example, the frontal neocortex. Although failure to activate the frontal cortex (hypofrontality) was the most robust finding with the largest effect size in a meta-analysis of functional imaging studies [4], volume deficits in the frontal lobe were not evident in many studies [18,22]. Inherent structural

high complexity and variability of the neocortical regions might be a factor that limited precise volumetric measures and caused inconsistent findings. Parcellating the frontal cortex into subregions for detecting volume differences can be a resolution for this problem [18], but we propose to investigate the cortical patterns for such regions. The neocortex may embrace developmental abnormalities in its bifurcation pattern formed earlier not in its volume. Cook et al. [3] noted that low FD tended to associate with poor overall intellectual function in patients with frontal lobe epilepsy. Examining if the cortical patterns in selected regions relate to cognitive functions and clinical features would be an interesting research topic. The FD revealed rightward asymmetry and the FD asymmetry index distinguished schizophrenics from the controls. In schizophrenics, the complexity of the left hemisphere was prominently reduced in consistent with many previous studies reporting left-sided structural abnormalities.

This is the first study to report that patients with OCD had a significant reduction of the brain FD compared with controls. Structural brain abnormalities in OCD have been poorly studied and seem to be subtler than those in schizophrenia [11]. Our results, however, strongly suggest that abnormalities in cortical patterns are involved in OCD. It is quite interesting that FD was significantly associated with volume measures only in the OCD group. Those high correlations were also noted in patients with anorexia nervosa [7]. Therefore, in some mental disorders, differing from schizophrenia, the cortical patterns may be closely linked to tissue volumes. It seems plausible to assume that the relation of brain FD to tissue volume may reflect the characteristic neuropathology specific to the condition. It also should be explored if those typical relations are specific to certain brain regions, because different brain regions are assumed to be involved in various mental disorders.

Neither FD nor FD asymmetry index was correlated with clinical symptom severity. While symptom severity is a state marker, FD measures are representative of trait, which may partially explain the absence of significant clinical correlations. Rather than symptom severity that changes highly during the course of an illness, clinical subtype may be a more appropriate variable to be examined how to relate with FD measures. The limitation of the current study includes that subjects were not individually matched for age and gender. Though the gender and age was not differ statistically between groups and we tried to control the age effect in statistical analyses, there is a possibility that the findings might reflect some different brain changes related to gender and age between groups.

In conclusion, we presented the three-dimensional FD as an indicator of high value for studying structural brain abnormalities in mental disorders. Further studies with demographically well-matched subjects and a longitudinal design are needed to confirm our findings. It also needs to study the FD in the brain subregions and to include various

diagnostic groups, patients with first-episode psychosis, and family members of schizophrenics.

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