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Schizophrenia and the Cerebellum: Focusing on the Differences of Clinical Stages and Sex

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Abstract

In recent years, the relationship between the cerebellum and schizophrenia has received renewed attention. Especially among cerebellar lobules, Crus I/II has anatomical and functional connections with the prefrontal cortex where it is associated with schizophrenia symptoms and cognitive impairment; thus, it has been suggested that Crus I/II is involved in schizophrenia. Although it has been reported that progressive brain volume changes occur during schizophrenia, the differences that occur in the structure of Crus I/II are unclear. The aim of this study was to investigate how specific morphological features in Crus I/II at different stages of the schizophrenia contribute to the disease. The study recruited 73 participants on the schizophrenia (28 with ultra-high-risk for psychosis, 17 with first-episode schizophrenia, and 28 with chronic schizophrenia) and 79 healthy controls. Using a semiautomated segmentation method

optimized for the cerebellum, we undertook a detailed investigation into differences of gray and white matter volumes in Crus I/II. We investigated the differences between the groups and sexes, as well as their interactions. We found that there were significant group \times sex interactions in the white matter of bilateral Crus I/II. Males with ultra-high-risk for psychosis demonstrated significantly larger white matter volumes than the other male groups, whereas no significant group differences were found in the female groups. White and gray matter volumes of Crus I/II had positive associations with symptom severity in the ultra-high-risk for psychosis group; on the other hand, gray matter volumes in the first-episode schizophrenia group were negatively associated with symptom severity. The findings of this study indicate that Crus I/II morphology is involved in schizophrenia and has sex and stage differences, and that deviations in the white matter volume of Crus I/II have the potential to be a biological indicator for early detection and treatment of high-risk for developing psychosis patients.

Keywords: schizophrenia, cerebellum, Crus I/II, clinical stages, sex difference

Introduction

The cerebellum (小脳: 'small brain'), as its name in Japanese suggests, is significantly smaller than the cerebrum (大脳: 'large brain'), with a volume approximately one-tenth that of the cerebrum. In contrast to its volume, the number of cells in the cerebellum accounts for approximately 80% of the total number of cells in the brain.¹⁾ These findings suggest that the cerebellum is involved in higher-order information functions. However, there has been a lack of research focusing specifically on the cerebellum in the field of psychiatry. Traditionally, the cerebellum has been considered primarily responsible for motor

functions. However, with recent advances in research on the cerebellum's functions and structure, it has become increasingly recognized as playing an important role in higher cognitive functions. As understanding of the cerebellum's role in brain functioning continues to advance, the suggestion that it may contribute to the pathophysiology of schizophrenia, a disorder characterized by disruptions in higher-order cognitive processes, has garnered increasing attention.¹⁾

Schizophrenia is characterized by positive symptoms such as hallucinations and delusions, and negative symptoms such as emotional blunting and decreased motivation,

presenting diverse pathological states of mental functioning. Its onset is typically during adolescence or young adulthood and it follows a chronic course, during which progressive changes in brain volume have been demonstrated. Changes in brain volume have been observed even during the ultra-high risk stage preceding the onset of psychosis,²⁾⁷⁾²⁹⁾ and studies have reported that the characteristics of these changes differ between individuals who later develop schizophrenia and those who do not.²⁸⁾ This suggests that distinct brain pathologies may be observed in each clinical stage of schizophrenia. Furthermore, elucidating the changes in brain structures associated with each clinical stage is considered useful as a candidate biomarker for preventing the onset of psychosis from the ultra-high risk state or suppressing symptom progression, and it is also expected to contribute to a better understanding of the pathophysiology.

