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Volume reduction and altered sulco-gyral pattern of the orbitofrontal cortex in first-episode schizophrenia

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ABSTRACT

Background: Although clinical and neuropsychological findings have implicated functional deficits of the orbitofrontal cortex (OFC) in schizophrenia, structural magnetic resonance imaging (MRI) studies of this region have yielded inconsistent findings. In addition, it remains elusive whether the OFC morphology in first-episode patients is related to their clinical features.
Method: MR images were acquired from 42 (24 males, 18 females) first-episode schizophrenia patients and 35 (20 males, 15 females) age-, gender-, and parental socio-economic status (SES)-matched healthy subjects. The OFC sub-regions (orbital gyrus and straight gyrus) were measured on contiguous 1-mm-thick coronal slices. The OFC sulco-gyral pattern was also evaluated for each subject. Furthermore, the relationships between OFC morphology and clinical measures were examined.
Results: The volumes of the bilateral orbital gyri were significantly reduced in schizophrenia patients compared with healthy subjects, whereas the volumes of the straight gyri did not show differences between the groups. Among the schizophrenia patients, the volume of the left orbital gyrus was inversely correlated with their SES and illness duration. The OFC sulco-gyral patterns were significantly different between the patients and controls in the right hemisphere.
Conclusion: This study demonstrated morphologic abnormalities of the OFC in first-episode schizophrenia patients, which may have reflected neurodevelopmental aberrations and neurodegenerative changes during the first episode of the illness. Our findings also suggest that such brain structural changes are related to the social dysfunction observed in schizophrenia.

1. Introduction

The orbitofrontal cortex (OFC), a part of the prefrontal cortex (PFC) located in the ventral surface of the frontal lobe, is a core component of the social brain network (Kringelbach, 2005; Rolls and Grabenhorst, 2008). The OFC, which has mutual connections with the amygdala, cingulate gyrus, dorsolateral prefrontal cortex (DLPFC), and hypothalamus (Carmichael and Price, 1995a,b; Rempel-Clower and Barbas, 1998; Öngür and Price, 2000), is thought to modulate human

Abbreviations: ANCOVA, Analysis of covariance; ANOVA, Analysis of variance; BPRS, Brief Psychiatric Rating Scale; DUP, Duration of untreated psychosis; ICC, Intraclass correlation coefficients; ICD-10, International Classification of Diseases, 10th edition; ICV, Intracranial volume; JART, Japanese version of the National Adult Reading Test; MRI, Magnetic resonance imaging; OFC, Orbitofrontal cortex; ROI, Region of interest; PFC, Prefrontal cortex; SES, Socio-economic status; VBM, Voxel-based morphometry.

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behavior through a stimulus-reinforcer association learning process, and it is also involved in various cognitive functions such as emotional processing and decision making ability (Haas, 2001; Kringelbach, 2005; Murray et al., 2007; Rolls and Grabenhorst, 2008). Individuals with OFC lesions have been reported to suffer social dysfunction due to impairment of decision making, lack of affects, inappropriate behavior, and irresponsibility, which are often observed in patients with schizophrenia (Eslinger and Damasio, 1985; Anderson et al., 1999; Blair and Cipolotti, 2000; Hornak et al., 2003).

Functional abnormalities of the OFC in schizophrenia have been demonstrated in neuropsychological studies using decision making (Shurman et al., 2005; Kester et al., 2006; Lee et al., 2007; Martino et al., 2007; Nakamura et al., 2008; Yip et al., 2009) and reversal learning (Waltz and Gold, 2007) tasks. Several functional neuroimaging studies have implicated dysfunctional neural networks including the OFC in emotional processing deficits (Dolan and Fullam, 2009; Reske et al., 2009) as well as in positive symptomatology (Parellada et al., 2008) of schizophrenia. However, structural magnetic resonance imaging (MRI) studies of schizophrenia have reported variable findings in this region, with decreased (Gur et al., 2000; Convit et al., 2001; Chemerinski et al., 2002; Kawasaki et al., 2004; Suzuki et al., 2005; Kim et al., 2007; Nakamura et al., 2008; Venkatasubramanian et al., 2008), normal (Baaré et al., 1999; Crespo-Facorro et al., 2000; Yamasue et al., 2004; Shad et al., 2006; Sapara et al., 2007), and even increased (Lacerda et al., 2007) volumes compared with healthy control subjects. The OFC volume deficits in schizophrenia have been associated with several clinical variables such as illness duration (Nakamura et al., 2008) and the severity of both positive (Nakamura et al., 2008) and negative (Baaré et al., 1999; Gur et al., 2000; Koutsouleris et al., 2007) symptoms, but others did not show these relationships (e.g., Suzuki et al., 2005; Kim et al., 2007; Venkatasubramanian et al., 2008). These inconsistencies between reports could be partly related to methodological differences, including different imaging techniques [e.g., region-of-interest (ROI) based or voxel-based, differences in anatomical ROI boundaries] and sample characteristics (e.g., first-episode versus chronic patients, medications status, and symptom severity). Interestingly, recent longitudinal MRI studies have demonstrated progressive gray matter reduction of the OFC during the earliest phases of schizophrenia (Pantelis et al., 2003; Borgwardt et al., 2008), suggesting a neurodegenerative pathology of the illness (Pantelis et al., 2005; Wood et al., 2008). However, most MRI studies of the OFC in schizophrenia have examined chronic patients who had already been exposed to several confounding factors such as antipsychotic medication or chronicity of the illness. In addition, only one ROI-based MRI study has investigated the OFC subregions (i.e., orbital gyrus and straight gyrus) in first-episode schizophrenia (Crespo-Facorro et al., 2000) and the relationship between these subregional volumes and the clinical features seen at the first-episode of the illness remains largely unknown.

The structural heterogeneity of the OFC sulco-gyral pattern is also an important consideration, since altered gross cortical folding patterns have been reported in schizophrenia, possibly reflecting a disturbance in neurodevelopment (Yücel et al., 2002; Le Provost et al., 2003; Fujiwara et al., 2007; Nakamura et al., 2007a, 2008). As for the high inter-individual structural variability of the OFC, Chiavaras and Petrides (2000) classified its sulco-gyral pattern into three types (Types I, II, and III) using the variations of the "H-shaped" sulcus. Based on this method, Nakamura et al. (2007a) demonstrated a significant difference in the distribution of the OFC sulco-gyral pattern between chronically medicated schizophrenia patients and healthy subjects, suggesting that the OFC deficits in schizophrenia at least partly reflect neurodevelopmental abnormalities. Furthermore, they demonstrated that the rarest form, Type III, was associated with poor socioeconomic status, poor cognitive functioning, and severe symptoms in schizophrenia. To the best of our knowledge, however, no MRI study has investigated the OFC sulco-gyral pattern in first-episode schizophrenia patients.

In this study, we used MRI to examine the OFC subregional volume and sulco-gyral pattern in patients with first-episode schizophrenia and matched healthy subjects. On the basis of previous neuroimaging findings, we hypothesized that (1) the OFC volume would be reduced even in first-episode schizophrenia patients compared with healthy subjects and that (2) the distribution of sulco-gyral patterns in patients would be different from that of the controls. We also explored the relationship between OFC morphology and clinical variables in schizophrenia.

2. Methods

2.1. Subjects

Forty-two patients (24 males, 18 females) with first-episode schizophrenia were recruited from the inpatient population at the Tokyo Metropolitan Matsuzawa Hospital. Inclusion criteria were (1) first psychiatric hospitalization, (2) younger than 45 years old, (3) currently psychotic as reflected by the presence of at least one "positive" symptom, and (4) a duration of psychosis of at least one month. Diagnoses were made according to the ICD-10 research criteria for schizophrenia (World Health Organization, 1993), based on direct interview as well as medical chart review. At least two experienced psychiatrists separately examined the patients within two weeks of admission and diagnostic consensus was confirmed. Furthermore, we checked the diagnostic stability of all the patients included in the present study during the follow-up periods (1 to 5 years) after first admission. All but three males were right-handed. All patients had already been treated with neuroleptics at the time of scanning (medication duration median = 57.4 days). Twenty patients were treated with atypical antipsychotics alone, and 22 patients received both typical and atypical antipsychotics. Clinical symptoms were assessed using the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962).

The control subjects consisted of 35 healthy volunteers (20 males, 15 females) who were recruited from the hospital staff and college students. All of the control subjects were right-handed. Control subjects with a personal or family history of psychiatric illness were excluded.

The premorbid IQ for schizophrenia patients and the present IQ for control subjects were estimated using the shortened version of the Japanese version of the National Adult Reading Test (JART) (Matsuoka et al., 2006; Matsuoka and Kim, 2006; Uetsuki et al., 2007).

