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Increased Brain Gyrification in the Schizophrenia Spectrum

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Abstract

Previous magnetic resonance imaging (MRI) studies in patients with schizophrenia have reported increased brain gyrification in widespread cortical areas, which could reflect early developmental deviations. However, potential gyral anomalies in patients with schizotypal disorder have not been well documented. This MRI study explored brain gyrification in 46 patients with schizotypal disorder, 101 patients with schizophrenia, and 77 healthy controls. We collected T1-weighted magnetic resonance images from each participant and conducted group comparisons of local gyrification index (LGI) across the groups using FreeSurfer software. Compared with healthy controls, schizophrenia and schizotypal disorder patients commonly exhibited a significantly higher LGI in the bilateral prefrontal and left parietal cortices, possibly representing vulnerability to schizophrenia. Further, increased LGI in the right prefrontal and left occipital regions, which was preferentially observed in schizophrenia patients than in schizotypal disorder patients, might be related to the manifestation of florid psychosis.

Keywords: schizophrenia spectrum, schizophrenia, schizotypal disorder, magnetic resonance imaging, local gyrification index

Introduction.

Schizotypal disorders are thought to be symptomatically and genetically part of the schizophrenia spectrum, and are characterized by mild or budding schizophrenia-like symptoms, but no overt or persistent psychotic symptoms 1)70). Patients with schizotypal disorder have a higher incidence of schizophrenia than the general population 12), but the majority of them remain stable for a long time despite presenting with symptoms 43). Schizotypal disorder is considered to be a condition in which patients are vulnerable to schizophrenia, but at the same time are protected from its manifestation. Therefore, brain morphology in patients with schizotypal disorders may reflect not only vulnerability, which is common in the schizophrenia spectrum, but also protective factors against the manifestation of psychotic symptoms. Previous reports of gray matter volumes using magnetic resonance imaging (MRI) region-of-interest methods in patients with schizophrenic disorders suggest that decreased gray matter volume in the hippocampus, amygdala, and superior temporal gyrus 60)63) reflects vulnerability, while unchanged or increased gray matter volume in the prefrontal cortex, cingulate gyrus, and insular gyrus 60-62) reflects protective factors. However, gray matter volume is affected by aging 58), chronicity 7), stress 38), antipsychotic drugs 67), and cannabis 32). Therefore, more fixed biological indices may be useful in elucidating the pathogenesis of the schizophrenia spectrum.

It is reported that the process of brain gyrus formation is generally completed by the late second or third trimester of embryonic life, and that the pattern of brain sulcus gyrus after birth is relatively unchanged 4)72). Therefore, the brain sulcus gyrus pattern is a candidate for a fixed biological index of early neurodevelopment. In addition, it has been reported that deviation of gyrus formation is closely related to changes in neural connections within and between brain regions 9). Although previous MRI studies in chronic schizophrenic patients have shown inconsistent results 22)23)41)45)48)49)56)65)68), hypergyria in widespread cortical areas has commonly been reported in patients with first-episode schizophrenia

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21)39)50)55)56). It has been reported that adolescents with delayed intellectual development who exceed the cutoff of the Structured Interview for Schizotypy 28) show an increase in the gyrification index of the right prefrontal cortex compared with those who fall below the cutoff 59). However, to the best of our knowledge, there has been no previous report on the gyral pattern in patients with schizophrenia-type disorders.

In this study, we compared brain gyrification pattern in schizophrenia patients, patients with schizotypal disorders, and healthy controls using the local gyrification index (LGI). The LGI is a new index to assess the three-dimensional pattern of the sulcus-brain gyrus at the whole-brain level, and is calculated by dividing the inner brain surface area penetrating into the sulcus by the outer brain surface area covering the surface of the gyrus.

I. Methods and results of the study

The subjects of this study were 101 patients with schizophrenia, 46 patients with schizotypal disorders, and 77 healthy controls (Table) who visited the Department of Neuropsychiatry, Toyama University Hospital, and met the diagnostic criteria of the ICD-10 70). The schizophrenic patients were subclassified into 64 patients with first-episode schizophrenia and 37 patients with chronic schizophrenia. First-episode patients were defined as those with schizophrenia within 1 year of onset or first psychiatric hospitalization 25). In this study, schizophrenia patients were those who visited the hospital due to problems in daily life (clinic-based), and most of them required pharmacotherapy, including small doses of antipsychotics, for subthreshold psychotic symptoms. It is important to note that we are dealing with a relatively severe group of schizophrenia patients. On the other hand, none of the patients in the schizophrenia group developed schizophrenia during the 2 years of clinical observation. We used the Positive Symptom Rating Scale 3) and the Negative Symptom Rating Scale 2) to evaluate clinical symptoms. This study was conducted in accordance with the Declaration of Helsinki and with the approval of the Ethical Review Committee of the University of Toyama, with all subjects informed of the purpose and methods of the study and providing written consent.