To date, numerous magnetic resonance imaging (MRI) studies have been conducted to examine differences in brain structure across the clinical stages of schizophrenia, with a focus on cerebral structures and subcortical volumes. However, regarding the cerebellum, most studies have focused on specific stages of schizophrenia, and differences in the cerebellar structure

across clinical stages remain unclear. Although research on the cerebellar structure in psychiatry is significantly less extensive than that on the cerebral cortex, some insights have been accumulated. Many early studies of the cerebellar structure in schizophrenia focused on the cerebellar vermis.¹⁵⁾¹⁶⁾³⁰⁾ In early studies, the structure of the cerebellar vermis was primarily assessed using manual tracing. However, with advances in neuroimaging analysis techniques, it has become possible to conduct automated evaluations that also include the cerebellar hemispheres. Previous analyses suggested that Crus I/II within the cerebellar lobular structure may be involved in schizophrenia. Crus I/II is located laterally and posteriorly in the cerebellar hemisphere, along with lobule VI (Figure 1a). In the human cerebellum, the lateral and posterior hemispheric regions are considered to be closely associated with higher-order functions and are also the most morphologically developed areas. Crus I is the most laterally protruding and largest region of the cerebellum. Crus II, however, is located just below and adjacent to Crus I, and is the second largest and most developed region. Crus I/II, with these morphological characteristics, is anatomically and functionally connected to the prefrontal cortex, which is associated with

schizophrenia symptoms and cognitive dysfunction.³⁾⁴⁾²⁶ Therefore, elucidating structural differences in cerebellar Crus I/II across clinical stages of schizophrenia may advance our understanding of its pathophysiology and contribute to the development of preventive and therapeutic interventions.

This study¹⁹⁾ aimed to outline structural differences in cerebellar Crus I/II across distinct clinical stages of schizophrenia, ultra-high risk of psychosis, first-episode schizophrenia, and chronic schizophrenia, and explore their associations with symptom severity at each stage. Building on these findings, we discuss future directions for research on the cerebellar structure in schizophrenia.

I. Methods and Results

1. Methods

The study included 73 participants with schizophrenia and 79 healthy controls (see Table). Participants with schizophrenia were classified based on the clinical stage as follows: 28 in the ultra-high risk of psychosis group, 17 in the first-episode schizophrenia group, and 28 in the chronic schizophrenia group. All participants underwent MRI, and assessments of handedness and estimated premorbid IQ were conducted. In addition, psychiatric symptoms in the ultra-high risk of psychosis, first-

episode schizophrenia, and chronic schizophrenia groups were assessed using the Positive and Negative Syndrome Scale (PANSS).¹³⁾ For image analysis, a semi-automated segmentation method was used to delineate the Crus I/II region, which was then further segmented into gray and white matter for detailed evaluation (Figure 1b). Additionally, multiple regression analysis was performed to examine the association between the cerebellar volume and severity of psychiatric symptoms.

This study was planned in accordance with the Declaration of Helsinki and conducted with the approval of the Ethics Committee of the University of Tokyo Hospital (Nos. 397 and 2226). Measurements were conducted after providing sufficient explanation regarding participation in the study and obtaining written informed consent from all participants.

2. Results

1) Differences in cerebellar volume across clinical stages of schizophrenia

A significant group-by-sex interaction was observed in the bilateral white matter of Crus I/II. Simple effects analysis revealed a significant main effect of group within male participants. Holm's method for multiple comparisons revealed that, in the male group, the white matter volume in left

Crus I/II was significantly increased in the ultra-high risk of psychosis group compared with the healthy control and chronic schizophrenia groups (Figure 2a). Additionally, the right Crus I/II white matter volume was significantly larger in the ultra-high risk of psychosis group than first-episode schizophrenia group (Figure 2b). Such significant volume differences were observed only in white matter; they were not detected in the gray matter volume or total volume of Crus I/II (gray matter + white matter). In the female group, no significant main effect of group was observed in any region.

2) Association between Crus I/II volume and schizophrenia severity

In the ultra-high risk of psychosis group, a positive association was observed between the left Crus I/II white matter volume and negative symptom severity, but no association was found with the right Crus I/II white matter volume (Figure 3a, d). In contrast to the ultra-high risk group, no significant correlation was observed between the bilateral white matter volume of Crus I/II and severity of negative symptoms in either the first-episode or chronic schizophrenia groups (Figure 3b, c, e, f). Additionally, regarding the gray matter volume in Crus I/II, a positive correlation was observed between positive symptom severity and gray matter volume in the

ultra-high risk of psychosis group, while a significant negative correlation was found between positive symptoms and the gray matter volume in the first-episode schizophrenia group (Figure 4a, b, d, e). However, none of these remained significant after correction for multiple comparisons. In contrast to the ultra-high risk and first-episode schizophrenia groups, no significant correlations were observed in the chronic schizophrenia group (Figure 4c, f).