The subjects' socio-economic status (SES) as well as parental SES was assessed using the Hollingshead's Index (Hollingshead, 1975). The educational level was scored on a seven-point scale according to the completed years of school, and occupation was coded on a nine-point scale. Greater score indicates higher educational/occupational level. When a patient was on a leave of absence due to the onset of psychosis, the occupational factor was scored by the current job unless he/she had quit it. The SES score was calculated by multiplying the scale value for education by a weight of 3 and the scale value for occupation by a weight of 5. Then the SES category (1 to 5) was assigned according to the SES score. A smaller numerical value indicates a higher social position.

Table 1 shows the demographic and clinical data of the subjects. The two groups (i.e., schizophrenia patients and control subjects) were matched for age, gender, and parental SES. The control subjects had a higher SES [ANOVA, $F=33.17$ ($df=1,72$), $p<0.001$] and a higher estimated IQ [ANOVA, $F=8.02(df=1,72)$, $p=0.006$].

All subjects were physically healthy at the time of the study, and none had a lifetime history of serious head trauma, neurological illness, serious medical or surgical illness, or significant alcohol or substance abuse disorder. All subjects participated in this study after providing written informed consent. This study was approved by the Committee on Medical Ethics of Tokyo Metropolitan Matsuzawa Hospital.

2.2. Magnetic resonance imaging procedures

MR images were obtained using a Philips Intera 1.5-T scanner (Philips Medical Systems, Best, The Netherlands) with a three-dimensional sequence yielding 192 contiguous T1-weighted slices of 1.0-mm thickness in the axial plane. The imaging parameters were as follows: repetition time = 21 ms, echo time = 9.2 ms, flip angle = 30°, field of view = 256 mm, matrix size = 256×256 pixels, voxel size = 1.0×1.0×1.0 mm^3. The intensity non-uniformity in MR data was corrected by the non-parametric non-uniform intensity normalization (N3) method (Sled et al., 1998).

Detailed procedures for the image volumetric analysis have been described elsewhere (Takayanagi et al., 2010). Briefly, on a UNIX workstation (Silicon Graphics, Inc., Mountain View, CA), the image data were randomly coded and analyzed with the Dr. View 5.3 software package (Asahi Kasei Joho System, Tokyo, Japan). Head tilt during the scanning was corrected in three dimensions. Brain images were then reconstructed into entire contiguous coronal images of 1-mm thickness vertical to the anterior commissure-posterior commissure line. The signal-intensity histogram distributions from the T1-weighted images across the whole brain for each subject were used to segment the voxels semi-automatically into gray matter, white matter, and cerebrospinal fluid (CSF) according to the Alpert algorithm (Alpert et al., 1996). Finally, obtained gray matter images were carefully inspected and corrected manually if a segmentation error was found, although we employed a signal intensity-inhomogeneity correction (N3) method.

2.3. Brain volumetric measurements

2.3.1. Orbitofrontal cortex volume measurements

Gray matter volumes of the orbital and straight gyri were measured in consecutive 1-mm thick coronal slices. As the lateral orbital sulcus (the lateral ramus of the "H-shaped" sulcus) and olfactory sulcus are less variable than other OFC sulci, we employed these two stably observed sulci as anatomical boundaries of the regions of interest (ROI), as was the case in a recent study (Nakamura et al., 2008). The boundaries of each ROI were defined as described in Table 2. Fig. 1 presents the delineation of both cortical regions.

2.3.2. Intracranial volume (ICV) measurements

For following statistical analyses, ICV was measured to correct for differences in head size. Brain images were reformatted into consecutive 5-mm-thick sagittal slices with each voxel as $1\times1\times5\ mm^3$. The intracranial cavity was manually traced in each slice, using the anatomical landmarks shown by Eritaia et al. (2000).

2.4. Identification of the OFC sulco-gyral pattern

We used the OFC sulco-gyral pattern classification method demonstrated by Chiavaras and Petrides (2000). Briefly, OFC sulco-gyral patterns were classified into the following three types according to the continuity of the "H-shaped" sulcus consisting of the medial orbital sulcus, transverse orbital sulcus, and lateral orbital sulcus. In type I, the medial orbital

Table 1
Demographic and clinical characteristics of the subjects.

	Schizophrenia patients		Control subjects		Analysis of variance			
	Male	Female	Male	Female	Diagnosis		Gender	
	($n=24$)	($n=18$)	($n=20$)	($n=15$)	F	p	F	p
Age (years)	28.6±5.9	29.7±5.7	30.6±5.5	28.5±4.5	0.11	0.741	0.16	0.688
Handedness (number of right handed subjects)	21	18	20	15				
Socio-economic status	2.7±1.2	2.9±1.1	1.7±0.5	1.6±0.5	33.17	<0.001	0.07	0.800
Parental socio-economic status	2.4±0.9	2.7±0.8	2.3±0.7	2.3±0.6	1.35	0.249	1.24	0.270
Estimated IQ[a]	102.6±9.8	102.1±7.7	108.9±7.2	107.2±9.0	8.02	0.006	0.81	0.776
Duration of untreated psychosis (months)	7.7±10.3	9.9±13.6						
Duration of illness (months)	10.5±12.0	13.7±13.1						
Duration of medication (days)	41.8±67.2	79.5±71.9						
Medication (mg/day, chlorpromazine equiv.)	1007.1±516.7	901.3±465.9						
Total BPRS score	40.7±11.1	37.9±9.5						

BPRS, Brief Psychiatric Rating Scale.
[a] Estimated IQ was measured using the shortened version of the Japanese version of the National Adult Reading Test (JART) (Matsuoka et al., 2006; Uetsuki et al., 2007).

Table 2
Anatomical boundaries of the regions of interest.

Region	Anatomical landmark
Orbital gyrus	
Anterior border	Frontomarginal sulcus
Lateral border, anterior part[a]	Frontomarginal sulcus
Lateral border, intermediate part	Lateral orbital sulcus (lateral ramus of "H-shaped" sulcus)
Lateral border, posterior part[a]	Inferior circular sulcus
Medial border, anterior part	Superior rostral sulcus
Medial border, intermediate and posterior part	Olfactory sulcus
Posterior border	Most posterior slice in which inferior circular sulcus was clearly seen
Straight gyrus	
Anterior border	Most anterior slice in which olfactory sulcus was clearly seen
Lateral border	Olfactory sulcus
Medial border	The nearest point on the midline from the deepest point of the olfactory sulcus
Posterior border	Olfactory trigone

[a] When two sulci were seen in the same slice, the lateral orbital sulcus was used as the lateral border.

sulcus was clearly interrupted between the rostral and caudal portions while other sulci were connected. In Type II, the H-shaped sulcus was uninterrupted. In Type III, the rostral and caudal portions of both the medial orbital sulcus and lateral orbital sulcus were interrupted (Fig. 2. Also see figures of Chiavaras and Petrides, 2000).

2.5. Reliability

All ROI measurements and the OFC sulco-gyral pattern classification were carried out by one rater (Y.T.) without knowledge of the subjects' gender or diagnosis. To evaluate the inter-rater reliability, a second rater (N.M.) blinded to the subjects' identity performed both the ROI delineation and sulco-gyral pattern classification. The intra- and inter-rater reliability for ROI measurements were established by measuring all regions in five randomly selected subjects. The intra- and inter-rater intraclass correlation coefficients (ICC) for ROI measurements ranged from 0.97 to 0.99 and from 0.91 to 0.96, respectively. To assess the intra- and inter-rater reliability for the OFC sulco-gyral pattern identification, 25 randomly chosen cases were evaluated (50 hemispheres). The intra- and inter-rater ICC (kappa) for the OFC sulco-gyral pattern classification were 0.93 and 0.83, respectively.

2.6. Statistical analysis

All statistical analyses were performed using the STATISTICA 06J software package (Statsoft, Tulsa, OK). Statistical differences in the regional volumetric measures were analyzed for each ROI, using repeated measures of analysis of covariance (ANCOVA) with ICV and age as covariates, group (patients, controls) and gender (male, female) as between-subject factors, and hemisphere (left, right) as a within-subject factor. For the comparison of ICV, only age was treated as a covariate. Group differences in sulco-gyral pattern distribution were evaluated using the Chi-square test. One-way ANCOVA using the OFC sulco-gyral pattern (Types I–III) as a between-subject factor was conducted for each hemisphere in order to investigate regional volumetric changes associated with different sulcogyral patterns. The relationships between sulco-gyral pattern and clinical parameters (e.g., SES, illness duration, BPRS scores) were analyzed for each hemisphere using ANOVA with the OFC sulco-gyral pattern (Types I–III) as a between-subject factor. Post hoc Tukey's honestly significant difference tests were used to follow up significant main effects or interactions. The relationships between the ROI volumes and estimated IQ, total and subscale BPRS scores, the medication dosage and the exact SES scores were examined with Pearson's r on the basis of normal distribution of these variables (Kolmogorov–Smirnov test), whereas Spearman's rho was used for analyses involving duration of untreated psychosis, duration of illness and duration of medication due to their skewed distribution, or the SES category (ranged 1 to 5), due to the ordinal nature of the data. To control for differences in head size, relative volume (regional volume/ICV) was used for correlation analyses. For these analyses, statistical significance was defined as $P<0.05$ (two-tailed).