The LGI values of all cortical areas were measured using 1.5 T T1-weighted magnetic resonance imaging and FreeSurfer software (ver. 5.3) 14) according to the method of Schaer, M. et al. 53). A general linear model with age, gender, medication dose, and duration of medication as covariates was used to

compare LGI between groups. To examine the relationship between LGI, clinical symptoms, and antipsychotic use in the patient groups, we performed partial correlation analyses using the mean LGI levels in the regions of interest that showed significant differences between the groups and each clinical variable.

Compared with the healthy control group, the schizophrenia group showed a significant increase in LGI values in a prominent and widespread cortical area of the medial frontal region of both hemispheres, while the schizotypal disorder group showed a significant increase in LGI values in a part of the bilateral frontal and left parietal cortices (Fig. 1). The schizophrenia group showed significant increases in LGI values in the right frontal and left occipital regions compared to the schizotypal disorder group (Fig. 1).

Although direct comparison between the first-episode schizophrenia group and the chronic schizophrenia group showed no significant difference, when compared with the healthy control group, the first-episode schizophrenia group showed increased LGI in a wide range of cortical regions, including frontal-temporal-parietal-occipital regions in both hemispheres. The first-episode schizophrenia group showed an increase in LGI levels in a wide range of cortical regions including frontal-temporal-parietal-occipital regions in both hemispheres, while the chronic schizophrenia group showed an increase in LGI only in bilateral frontal regions (Fig. 2).

In the schizophrenia and schizotypal disorder groups, there were no significant correlations between LGI and each clinical indicator (age at onset, duration of illness, positive and negative symptom rating scales, medication dose, and medication duration).

II. Discussion

We used the measure of LGI for the first time to examine whole-brain gyrification pattern in patients with schizotypal disorders and compared them with healthy controls and patients with schizophrenia. Both groups showed increased LGI in cortical areas, including bilateral prefrontal and left parietal cortices, suggesting that prenatal and perinatal neurodevelopmental deficits in these areas form a common vulnerability in the schizophrenia spectrum. On the other hand, increased LGI in the right prefrontal and left occipital regions in the schizophrenia group compared to the schizotypal disorder group may be related to the manifestation of psychotic symptoms.

In the present study, hypergyria in a wide range of cortical areas was

suggested in the schizophrenia group, and was particularly prominent in the first episode group. The results are similar to those of previous studies of schizophrenia patients 21)39)50)55)56)65)66)68). Based on multimodal brain imaging studies showing a relationship between gyrus formation and functional 45) or white matter 11)54)57) neural connectivity, as well as results from animal studies using monkeys that underwent a frontal lobotomy in utero 18), it is possible that the widespread hypergyria in the schizophrenia group found in the present study may result in widespread neural connectivity loss 13)15). The effect of the illness stage on the findings suggests that LGI may be influenced by chronicity and antipsychotic medications.

In the present study, hypergyria in bilateral frontal and left parietal regions was suggested in patients with schizophrenia. This finding was partly shared by the schizotypal group. Previous studies have reported hypergyria in frontal regions in intellectually retarded adolescents with schizotypy 59), as well as altered gyral patterns in the orbitofrontal cortex 42)64) and reduced gray matter volume in frontal-parietal regions 5)60)71) of patients with schizotypal disorder. It has also been suggested that reduced neural connectivity in the frontal lobes of patients with schizotypal disorder is involved in clinical characteristics such as cognitive impairments 24)29)37)69). Patients with schizophrenia are reported to show a decrease in gray matter volume in medial and lateral temporal regions 10)23)27)60)63), while in the present study, no significant changes in LGI values in the same regions were detected, suggesting that changes in brain gyrification and gray matter volume may have different spatial distributions 44). It is necessary to further investigate the relationship between the two and the functional significance of brain morphological changes.