II. Discussion, including the significance of this study, challenges, and innovative approaches

In this study, we examined characteristics of the cerebellar structure and their associations with symptom severity across clinical stages of schizophrenia, ultra-high risk of psychosis, first-episode schizophrenia, and chronic schizophrenia, while accounting for sex differences. Although this study involved a limited sample and the results are preliminary, it is the first to examine the volume of cerebellar Crus I/II across clinical stages of schizophrenia in detail. The analysis revealed a significant increase in the bilateral cerebellar Crus I/II white matter volume in males at ultra-high risk of psychosis. Furthermore, distinct patterns of association between the cerebellar Crus I/II volume and severity

of psychotic symptoms were identified across different clinical stages. The findings of this study suggest that cerebellum-related neural mechanisms in schizophrenia may vary by clinical stage and sex, underscoring the importance of considering both factors in the understanding and treatment of the disorder.

In schizophrenia, sex differences have been reported from various aspects, including epidemiological characteristics, response to antipsychotic medications, and the disease course. However, few studies have examined sex differences in brain structure. Consistent with the findings of the present study, some previous research reported structural differences in multiple brain regions between males and females with schizophrenia.⁵⁾²⁰⁾²⁷⁾ Clinically, males tend to have an earlier age at onset, more severe negative symptoms, and a higher risk of transitioning from an ultra-high risk state to full-blown psychosis compared with females.⁶⁾¹⁷⁾²²⁾ Considering these male-specific characteristics, the changes in white matter volume observed in men at ultra-high risk of psychosis in this study may reflect sex differences in clinical symptoms of schizophrenia. This study also confirmed a positive association between the left Crus I/II white matter volume and severity of negative

symptoms in individuals at ultra-high risk of psychosis. These findings suggest that an increased white matter volume in Crus I/II may represent a biological feature associated with clinical symptoms in this population and could serve as a potential target for early detection and intervention. To verify this more accurately, further studies with a larger sample size are necessary.

In contrast to several previous studies^{14,18)} that reported a reduction in gray matter volume in individuals with schizophrenia, the present study found no significant difference in this volume. This may be attributable to differences in the study design, such as the use of large samples comprising hundreds to thousands of participants, and lack of consideration for disease stage or sex differences in previous studies. However, the finding in this study of an inverse association between the bilateral Crus I/II gray matter volume and positive symptoms in both the ultra-high risk of psychosis group and first-episode schizophrenia group is noteworthy, suggesting that cerebellar involvement may differ depending on the clinical stage.

While structural brain imaging can help detect anatomical features such as volume changes, it cannot clarify the underlying mechanisms driving these alterations. Therefore, drawing on existing evidence, we aim to discuss

potential factors contributing to the increased white matter volume observed in males at ultra-high risk of psychosis, as well as possible reasons for the differing associations between the gray matter volume and positive symptoms in the ultra-high risk and first-episode schizophrenia groups. First, sex differences in the white matter volume observed in the ultra-high risk of psychosis group in this study may have been influenced by sex steroid hormones. Such hormones are known to play a role in the development of white matter structure during puberty, with effects that differ between males and females.⁹⁾²³⁾ For example, in adolescent boys, testosterone has been shown to exhibit a positive correlation with fractional anisotropy (FA) and axon length, while in girls, these indicators reportedly show a negative correlation with blood estradiol levels.¹²⁾ Furthermore, abnormal levels of sex steroid hormones have been reported in the ultra-high risk of psychosis group compared with healthy controls.¹⁰⁾ Based on these findings, sex steroid hormones may be a factor contributing to the sex differences in white matter volume observed in this study. Next, to account for the differing patterns of association between the Crus I/II gray matter volume and positive symptoms observed in the ultra-high risk of psychosis and first-episode