3. Results

3.1. Comparison of volumes of regions of interest (ROI) between groups

Repeated measures ANCOVA revealed a significant main effect of diagnosis for the orbital gyrus ($F=7.18$, $df=1,71$, $p=0.009$), but not for the straight gyrus ($F=2.53$, $df=1,71$, $p=0.116$). The post hoc test showed a significant cortical volume reduction of the bilateral orbital gyri in the schizophrenia patients ($p=0.022$ for the left hemisphere and $p<0.001$ for the right hemisphere, respectively). There was no significant difference in the ICV between the groups. Neither a significant main effect of gender/hemisphere nor an interaction among the factors was observed (Table 3).

3.2. Sulco-gyral pattern and volume of ROI

In schizophrenia patients, the OFC sulco-gyral pattern distribution of the right hemisphere was significantly different from that of the healthy subjects ($\chi^2=7.73$, $p=0.021$), while that of the left hemisphere did not differ between the groups ($\chi^2=0.24$, $p=0.89$). The alterations in the distribution of the right OFC sulco-gyral pattern in the schizophrenia patients was accounted for by decreased Type I expression and increased Type III expression among the patients compared with the healthy subjects (Table 4).

One-way ANCOVAs for volumes of the orbital gyrus and the straight gyrus with the OFC sulco-gyral pattern as a between-subject factor did not show any significant main effect or interaction.

3.3. OFC volume and clinical measures

For schizophrenia patients, the relative left orbital gyrus volume was significantly correlated with their SES scores ($r=0.360$, $p=0.019$), SES category (rho $=-0.393$, $p=0.010$) (Fig. 3), and illness duration (rho $=-0.347$, $p=0.024$) (Fig. 4). When we analyzed the education/occupation scores of SES

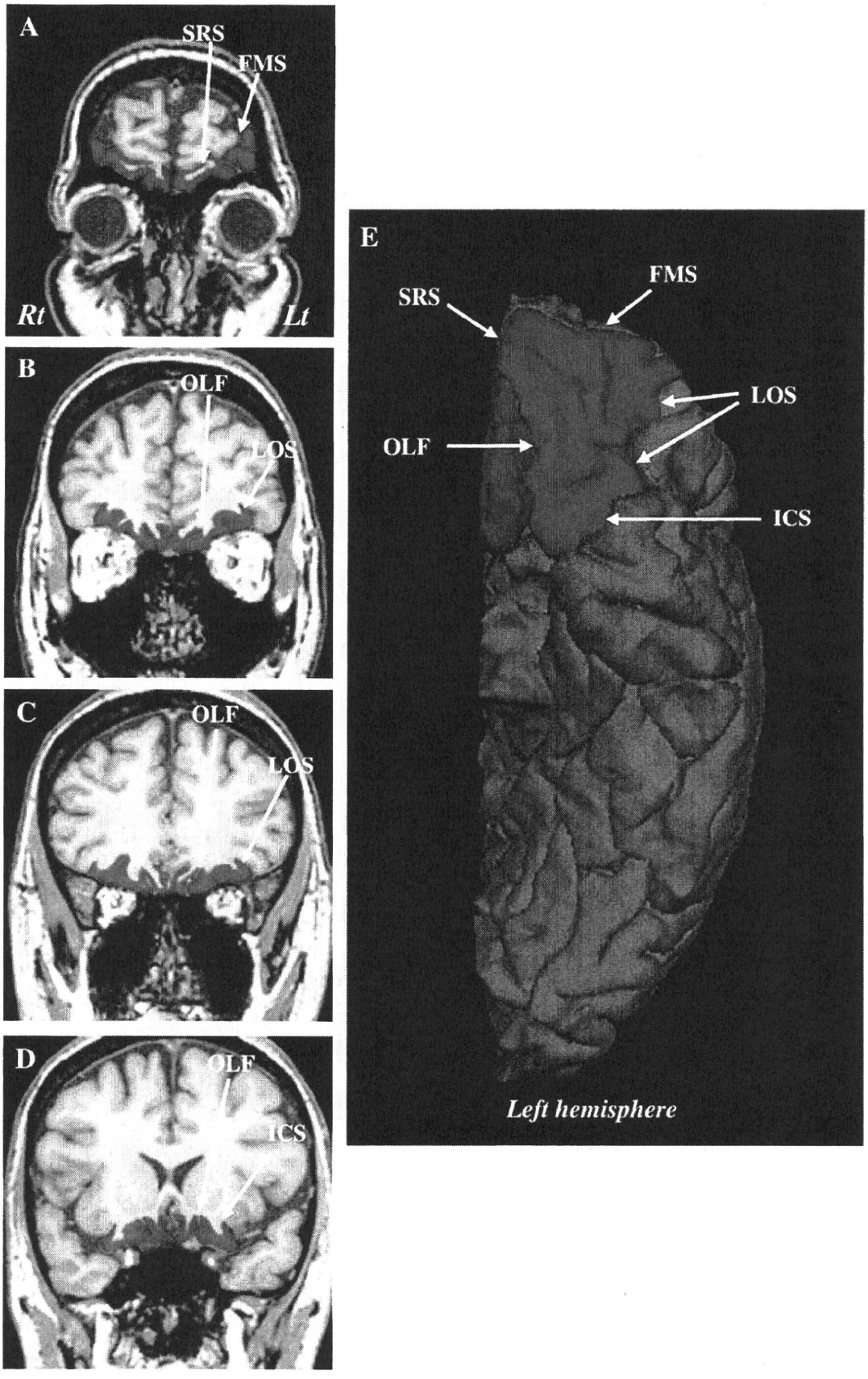

Fig. 1. Examples of regions of interest measured in this study on coronal view [(A) anterior part, (B) (C) intermediate part, and (D) posterior part] and ventral view (E). The OFC subregions are differentially colored in blue (orbital gyrus) and red (straight gyrus). Lt, left hemisphere; Rt, right hemisphere; FMS, frontomarginal sulcus; ICS, inferior circular sulcus; LOS, lateral orbital sulcus; OLF, olfactory sulcus; SRS, superior rostral sulcus.

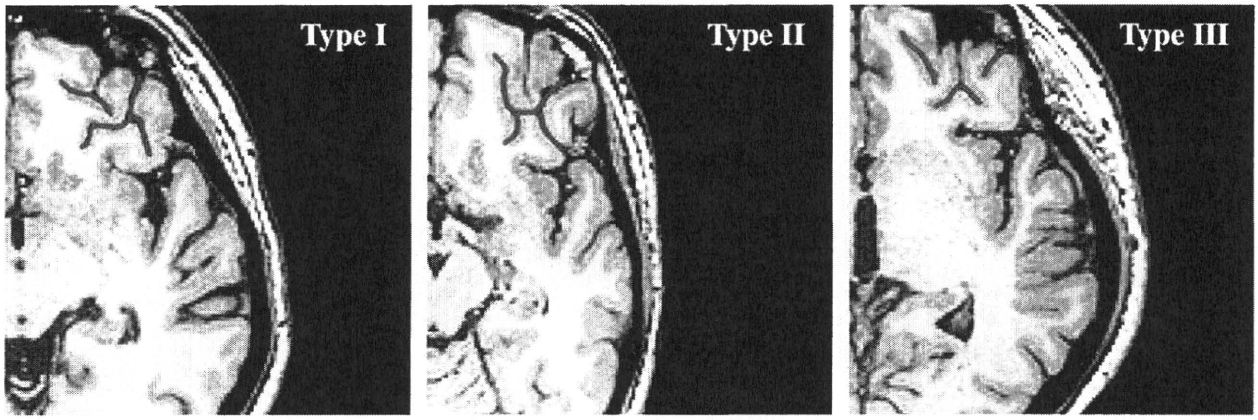

Fig. 2. Examples of the OFC sulco-gyral patterns (Types I, II, and III) from three left hemispheres on the axial view.

separately, both the education scores ($r=0.325, p=0.037$) and the occupation scores ($r=0.305$, $p=0.049$) were correlated with the left orbital gyrus volume. No significant correlation was found between ROI volumes and other clinical variables among patients (i.e., parental SES, duration of untreated psychosis, duration of medication, daily antipsychotic dosage, BPRS total and positive/negative scores).