Differences in the degree of gyral formation in the right frontal and left occipital regions of the brain between schizophrenia and schizotypal disorders may be related to the manifestation of psychotic symptoms and may provide clues about brain functions that protect against psychotic manifestation. It has been repeatedly reported that schizophrenia is associated with reduced gray matter volume in frontal regions 23)27)60). In a clinical high-risk group for psychotic disorders, hypergyria in the right frontal 20) and left occipital 51) regions has been suggested to be associated with later development of psychotic disorders. Given that dysfunction of the prefrontal cortex triggers excessive dopaminergic

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transmission in the striatum in schizophrenia 6)34), a reduction in inhibitory regulation of other brain regions by the prefrontal cortex 17)33), may manifest psychotic symptoms. The role of the occipital cortex in schizophrenia is not well known, but this brain region seems to be involved in key clinical features of schizophrenia, such as hallucinations 16) and social cognition 26)36)47).

Limitations of the present study include the fact that some of the schizophrenia and schizotypal disorder groups were taking antipsychotic medication and that longitudinal changes in LGI values could not be taken into account because of the cross-sectional nature of the study. Therefore, it is necessary to conduct longitudinal analyses at various stages of schizophrenia and in healthy subjects to verify the stability of morphological features of the brain gyrification over time.

Conclusion.

Assessment of brain gyral pattern is useful in capturing widespread disturbances of neural connections in schizophrenia, and measurement of LGI is becoming common in studies of psychiatric disorders; however, this measure is limited to assessment of local changes. As more detailed knowledge of neural circuits can be obtained by examining abnormalities in the relationships between brain regions 46), graph theory is also being applied to connectome analysis of brain gyrus formation 8). In addition, while deviated brain gyrification patterns have been reported in other psychiatric disorders, including bipolar disorder 40), major depressive disorder 19), and autism spectrum disorder 30), the commonality and specificity of these disorders are not well understood. Therefore, it is necessary to accumulate comprehensive knowledge on the relationship between gyral formation and clinical phenotype using a cross-disease approach 35).

This paper is a revised version of a recent research paper 52) published in PCN, written in Japanese by one of the authors at the request of the editorial board, with additional comments on its significance and prospects.

There are no conflicts of interest to be disclosed in relation to this paper.

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表　研究対象者の特性

	統合失調症群	統合失調型障害群	健常対照群	*P* value
対象者数	101	46	77	
男性/女性	55/46	29/17	44/33	0.62
年齢（年）	25.6±5.5	25.0±5.5	24.2±5.7	0.28
身長（cm）	164.7±8.0	166.2±8.7	166.9±7.8	0.21
体重（kg）	60.0±11.6	61.8±11.5	59.2±10.5	0.46
教育年数（年）	13.5±1.9	13.0±2.0	16.0±2.6	<0.001
親の教育年数（年）	12.4±2.1	12.4±1.7	12.9±2.4	0.3
発症年齢（年）	22.1±4.6			
罹病期間（月）	43.0±56.0			
服薬量（ハロペリドール換算）（mg/日）	10.6±8.9	5.9±5.9		<0.01
服薬期間（月）	31.2±47.0	22.1±38.5		0.28
陽性症状評価尺度総得点	27.9±21.4	16.1±9.3		<0.001
陰性症状評価尺度総得点	49.1±23.5	41.0±21.1		0.054
頭蓋内容積（cm^3）	1,512.0±159.2	1,533.9±155.2	1,515.9±142.6	0.72

（文献 52 より和訳して引用）

Table Characteristics of the study subjects

Schizophrenia group Schizotypal disorder group Normal control group P value

Number of subjects 101 46 77

Male/female 55/46 29/17 44/33 0.62

Age (years) 25.6±5.5 25.0±5.5 24.2±5.7 0.28

Height (cm) 164.7±8.0 166.2±8.7 166.9±7.8 0.21

Weight (kg) 60.0±11.6 61.8±11.5 59.2±10.5 0.46

Years of education (years) 13.5±1.9 13.0±2.0 16.0±2.6 <0.001

Years of parental education (years) 12.4±2.1 12.4±1.7 12.9±2.4 0.3

Age of onset (years) 22.1±4.6

Disease duration (months) 43.0±56.0

Dose (haloperidol equivalent) (mg/day) 10.6±8.9 5.9±5.9 <0.01

Duration of medication (months) 31.2±47.0 22.1±38.5 0.28

Positive symptom rating scale total score 27.9±21.4 16.1±9.3 <0.001

Negative symptom rating scale total score 49.1±23.5 41.0±21.1 0.054

Intracranial volume (cm3) 1,512.0±159.2 1,533.9±155.2 1,515.9±142.6 0.72

(Japanese translation taken from reference 52)