schizophrenia groups, we propose an explanation based on the cytokine-induced neuroinflammation hypothesis. In diseases characterized by progressive structural brain changes, such as prion and Alzheimer's diseases, microglial activation is known to occur prior to neuronal loss and the onset of clinical symptoms. Moreover, this activation has been shown to induce an increase in gray matter volume.⁸⁾ Given this, the positive correlation observed between the gray matter volume in Crus I/II and positive symptoms in the ultra-high risk of psychosis group may be influenced by microglial activation. In contrast, the negative correlation observed in the first-episode schizophrenia group may reflect neuronal loss that occurs following microglial activation.

We would like to describe the challenges encountered and methodological considerations applied in conducting this study. In particular, the most difficult task was segmenting the cerebellum into individual lobules. In this study, we employed an automatic cerebellar segmentation method developed by a research group in the United States.³¹⁾ Since around 2010, several research groups in Europe and the United States have developed techniques for automatically segmenting the cerebellum using structural images. However, these methods are based on brain atlases

derived from Western populations and may not be optimal for cerebellar segmentation in Japanese individuals. In fact, in this study, the segmentation often included regions outside the cerebellar parenchyma, necessitating manual corrections. In recent years, international large-scale studies on psychiatric disorders have become increasingly common. Going forward, to advance research focusing on the cerebellum, it will be important to develop atlases and templates that account for racial and ethnic differences, and devise methods that facilitate more accurate structural analysis.

Conclusion

Currently, the authors are conducting a longitudinal analysis using Tokyo Teen Cohort MRI data²¹⁾ to examine the relationship between cerebellar development during adolescence and mental health and social behavioral problems in this period. This analysis incorporates data on physical and psychological development as well as social environmental factors during infancy and adolescence, periods critical for mental health. In addition, we plan to conduct further research aimed at characterizing the cerebellar structure and function across psychiatric disorders, using large-scale datasets from several thousand individuals in Japan, including those with

schizophrenia, mood, and developmental disorders. Through these analyses, we aim to evaluate the relevance and consistency of our findings, and deepen understanding of the relationship between the cerebellum and mental disorders.

In this study, we demonstrated differences in cerebellar structure based on the clinical stage and sex of schizophrenia patients. However, to elucidate the mechanisms underlying these differences, interdisciplinary research, including studies on biochemical factors such as genes and hormones, as well as animal-based reverse translational research, will be essential. The results of this study were presented at the Cerebellar System Research Section seminar of the Japanese Society for Cerebellar Research, where basic researchers suggested that evaluating cerebrospinal fluid could be a useful approach for validating the cytokine-induced neuroinflammation hypothesis, providing important insights for future research. Moving forward, we intend to continue investigating the pathophysiological mechanisms of schizophrenia involving the cerebellum, sharing knowledge and techniques with researchers from other fields.

In this study, automatic segmentation alone did not provide sufficiently accurate results, necessitating manual

corrections. This experience underscored the challenges associated with cerebellar segmentation. For future studies, it will be essential to develop a protocol for more precise cerebellar automatic segmentation. To this end, the authors are currently developing a Japanese cerebellar atlas and implementing an analysis protocol based on it. This approach has yielded better segmentation results than previous methods, and its effectiveness has been demonstrated in preliminary analyses. In psychiatric research, brain imaging studies involving hundreds to thousands of participants are common, and large-scale studies are crucial for accurately capturing the heterogeneous features of psychiatric disorders. Also, establishing an automatic segmentation method capable of accurately evaluating various structural characteristics is indispensable. Moving forward, we aim to contribute to the advancement of cerebellar brain image analysis through improving these analysis protocols and developing a Japanese cerebellar template.

This paper is a translation of the latest research article published in PCN,¹⁹⁾ commissioned by the editorial board, with additional commentary on its significance and future perspectives provided by one of the authors.