In healthy subjects, no significant correlation was found between regional brain volumes and demographic measures including the SES.

3.4. Sulco-gyral pattern and clinical measures

In schizophrenia patients, ANOVA did not show any significant main effect of the OFC sulco-gyral pattern on any of the clinical measures used as a dependent variable (Table 5). Among the control subjects, a significant main effect of the OFC sulco-gyral pattern for parental SES was observed in the left hemisphere ($F=3.59$, $p=0.040$). However, a post hoc test did not show statistical significance ($p=0.095$ for Type I versus Type II, $p=0.095$ for Type I versus Type III, and $p=0.944$ for Type II versus Type III, respectively) (Table 5).

4. Discussion

To the best of our knowledge, this is the first MRI study to report both the subregional volumes and sulco-gyral pattern of the OFC in first-episode schizophrenia. In this study, we demonstrated bilateral gray matter reduction of the orbital gyrus, but not of the straight gyrus, in patients with first-episode schizophrenia. These patients also exhibited altered OFC sulco-gyral patterns (decreased Type I and increased Type III expression) compared with the healthy controls in the right hemisphere. In addition, the smaller volume of the left orbital gyrus seen in the schizophrenia patients was related to lower SES and longer illness duration. Our findings implicate OFC morphologic changes, which are unlikely to be due to chronicity of the illness or medication effects, in the pathophysiology of schizophrenia.

4.1. OFC volume reduction in schizophrenia patients

Consistent with recent MRI studies (Kim et al., 2007; Nakamura et al., 2008; Venkatasubramanian et al., 2008; Schobel et al., 2009; Witthaus et al., 2009), we demonstrated that the cortical volumes of the bilateral orbital gyri were significantly reduced in schizophrenia patients compared with those in healthy subjects. The discrepancy between the results of this study and those of other ROI-based studies (Baaré et al., 1999; Crespo-Facorro et al., 2000; Yamasue et al., 2004; Shad et al., 2006; Lacerda et al., 2007; Sapara et al., 2007) can be partly explained by the different ROI definitions used. We measured the OFC subregions (i.e., the orbital gyrus and straight gyrus) on the basis of the optimized ROI definition used by Nakamura et al. (2008), who found similar

Table 3
Comparison of the ROI volumes.

Regions of interest	Schizophrenia patients ($n=42$)	Control subjects ($n=35$)	ANCOVA main effects					
			Diagnosis		Gender		Hemisphere	
			F	*p*	*F*	*p*	*F*	*p*
Intracranial volume	1492.1 ± 141.8	1533.9 ± 127.9	2.70	0.105				
Orbital gyrus								
Left	12.07 ± 2.01	13.25 ± 1.99	7.18	0.009*	0.04	0.841	0.15	0.699
Right	11.56 ± 1.63	12.91 ± 2.60						
Straight gyrus								
Left	3.05 ± 0.46	3.24 ± 0.42	2.53	0.116	0.07	0.789	1.81	0.183
Right	3.36 ± 0.56	3.64 ± 0.58						

Values represent mean ± SD of measured volume (cm^3). ANCOVA, analysis of covariance.
* For the results of the post-hoc tests, see the text.

Table 4
Distribution of OFC sulco-gyral pattern.

	Schizophrenia patients		Control subjects		Chi-square test	
	N	%	*N*	%	χ^2	*p*
Left hemisphere						
Sulco-gyral pattern						
Type I	20	48	18	51		
Type II	13	31	11	31	0.24	0.89
Type III	9	21	6	17		
Right hemisphere						
Sulco-gyral pattern						
Type I	13	31	20	57		
Type II	16	38	12	34	7.73	0.021
Type III	13	31	3	9		

OFC changes as in this study. Lacerda et al. (2007) demonstrated volume increase of the left OFC in first-episode schizophrenia, but their 'geometrical method' only assessed the anterior part of the OFC. Differences in sample characteristics (first-episode or chronic patients, gender ratio, severity of symptoms) might have also been related to the inconsistent OFC findings. The negative findings of several previous studies that mainly employed chronically treated patients (Baaré et al., 1999; Yamasue et al., 2004; Sapara et al., 2007) might have been partly due to the neuroprotective effect of antipsychotics (Lieberman et al., 2005; Molina et al., 2005; Van Haren et al., 2007). Several ROI-based studies examined only male patients (Baaré et al., 1999; Crespo-Facorro et al., 2000; Convit et al., 2001; Chemerinski et al., 2002; Nakamura et al., 2008), whereas one study demonstrated OFC volume reduction in female patients only (Gur et al., 2000). Since the severity of both positive (Nakamura et al., 2008) and negative (Baaré et al., 1999; Gur et al., 2000) symptoms as well as poor social functioning (Gur et al., 2000; Chemerinski et al., 2002; Koutsouleris et al., 2007) has been linked with smaller OFC

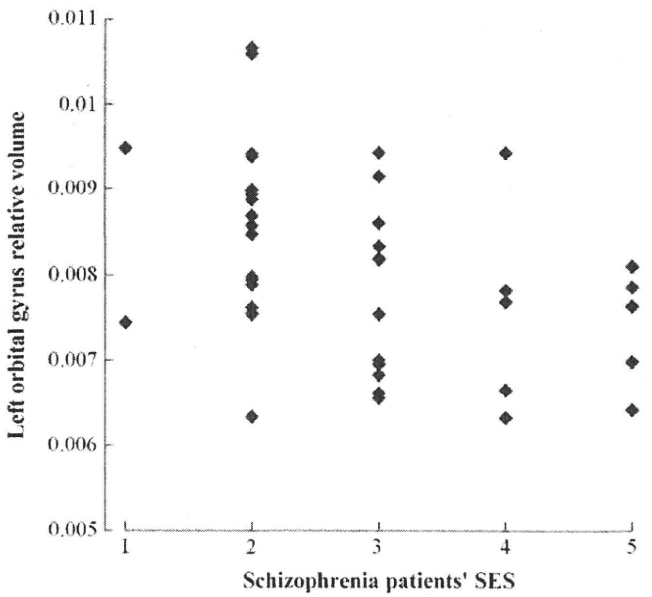

Fig. 3. Correlation between schizophrenia patients' SES and the relative volume of the left orbital gyrus. A smaller left orbital gyrus volume was negatively associated with the patients' SES (rho = −0.395, $p = 0.010$). Note that a smaller numerical value of SES indicates a higher social position.

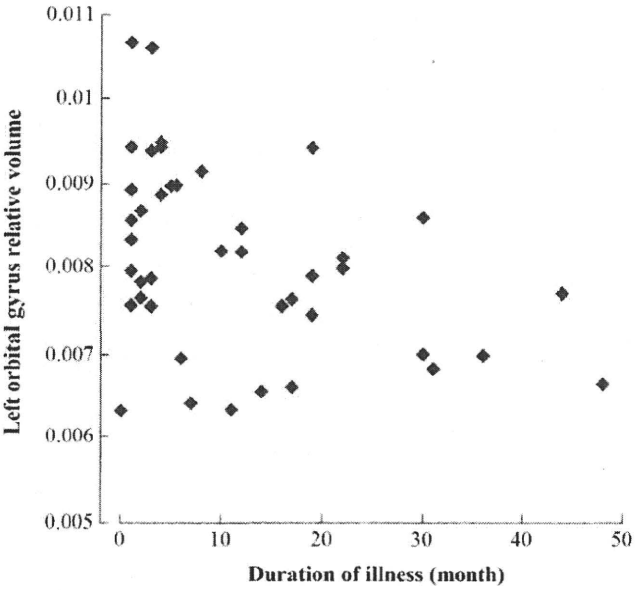

Fig. 4. Correlation between duration of illness and relative volume of the left orbital gyrus. There was a significant inverse correlation between the illness duration and the volume of the left orbital gyrus (rho = −0.347, $p = 0.024$).

volumes in schizophrenia, differences in these clinical factors might also be relevant to the discrepancies in OFC volumetric analysis results.

There is evidence for gender differences in brain structures among healthy subjects (Cosgrove et al., 2007) and gender-specific brain morphologic changes have been described in schizophrenia (Goldstein et al., 2002; Gur et al., 2000; Takahashi et al., 2002). Especially, Gur et al. (2000) demonstrated volume reduction of the OFC only in female patients. Although the present study showed no gender effects on the OFC volume in both schizophrenia patients and healthy controls, possible gender differences of the OFC morphology need to be further tested in a larger sample.