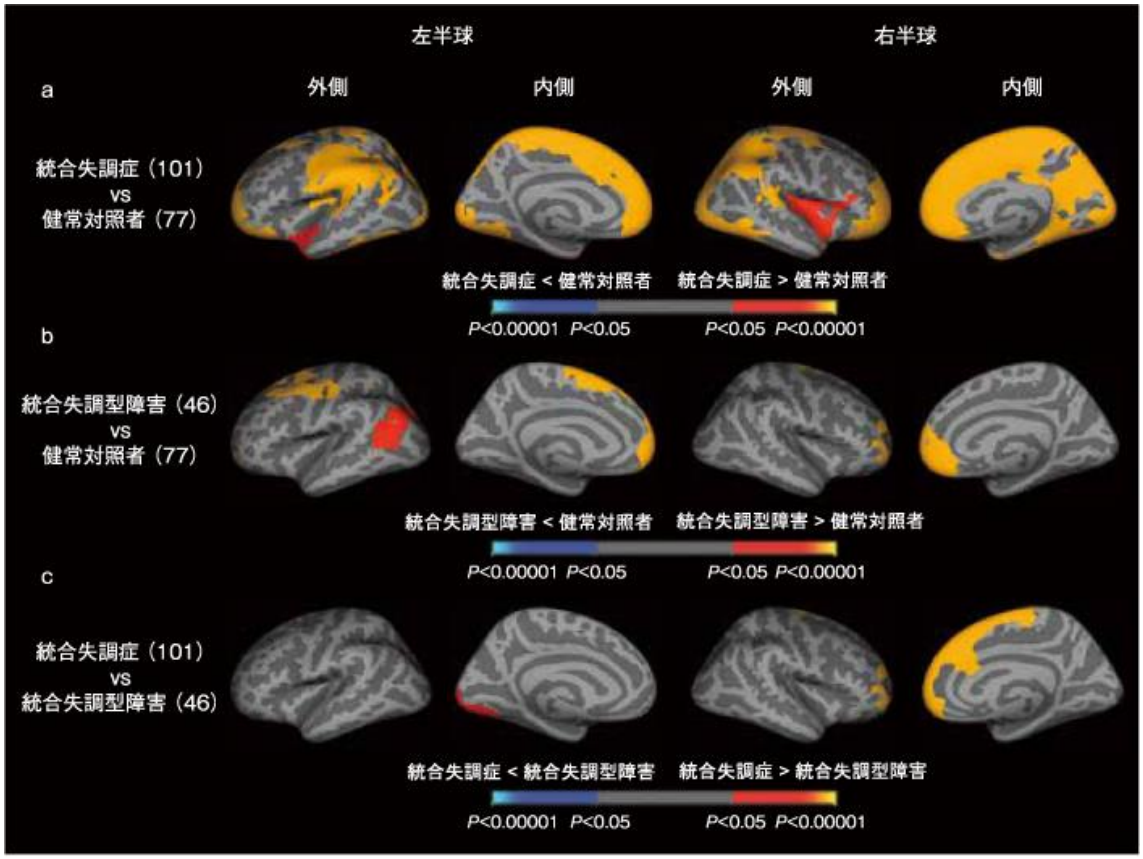

図1　統合失調症，統合失調型障害，健常対照者における局所脳回指数値の群間比較
a：統合失調症群において，健常対照群と比較して局所脳回指数値の増加を示した脳領域，b：統合失調型障害群において，健常対照群と比較して局所脳回指数値の増加を示した脳領域，c：統合失調症群において，統合失調型障害群と比較して局所脳回指数値の増加を示した脳領域．（文献 52 より和訳して引用）

Fig. 1 Comparison of regional brain gyrus index values between groups of schizophrenia patients, schizotypal disorder patients, and healthy controls.
a: brain regions with increased regional gyrus index values in the schizophrenia group compared to the healthy controls, b: brain regions with increased regional gyrus index values in the schizotypal disorder group compared to the healthy controls, c: brain regions with increased regional gyrus index values in the schizophrenia group compared to the schizotypal disorder group. (Japanese translation taken from ref. 52)