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

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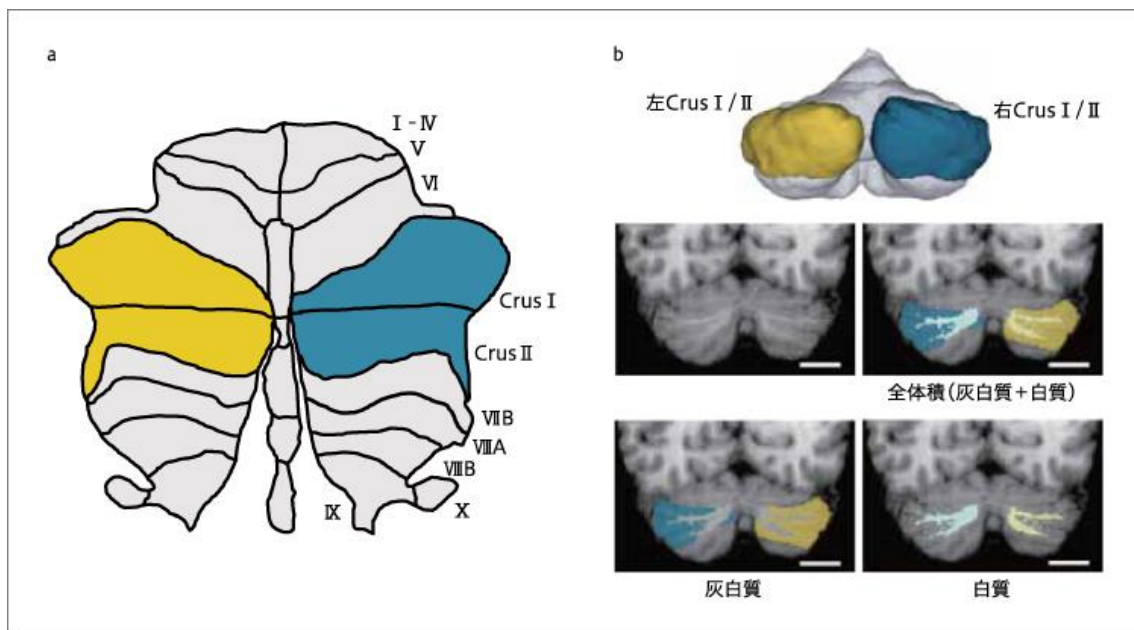


図1 小脳アトラスと小脳セグメンテーションの結果

a: 小脳フラットマップ. Schmahmann, J. D. ら²⁴⁾によるヒト小脳 MRI アトラスに基づき著者が作成, b: 両側の Crus I/II に対する小脳セグメンテーションの結果. スケールバー: 20 mm. (文献 19 より引用)

Figure 1: Results of cerebellar segmentation and the atlas.

a: Flat cerebellar map. Created by the author based on the human cerebellar MRI atlas by Schmahmann, J.D. et al.²⁴⁾

b: Results of cerebellar segmentation for both Crus I/II. Scale bar: 20 mm.
(Reproduced from reference 19)

表 研究参加者のプロフィールと臨床特性

	健常対照群	精神病発症 ハイリスク群	初回エピソード 統合失調症群	慢性期 統合失調症群	P 値
男性/女性	49/30	17/11	12/5	16/12	0.839
年齢	28.44±5.29	21.07±3.57	23.94±5.57	33.64±9.21	<0.001
利き手 (右/両利き/左)	77/2/0	22/6/0	15/2/0	28/0/0	0.003
身長	168.07±8.77	166.38±7.59	166.24±7.69	166.48±8.76	0.265
体重	61.21±11.39	57.46±8.72	59.65±9.87	66.15±13.47	0.034
病前推定 IQ (JART 25) [†]	108.24±8.45	104.43±10.44	106.25±10.12	100.60±9.10	0.002
クロルプロマジン換算量 (mg)	—	88.21±174.35	483.82±451.30	849.00±702.31	<0.001
罹病期間 (年)	—	—	—	7.79±5.88	—
陽性・陰性症状評価尺度					
陽性症状	—	13.93±3.23	15.24±4.98	17.32±5.45	0.026
陰性症状	—	19.11±5.67	18.88±5.43	22.75±5.83	0.029
総合精神病理	—	34.36±7.11	35.12±9.04	40.39±9.34	0.022