Our finding of a negative correlation between the volume of the left orbital gyrus and illness duration suggests the possibility of progressive volume reduction of the OFC during the early course of schizophrenia. Although no ROI-based MRI study has ever specifically examined OFC volume changes over time, recent longitudinal MRI studies demonstrated progressive volume reduction of the PFC in first-episode schizophrenia (Farrow et al., 2005; Nakamura et al., 2007b; Reig et al., 2009; Sun et al., 2008). Moreover, VBM studies in individuals at high risk of developing psychosis have demonstrated progressive OFC volume decrease during the transition to psychosis (Pantelis et al., 2003; Borgwardt et al., 2008). The present and these previous findings thus support the notion that dynamic brain changes occur during the earliest stages of schizophrenia (Pantelis et al., 2005).

4.2. OFC sulco-gyral pattern

In the present study, the distribution of OFC sulco-gyral patterns in the schizophrenia patients was significantly different from that of the healthy subjects. Consistent with a previous study (Nakamura et al., 2007a), alterations in the OFC sulco-gyral pattern distribution due to deceased Type I expression and increased Type III expression in schizophrenia

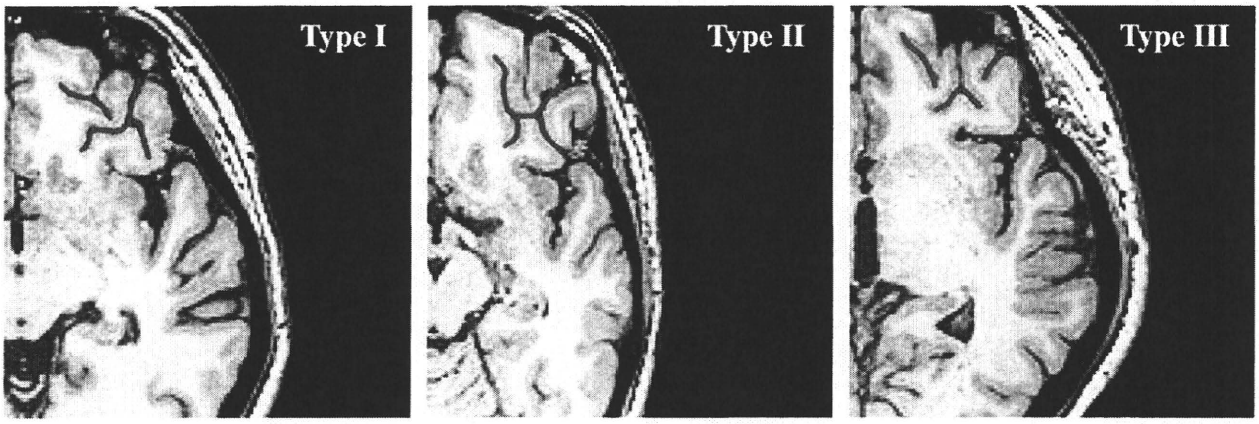

Fig. 2. Examples of the OFC sulco-gyral patterns (Types I, II, and III) from three left hemispheres on the axial view.

separately, both the education scores ($r=0.325, p=0.037$) and the occupation scores ($r=0.305$, $p=0.049$) were correlated with the left orbital gyrus volume. No significant correlation was found between ROI volumes and other clinical variables among patients (i.e., parental SES, duration of untreated psychosis, duration of medication, daily antipsychotic dosage, BPRS total and positive/negative scores).

In healthy subjects, no significant correlation was found between regional brain volumes and demographic measures including the SES.

3.4. Sulco-gyral pattern and clinical measures

In schizophrenia patients, ANOVA did not show any significant main effect of the OFC sulco-gyral pattern on any of the clinical measures used as a dependent variable (Table 5). Among the control subjects, a significant main effect of the OFC sulco-gyral pattern for parental SES was observed in the left hemisphere ($F=3.59$, $p=0.040$). However, a post hoc test did not show statistical significance ($p=0.095$ for Type I versus Type II, $p=0.095$ for Type I versus Type III, and $p=0.944$ for Type II versus Type III, respectively) (Table 5).

4. Discussion

To the best of our knowledge, this is the first MRI study to report both the subregional volumes and sulco-gyral pattern of the OFC in first-episode schizophrenia. In this study, we demonstrated bilateral gray matter reduction of the orbital gyrus, but not of the straight gyrus, in patients with first-episode schizophrenia. These patients also exhibited altered OFC sulco-gyral patterns (decreased Type I and increased Type III expression) compared with the healthy controls in the right hemisphere. In addition, the smaller volume of the left orbital gyrus seen in the schizophrenia patients was related to lower SES and longer illness duration. Our findings implicate OFC morphologic changes, which are unlikely to be due to chronicity of the illness or medication effects, in the pathophysiology of schizophrenia.

4.1. OFC volume reduction in schizophrenia patients

Consistent with recent MRI studies (Kim et al., 2007; Nakamura et al., 2008; Venkatasubramanian et al., 2008; Schobel et al., 2009; Witthaus et al., 2009), we demonstrated that the cortical volumes of the bilateral orbital gyri were significantly reduced in schizophrenia patients compared with those in healthy subjects. The discrepancy between the results of this study and those of other ROI-based studies (Baaré et al., 1999; Crespo-Facorro et al., 2000; Yamasue et al., 2004; Shad et al., 2006; Lacerda et al., 2007; Sapara et al., 2007) can be partly explained by the different ROI definitions used. We measured the OFC subregions (i.e., the orbital gyrus and straight gyrus) on the basis of the optimized ROI definition used by Nakamura et al. (2008), who found similar

Table 3
Comparison of the ROI volumes.

Regions of interest	Schizophrenia patients ($n=42$)	Control subjects ($n=35$)	ANCOVA main effects					
			Diagnosis		Gender		Hemisphere	
			F	*p*	*F*	*p*	*F*	*p*
Intracranial volume	1492.1 ± 141.8	1533.9 ± 127.9	2.70	0.105				
Orbital gyrus								
Left	12.07 ± 2.01	13.25 ± 1.99	7.18	0.009*	0.04	0.841	0.15	0.699
Right	11.56 ± 1.63	12.91 ± 2.60						
Straight gyrus								
Left	3.05 ± 0.46	3.24 ± 0.42	2.53	0.116	0.07	0.789	1.81	0.183
Right	3.36 ± 0.56	3.64 ± 0.58						

Values represent mean ± SD of measured volume (cm^3). ANCOVA, analysis of covariance.
* For the results of the post-hoc tests, see the text.

Table 5
Clinical parameters and sulco-gyral pattern.

Clinical measures	Hemisphere	ANOVA main effect of sulco-gyral pattern (Types I–III)			
		Schizophrenia patients		Control subjects	
		F	*p*	*F*	*p*
Subjects' SES	Left	0.61	0.212	3.23	0.053
	Right	0.59	0.558	0.00	0.995
Parental SES	Left	1.46	0.246	3.59	0.040[a]
	Right	1.42	0.254	0.38	0.69
Estimated IQ	Left	1.32	0.279	0.01	0.931
	Right	1.08	0.350	0.85	0.435
Duration of untreated psychosis	Left	0.11	0.900		
	Right	0.18	0.834		
Duration of illness	Left	0.04	0.965		
	Right	0.25	0.781		
BPRS total score	Left	0.52	0.600		
	Right	0.71	0.500		
BPRS positive score	Left	0.13	0.875		
	Right	1.42	0.254		
BPRS negative score	Left	1.58	0.218		
	Right	0.68	0.514		

ANOVA, Analysis of variance; BPRS, Brief Psychiatric Rating Scale; SES, Socio-economic status.
[a] For the results of the post-hoc tests, see the text.

patients was limited to the right hemisphere. Moreover, in our sample, the alteration of the OFC sulco-gyral pattern distribution in patients was independent of the OFC volume changes. Since sulcal/gyral folding is almost completed by the third trimester of gestation (Chi et al., 1977; Worthen et al., 1986) and structural stability of the folding is generally achieved from soon after birth (Armstrong et al., 1995), the altered sulco-gyral pattern of the OFC seen in the patient group may reflect a neurodevelopmental abnormality in schizophrenia.

Gross brain abnormalities in schizophrenia have already been reported, including the lack of normal leftward sulcal asymmetry of the anterior cingulate cortex (Yücel et al., 2002; Le Provost et al., 2003; Fujiwara et al., 2007). Abnormal asymmetry of prefrontal gyral complexity in schizophrenia has also been demonstrated by both postmortem (Vogeley et al., 2000) and MRI studies (Vogeley et al., 2001; Wiegand et al., 2005). The altered OFC sulco-gyral pattern confined to the right hemisphere in the patient group may have been caused by a neurodevelopmental abnormality occurring in the earliest period of life. Genetic aberrations and/or their interactions with the environment may have contributed to these hemisphere specific-changes, since several sets of genes have been identified as candidates for the evolution of human hemispheric asymmetry (Sun et al., 2005; Sun et al., 2006), which is present as early as 20–22 weeks gestational age (Hering-Hanit et al., 2001).