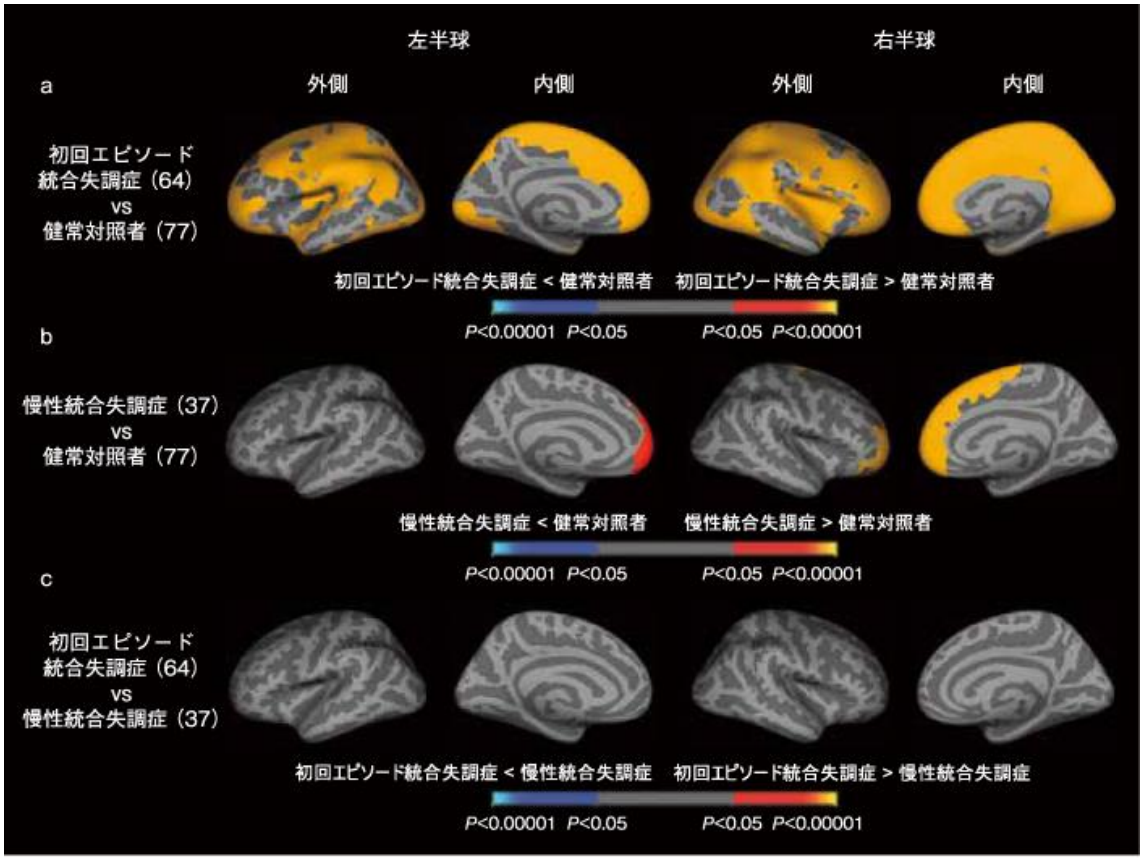

図2　初回エピソード統合失調症，慢性統合失調症，健常対照者における局所脳回指数値の群間比較
a：初回エピソード統合失調症群において，健常対照群と比較して局所脳回指数値の増加を示した脳領域，b：慢性統合失調症群において，健常対照群と比較して局所脳回指数値の増加を示した脳領域，c：初回エピソード統合失調症群において，慢性統合失調症群と比較して局所脳回指数値の増加を示した脳領域．（文献52より和訳して引用）

Fig. 2 Comparison of regional brain gyrus index values between groups of first-episode schizophrenia patients, chronic schizophrenia patients, and healthy controls
a: Brain regions with increased regional gyrus index values in the first-episode schizophrenia group compared to the healthy control group, b: Brain regions with increased regional gyrus index values in the chronic schizophrenia group compared to the healthy control group, c: Brain regions with increased regional gyrus index values in the first-episode schizophrenia group compared to the chronic schizophrenia group. c: brain regions that showed an increase in the regional gyrus index in the first-episode schizophrenia group compared to the chronic schizophrenia group. (Japanese translation taken from ref. 52)