[†]病前推定 IQ は JART25 (25 item version of the Japanese Adult Reading Test) を用いて算出した。年齢, 身長, 体重, 病前推定 IQ, クロルプロマジン換算量, 罹病期間, 陽性・陰性症状評価尺度の得点の値は平均±標準偏差で示す。
(文献 19 より引用)

Table: Clinical and demographic characteristics of participants

	Healthy control group	High-risk of psychosis group	First-episode schizophrenia group	Chronic schizophrenia group	P-value
Male/female	49/30	17/11	12/5	16/12	0.839
Age	28.44±5.29	21.07±3.57	23.94±5.57	33.64±9.21	<0.001
Handedness (right/mixed/left)	77/2/0	22/6/0	15/2/0	28/0/0	0.003
Height	168.07±8.77	166.38±7.59	166.24±7.69	166.48±8.76	0.265
Weight	61.21±11.39	57.46±8.72	59.65±9.87	66.15±13.47	0.034
Pre-illness estimated IQ (JART 25) [†]	108.24±8.45	104.43±10.44	106.25±10.12	100.60±9.10	0.002
Chlorpromazine-equivalent dose (mg)	—	88.21±174.35	483.82±451.30	849.00±702.31	<0.001
Duration of illness (years)	—	—	—	7.79±5.88	—

Positive and negative symptom rating scale

Positive symptoms	—	13.93±3.23	15.24±4.98	17.32±5.45	0.026
Negative symptoms	—	19.11±5.67	18.88±5.43	22.75±5.83	0.029
General psychopathology	—	34.36±7.11	35.12±9.04	40.39±9.34	0.022

†Pre-illness estimated IQ calculated by JART 25 (25-item version of the Japanese Adult Reading Test).

Age, height, weight, pre-illness estimated IQ, chlorpromazine-equivalent dose, duration of illness, and scores on positive and negative symptom scales are presented as mean ± standard deviation.

(Adapted from Reference 19)