Nakamura et al. (2007a) examined the OFC sulco-gyral pattern of established schizophrenia patients (duration of illness median = 19.5 years) and found relationships between Type III expression, which was increased among patients, and lower SES, poorer cognitive function, and more severe symptoms, whereas Type I expression was implicated in better cognitive function and milder symptoms. However, we did not find any relationship between the OFC sulco-gyral pattern and clinical variables in first-episode patients. These findings suggest that the altered sulco-gyral pattern could affect the later clinical course of schizophrenia, as demonstrated in chronic patients (Nakamura et al., 2007a), rather than the clinical features of the early phase of illness.

4.3. OFC volume and socio-economic status in schizophrenia patients

In this study, the SES of the first-episode schizophrenia patients was significantly related to the left orbital gyrus volume reduction. Lower social functioning and social status have been repeatedly described in schizophrenia patients (Goldberg and Morrison, 1963; Cohen, 1993; Agerbo et al., 2004). The social dysfunction of schizophrenia patients is probably due to multiple factors such as neurocognitive deficits, lower childhood socio-economic status, and positive and negative symptoms (Wicks et al., 2005; Mohamed et al., 2008). Given the functional significance of the OFC in various cognitive and emotional functions (Hornak et al., 2003; Kringelbach, 2005; Rolls and Grabenhorst, 2008), it can be speculated that the OFC volume deficit gives rise to impaired decision making, lack of affects, inappropriate behavior, and irresponsibility, all of which could affect their social functioning.

Epidemiologic studies have shown that such social impairments are already seen in individuals in the prodromal phase (Häfner et al., 1995; Yung et al., 2003; Mason et al., 2004; Addington et al., 2008). Although the current study cannot address the question of whether the OFC volume reduction occurs and affects subjects' social functioning during the prodromal phase of schizophrenia, the relationship between smaller OFC volume and worse premorbid social functioning in chronic schizophrenia patients (Gur et al., 2000; Chemerinski et al., 2002) and the progressive OFC volume decrease during the transition to psychosis demonstrated previously (Pantelis et al., 2003; Borgwardt et al., 2008) suggest that the structural changes in the OFC and social dysfunction may have developed before/during the onset of overt psychosis.

4.4. Limitations

A few potential confounding factors in this study should be taken into account. First, this study was partly limited by a lack of a comprehensive assessment of neuropsychological functioning (e.g., decision making ability), as previous MRI studies demonstrated the relationship between OFC morphology and cognitive functioning in both schizophrenia patients and healthy control subjects (Nakamura et al., 2007a, 2008). Second, other brain regions that might be associated with social functioning were not measured in the current study. For example, several studies have suggested relationships between social impairment and structural changes in brain regions including the DLPFC (Prasad et al., 2005), anterior cingulate cortex (Fujiwara et al., 2008), and fusiform gyrus (Onitsuka et al., 2005) in patients with schizophrenia. Third, although we examined the patients during their first-episode, all patients had received antipsychotics prior to scanning, even if only for a short period. As there is evidence for antipsychotic medication affecting brain morphology (Lieberman et al., 2005; Molina et al., 2005; Van Haren et al., 2007), future research should examine drug-naïve

patients to fully exclude the influence of antipsychotic medication. Fourth, the patient group in this study was relatively old for first-episode psychosis group (approximately 29 years old), raising the possibility that our sample might not be representative of the general population. Thus, potential sampling bias may limit the ability to generalize the findings from the present study. Finally, since abnormalities of the OFC are likely to be involved in the pathophysiology of other psychiatric disorders (e.g., bipolar disorder; Stanfield et al., 2009), the disease specificity of our findings needs to be tested in future studies.

5. Conclusion

We demonstrated both gray matter reduction, which was localized to the orbital gyrus, and an altered sulco-gyral pattern of the OFC in patients with first-episode schizophrenia. These OFC structural abnormalities might reflect both neurodevelopmental (sulco-gyral pattern) and neurodegenerative (gray matter reduction) changes in schizophrenia patients. Our findings also suggested a relationship between the OFC volume deficits and social functioning impairment in schizophrenia patients even at their first hospitalization.

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Contributors

Authors YT and MS designed the study and wrote the protocol. Authors YT, LO, YM and YS did MRI/clinical data gathering. Authors YT and NM performed MRI data analyses. Author YT wrote the first draft of the manuscript. Authors MS, TT, YK and KN supervised the brain volumetric analyses and the statistical analyses. Authors MS, TT, YK, KN, MI, HY, KK and YO supervised the overall research project and revised the manuscript. Authors MS and TT contributed to editing the final manuscript. All authors have approved the final manuscript.

Conflict of Interest

All authors declare that they have no conflict of interest.

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References

Addington, J., Penn, D., Woods, S.W., Addington, D., Perkins, D.O., 2008. Social functioning in individuals at clinical high risk for psychosis. Schizophr. Res. 99, 119–124.

Agerbo, E., Byrne, M., Eaton, W.W., Mortensen, P.B., 2004. Marital and labor market status in the long run in schizophrenia. Arch. Gen. Psychiatry 61, 28–33.

Alpert, N.M., Berdichevsky, D., Levin, Z., Morris, E.D., Fischman, A.J., 1996. Improved methods for image registration. Neuroimage 3, 10–18.

Anderson, S.W., Bechara, A., Damasio, H., Tranel, D., Damasio, A.R., 1999. Impairment of social and moral behavior related to early damage in human prefrontal cortex. Nat. Neurosci. 2, 1032–1037.

Armstrong, E., Schleicher, A., Omran, H., Curtis, M., Zilles, K., 1995. The ontogeny of human gyrification. Cereb. Cortex 5, 56–63.

Baaré, W.F., Hulshoff Pol, H.E., Hijman, R., Mali, W.P., Viergever, M.A., Kahn, R.S., 1999. Volumetric analysis of frontal lobe regions in schizophrenia: relation to cognitive function and symptomatology. Biol. Psychiatry 45, 1597–1605.

Blair, R.J., Cipolotti, L., 2000. Impaired social response reversal. A case of 'acquired sociopathy'. Brain 123, 1122–1141.

Borgwardt, S.J., McGuire, P.K., Aston, J., Gschwandtner, U., Pflüger, M.O., Stieglitz, R.D., Radue, E.W., Riecher-Rössler, A., 2008. Reductions in frontal, temporal and parietal volume associated with the onset of psychosis. Schizophr. Res. 106, 108–114.

Carmichael, S.T., Price, J.L., 1995a. Limbic connections of the orbital and medial prefrontal cortex in macaque monkeys. J. Comp. Neurol. 363, 615–641.

Carmichael, S.T., Price, J.L., 1995b. Sensory and premotor connections of the orbital and medial prefrontal cortex of macaque monkeys. J. Comp. Neurol. 363, 642–664.

Chemerinski, E., Nopoulos, P.C., Crespo-Facorro, B., Andreasen, N.C., Magnotta, V., 2002. Morphology of the ventral frontal cortex in schizophrenia: relationship with social dysfunction. Biol. Psychiatry 52, 1–8.

Chi, J.G., Dooling, E.C., Gilles, F.H., 1977. Gyral development of the human brain. Ann. Neurol. 1, 86–93.

Chiavaras, M.M., Petrides, M., 2000. Orbitofrontal sulci of the human and macaque monkey brain. J. Comp. Neurol. 422, 35–54.

Cohen, C.I., 1993. Poverty and the course of schizophrenia: implications for research and policy. Hosp. Community Psych. 44, 951–958.

Convit, A., Wolf, O.T., de Leon, M.J., Patalinjug, M., Kandil, E., Caraos, C., Scherer, A., Saint Louis, L.A., Cancro, R., 2001. Volumetric analysis of the pre-frontal regions: findings in aging and schizophrenia. Psychiatry Res. 107, 61–73.

Cosgrove, K.P., Mazure, C.M., Staley, J.K., 2007. Evolving knowledge of sex differences in brain structure, function, and chemistry. Biol. Psychiatry 62, 847–855.

Crespo-Facorro, B., Kim, J., Andreasen, N.C., O'Leary, D.S., Magnotta, V., 2000. Regional frontal abnormalities in schizophrenia: a quantitative gray matter volume and cortical surface size study. Biol. Psychiatry 48, 110–119.