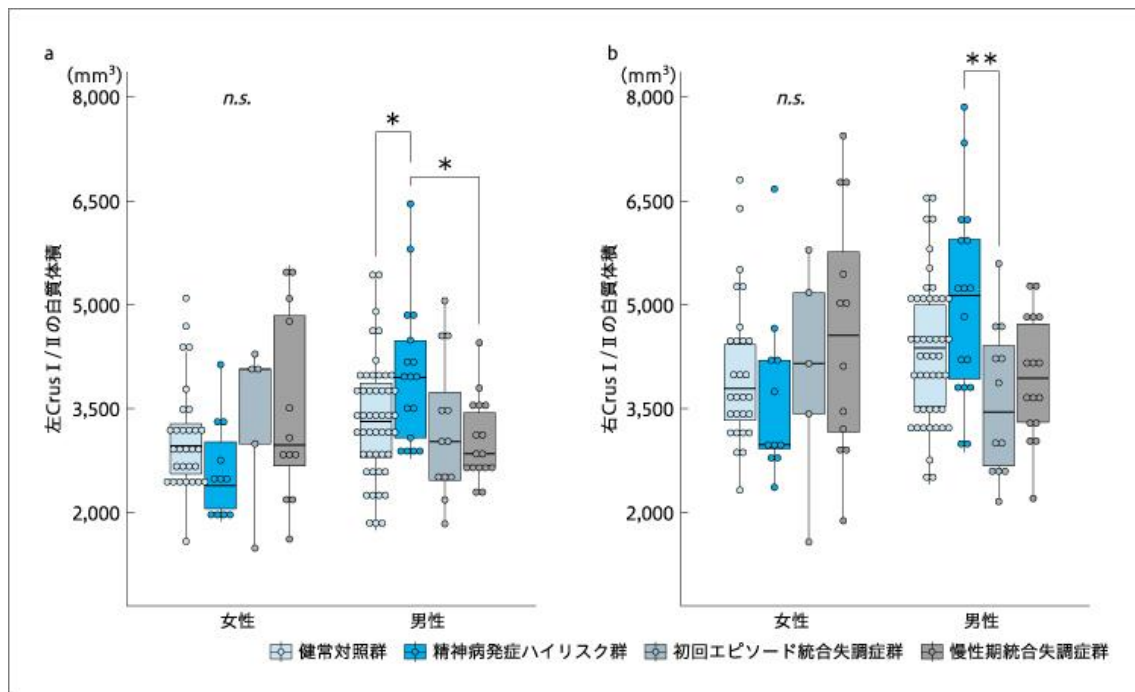


図2 Crus I/IIの白質体積

a: 左 Crus I/IIの白質体積, b: 右 Crus I/IIの白質体積. 共分散分析による有意差なし (n.s), $P > 0.05$; および Post hoc 検定による $*P < 0.05$; $**P < 0.01$. (文献 19 より引用)

Figure 2 White matter volume of Crus I/II

a: White matter volume of the left Crus I/II, b: White matter volume of the right Crus I/II. No significant difference by covariance analysis (n.s), $P > 0.05$; or by post-hoc test

$*P < 0.05$; $**P < 0.01$. (Adapted from Reference 19)

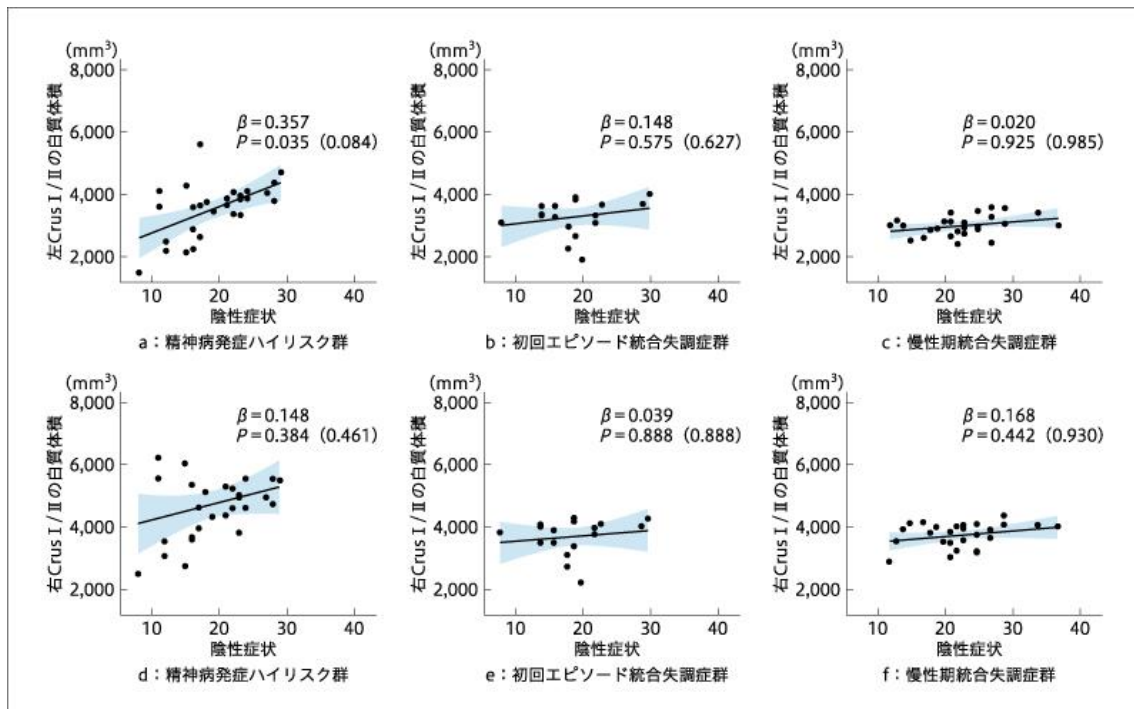


図3 統合失調症サブグループにおける陰性症状と Crus I/II の白質体積の関係

Crus I/II の白質体積は、年齢、クロルプロマジン換算抗精神病薬処方量、頭蓋内容積で調整されている。括弧内の数値は補正後 P 値を示す。(文献 19 より引用)

Figure 3 Relationship between negative symptoms and white matter volume of Crus I/II in schizophrenia subgroups

White matter volume of Crus I/II adjusted for age, chlorpromazine-equivalent antipsychotic medication dosage, and cranial volume. Values in parentheses indicate adjusted P-values. (Adapted from Reference 19)

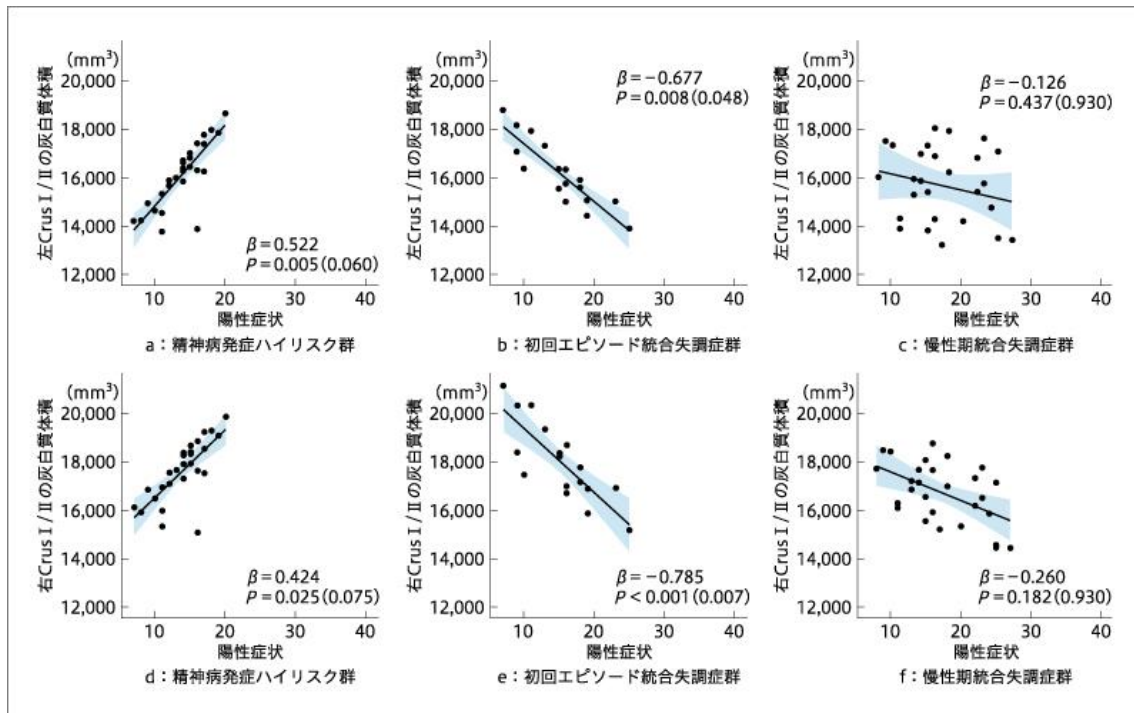


図4 統合失調症サブグループにおける陽性症状と Crus I/II の灰白質体積の関係

Crus I/II の灰白質体積は、年齢、クロルプロマジン換算抗精神病薬処方量、頭蓋内容積で調整されている。括弧内の数値は補正後 P 値を示す。(文献 19 より引用)

Figure 4 Relationship between positive symptoms and Crus I/II gray matter volume in schizophrenia subgroups

Crus I/II gray matter volume adjusted for age, chlorpromazine-equivalent antipsychotic medication dosage, and cranial volume. The numbers in parentheses indicate adjusted P-values. (Adapted from Reference 19)