Dolan, M.C., Fullam, R.S., 2009. Psychopathy and functional magnetic resonance imaging blood oxygenation level-dependent responses to emotional faces in violent patients with schizophrenia. Biol. Psychiatry 66, 570–577.

Eritaia, J., Wood, S.J., Stuart, G.W., Bridle, N., Dudgeon, P., Maruff, P., Velakoulis, D., Pantelis, C., 2000. An optimized method for estimating intracranial volume from magnetic resonance images. Magn. Reson. Med. 44, 973–977.

Eslinger, P.J., Damasio, A.R., 1985. Severe disturbance of higher cognition after bilateral frontal lobe ablation: patient EVR. Neurology 35, 1731–1741.

Farrow, T.F., Whitford, T.J., Williams, L.M., Gomes, L., Harris, A.W., 2005. Diagnosis-related regional gray matter loss over two years in first episode schizophrenia and bipolar disorder. Biol. Psychiatry 58, 713–723.

Fujiwara, H., Hirao, K., Namiki, C., Yamada, M., Shimizu, M., Fukuyama, H., Hayashi, T., Murai, T., 2007. Anterior cingulate pathology and social cognition in schizophrenia: a study of gray matter, white matter and sulcal morphometry. Neuroimage 36, 1236–1245.

Fujiwara, H., Shimizu, M., Hirao, K., Miyata, J., Namiki, C., Sawamoto, N., Fukuyama, H., Hayashi, T., Murai, T., 2008. Female specific anterior cingulate abnormality and its association with empathic disability in schizophrenia. Prog. Neuropsychopharmacol. Biol. Psychiatry 32, 1728–1734.

Goldberg, E.M., Morrison, S.L., 1963. Schizophrenia and social class. Br. J. Psychiatry 109, 785–802.

Goldstein, J.M., Seidman, L.J., O'Brien, L.M., Horton, N.J., Kennedy, D.N., Makris, N., Caviness Jr, V.S., Faraone, S.V., Tsuang, M.T., 2002. Impact of normal sexual dimorphisms on sex differences in structural brain abnormalities in schizophrenia assessed by magnetic resonance imaging. Arch. Gen. Psychiatry 59, 154–164.

Gur, R.E., Cowell, P.E., Latshaw, A., Turetsky, B.I., Grossman, R.I., Arnold, S.E., Bilker, W.B., Gur, R.C., 2000. Reduced dorsal and orbital prefrontal gray matter volumes in schizophrenia. Arch. Gen. Psychiatry 57, 761–768.

Haas, L.F., 2001. Phineas Gage and the science of brain localization. J. Neurol. Neurosurg. Psychiatry 71, 761.

Häfner, H., Nowotny, B., Löffler, W., an der Heiden, W., Maurer, K., 1995. When and how does schizophrenia produce social deficits? Eur. Arch. Psychiatry Clin. Neurosci. 246, 17–28.

Hering-Hanit, R., Achiron, R., Lipitz, S., Achiron, A., 2001. Asymmetry of fetal cerebral hemispheres: in utero ultrasound study. Arch. Dis. Child., Fetal Neonatal Ed. 85, 194–196.

Hollingshead, A.B., 1975. Four Factor Index of Social position. Yale Press, New Heaven, CT.

Hornak, J., Bramham, J., Rolls, E.T., Morris, R.G., O'Doherty, J., Bullock, P.R., Polkey, C.E., 2003. Changes in emotion after circumscribed surgical lesions of the orbitofrontal and cingulate cortices. Brain 126, 1691–1712.

Kawasaki, Y., Suzuki, M., Nohara, S., Hagino, H., Takahashi, T., Matsui, M., Yamashita, I., Chitnis, X.A., McGuire, P.K., Seto, H., Kurachi, M., 2004.

Structural brain differences in patients with schizophrenia and schizotypal disorder demonstrated by voxel-based morphometry. Eur. Arch. Psychiatry Clin. Neurosci. 254, 406–414.
Kester, H.M., Sevy, S., Yechiam, E., Burdick, K.E., Cervellione, K.L., Kumra, S., 2006. Decision-making impairments in adolescents with early-onset schizophrenia. Schizophr. Res. 85, 113–123.
Kim, J.J., Kim, D.J., Kim, T.G., Seok, J.H., Chun, J.W., Oh, M.K., Park, H.J., 2007. Volumetric abnormalities in connectivity-based subregions of the thalamus in patients with chronic schizophrenia. Schizophr. Res. 97, 226–235.
Koutsouleris, N., Gaser, C., Jäger, M., Bottlender, R., Frodl, T., Holzinger, S., Schmitt, G.J., Zetzsche, T., Burgermeister, B., Scheuerecker, J., Born, C., Reiser, M., Möller, H.J., Meisenzahl, E.M., 2007. Structural correlates of psychopathological symptom dimensions in schizophrenia: a voxel-based morphometric study. Neuroimage 39, 1600–1612.
Kringelbach, M.L., 2005. The human orbitofrontal cortex: linking reward to hedonic experience. Nat. Rev., Neurosci. 6, 691–702.
Lacerda, A.L., Hardan, A.Y., Yorbik, O., Vemulapalli, M., Prasad, K.M., Keshavan, M.S., 2007. Morphology of the orbitofrontal cortex in first-episode schizophrenia: relationship with negative symptomatology. Prog. Neuropsychopharmacol. Biol. Psychiatry 31, 510–516.
Le Provost, J.B., Bartres-Faz, D., Paillere-Martinot, M.L., Artiges, E., Pappata, S., Recasens, C., Perez-Gomez, M., Bernardo, M., Baeza, I., Bayle, F., Martinot, J.L., 2003. Paracingulate sulcus morphology in men with early-onset schizophrenia. Br. J. Psychiatry 182, 228–232.
Lee, Y., Kim, Y.T., Seo, E., Park, O., Jeong, S.H., Kim, S.H., Lee, S.J., 2007. Dissociation of emotional decision-making from cognitive decision-making in chronic schizophrenia. Psychiatry Res. 152, 113–120.
Lieberman, J.A., Tollefson, G.D., Charles, C., Zipursky, R., Sharma, T., Kahn, R.S., Keefe, R.S., Green, A.I., Gur, R.E., McEvoy, J., Perkins, D., Hamer, R.M., Gu, H., Tohen, M., HGDH Study Group, 2005. Antipsychotic drug effects on brain morphology in first-episode psychosis. Arch. Gen. Psychiatry 62, 361–370.
Martino, D.J., Bucay, D., Butman, J.T., Allegri, R.F., 2007. Neuropsychological frontal impairments and negative symptoms in schizophrenia. Psychiatry Res. 152, 121–128.
Mason, O., Startup, M., Halpin, S., Schall, U., Conrad, A., Carr, V., 2004. Risk factors for transition to first episode psychosis among individuals with 'at-risk mental states'. Schizophr. Res. 71, 227–237.
Matsuoka, K., Kim, Y., 2006. Japanese Adult Reading Test (JART). Shinkou-Igaku publishers, Tokyo.
Matsuoka, K., Uno, M., Kasai, K., Koyama, K., Kim, Y., 2006. Estimation of premorbid IQ in individuals with Alzheimer's disease using Japanese ideographic script (Kanji) compound words: Japanese version of National Adult Reading Test. Psychiatry Clin. Neurosci. 60, 332–339.
Mohamed, S., Rosenheck, R., Swartz, M., Stroup, S., Lieberman, J.A., Keefe, R.S., 2008. Relationship of cognition and psychopathology to functional impairment in schizophrenia. Am. J. Psychiatry 165, 978–987.
Molina, V., Reig, S., Sanz, J., Palomo, T., Benito, C., Sánchez, J., Sarramea, F., Pascau, J., Desco, M., 2005. Increase in gray matter and decrease in white matter volumes in the cortex during treatment with atypical neuroleptics in schizophrenia. Schizophr. Res. 80, 61–71.
Murray, E.A., O'Doherty, J.P., Schoenbaum, G., 2007. What we know and do not know about the functions of the orbitofrontal cortex after 20 years of cross-species studies. J. Neurosci. 27, 8166–8169.
Nakamura, M., Nestor, P.G., McCarley, R.W., Levitt, J.J., Hsu, L., Kawashima, T., Niznikiewicz, M., Shenton, M.E., 2007a. Altered orbitofrontal sulcogyral pattern in schizophrenia. Brain 130, 693–707.
Nakamura, M., Salisbury, D.F., Hirayasu, Y., Bouix, S., Pohl, K.M., Yoshida, T., Koo, M.S., Shenton, M.E., McCarley, R.W., 2007b. Neocortical gray matter volume in first-episode schizophrenia and first-episode affective psychosis: a cross-sectional and longitudinal MRI study. Biol. Psychiatry 62, 773–783.
Nakamura, M., Nestor, P.G., Levitt, J.J., Cohen, A.S., Kawashima, T., Shenton, M.E., McCarley, R.W., 2008. Orbitofrontal volume deficit in schizophrenia and thought disorder. Brain 131, 180–195.
Öngür, D., Price, J.L., 2000. The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. Cereb. Cortex 10, 206–219.
Onitsuka, T., Nestor, P.G., Gurrera, R.J., Shenton, M.E., Kasai, K., Frumin, M., Niznikiewicz, M.A., McCarley, R.W., 2005. Association between reduced extraversion and right posterior fusiform gyrus gray matter reduction in chronic schizophrenia. Am. J. Psychiatry 162, 599–601.
Overall, J.E., Gorham, D.R., 1962. The Brief Psychiatric Rating Scale. Psychol. Rep. 10, 799–812.
Pantelis, C., Velakoulis, D., McGorry, P.D., Wood, S.J., Suckling, J., Phillips, L.J., Yung, A.R., Bullmore, E.T., Brewer, W., Soulsby, B., Desmond, P., McGuire, P.K., 2003. Neuroanatomical abnormalities before and after onset of psychosis: a cross-sectional and longitudinal MRI comparison. Lancet 361, 281–288.
Pantelis, C., Yücel, M., Wood, S.J., Velakoulis, D., Sun, D., Berger, G., Stuart, G.W., Yung, A., Phillips, L., McGorry, P.D., 2005. Structural brain imaging evidence for multiple pathological processes at different stages of brain development in schizophrenia. Schizophr. Bull. 31, 672–696.
Parellada, E., Lomena, F., Font, M., Pareto, D., Gutierrez, F., Simo, M., Fernández-Egea, E., Pavia, J., Ros, D., Bernardo, M., 2008. Fluordeoxyglucose-PET study in first-episode schizophrenic patients during the hallucinatory state, after remission and during linguistic–auditory activation. Nucl. Med. Commun. 29, 894–900.
Prasad, K.M., Sahni, S.D., Rohm, B.R., Keshavan, M.S., 2005. Dorsolateral prefrontal cortex morphology and short-term outcome in first-episode schizophrenia. Psychiatry Res. 140, 147–155.
Reig, S., Moreno, C., Moreno, D., Burdalo, M., Janssen, J., Parellada, M., Zabala, A., Desco, M., Arango, C., 2009. Progression of brain volume changes in adolescent-onset psychosis. Schizophr. Bull. 35, 233–243.
Rempel-Clower, N.L., Barbas, H., 1998. Topographic organization of connections between the hypothalamus and prefrontal cortex in the rhesus monkey. J. Comp. Neurol. 398, 393–419.
Reske, M., Habel, U., Kellermann, T., Backes, V., Jon Shah, N., von Wilmsdorff, M., Gaebel, W., Zilles, K., Schneider, F., 2009. Differential brain activation during facial emotion discrimination in first-episode schizophrenia. J. Psychiatr. Res. 43, 592–599.
Rolls, E.T., Grabenhorst, F., 2008. The orbitofrontal cortex and beyond: from affect to decision-making. Prog. Neurobiol. 86, 216–244.
Sapara, A., Cooke, M., Fannon, D., Francis, A., Buchanan, R.W., Anilkumar, A.P., Barkataki, I., Aasen, I., Kuipers, E., Kumari, V., 2007. Prefrontal cortex and insight in schizophrenia: a volumetric MRI study. Schizophr. Res. 89, 22–34.
Schobel, S.A., Kelly, M.A., Corcoran, C.M., Van Heertum, K., Seckinger, R., Goetz, R., Harkavy-Friedman, J., Malaspina, D., 2009. Anterior hippocampal and orbitofrontal cortical structural brain abnormalities in association with cognitive deficits in schizophrenia. Schizophr. Res. 114, 110–118.
Shad, M.U., Muddasani, S., Keshavan, M.S., 2006. Prefrontal subregions and dimensions of insight in first-episode schizophrenia—a pilot study. Psychiatry Res. 146, 35–42.
Shurman, B., Horan, W.P., Nuechterlein, K.H., 2005. Schizophrenia patients demonstrate a distinctive pattern of decision-making impairment on the Iowa Gambling Task. Schizophr. Res. 72, 215–224.
Sled, J.G., Zijdenbos, A.P., Evans, A.C., 1998. A nonparametric method for automatic correction of intensity nonuniformity in MRI data. IEEE Trans. Med. Imag. 17, 87–97.
Stanfield, A.C., Moorhead, T.W., Job, D.E., McKirdy, J., Sussmann, J.E., Hall, J., Giles, S., Johnstone, E.C., Lawrie, S.M., McIntosh, A.M., 2009. Structural abnormalities of ventrolateral and orbitofrontal cortex in patients with familial bipolar disorder. Bipolar Disord. 11, 135–144.
Sun, T., Patoine, C., Abu-Khalil, A., Visvader, J., Sum, E., Cherry, T.J., Orkin, S.H., Geschwind, D.H., Walsh, C.A., 2005. Early asymmetry of gene transcription in embryonic human left and right cerebral cortex. Science 308, 1794–1798.
Sun, T., Collura, R.V., Ruvolo, M., Walsh, C.A., 2006. Genomic and evolutionary analyses of asymmetrically expressed genes in human fetal left and right cerebral cortex. Cereb. Cortex 16, 18–25.
Sun, D., Stuart, G.W., Jenkinson, M., Wood, S.J., McGorry, P.D., Velakoulis, D., van Erp, T.G., Thompson, P.M., Toga, A.W., Smith, D.J., Cannon, T.D., Pantelis, C., 2008. Brain surface contraction mapped in first-episode schizophrenia: a longitudinal magnetic resonance imaging study. Mol. Psychiatry 14, 976–986.
Suzuki, M., Zhou, S.Y., Takahashi, T., Hagino, H., Kawasaki, Y., Niu, L., Matsui, M., Seto, H., Kurachi, M., 2005. Differential contributions of prefrontal and temporolimbic pathology to mechanisms of psychosis. Brain 128, 2109–2122.
Takahashi, T., Kawasaki, Y., Kurokawa, K., Hagino, H., Nohara, S., Yamashita, I., Nakamura, K., Murata, M., Matsui, M., Suzuki, M., Seto, H., Kurachi, M., 2002. Lack of normal structural asymmetry of the anterior cingulate gyrus in female patients with schizophrenia: a volumetric magnetic resonance imaging study. Schizophr. Res. 55, 69–81.
Takayanagi, Y., Kawasaki, Y., Nakamura, K., Takahashi, T., Orikabe, L., Toyoda, E., Mozue, Y., Sato, Y., Itokawa, M., Yamasue, H., Kasai, K., Kurachi, M., Okazaki, Y., Matsushita, M., Suzuki, M., 2010. Differentiation of first-episode schizophrenia patients from healthy controls using ROI-based multiple structural brain variables. Prog. Neuropsychopharmacol. Biol. Psychiatry 34, 10–17.
Uetsuki, M., Matsuoka, K., Kasai, K., Araki, T., Suga, M., Yamasue, H., Maeda, K., Yamasaki, S., Furukawa, S., Iwanami, A., Kato, N., Kim, Y., 2007. Estimation of premorbid IQ by shortened version of JARTs in schizophrenia. Seishin Igaku 49, 17–23.
van Haren, N.E., Hulshoff Pol, H.E., Schnack, H.G., Cahn, W., Mandl, R.C., Collins, D.L., Evans, A.C., Kahn, R.S., 2007. Focal gray matter changes in schizophrenia across the course of the illness: a 5-year follow-up study. Neuropsychopharmacology 32, 2057–2066.
Venkatasubramanian, G., Jayakumar, P.N., Gangadhar, B.N., Keshavan, M.S., 2008. Automated MRI parcellation study of regional volume and thickness

of prefrontal cortex (PFC) in antipsychotic-naïve schizophrenia. Acta Psychiatr. Scand. 117, 420–431.
Vogeley, K., Schneider-Axmann, T., Pfeiffer, U., Tepest, R., Bayer, T.A., Bogerts, B., Honer, W.G., Falkai, P., 2000. Disturbed gyrification of the prefrontal region in male schizophrenic patients: a morphometric postmortem study. Am. J. Psychiatry 157, 34–39.
Vogeley, K., Tepest, R., Pfeiffer, U., Schneider-Axmann, T., Maier, W., Honer, W. G., Falkai, P., 2001. Right frontal hypergyria differentiation in affected and unaffected siblings from families multiply affected with schizophrenia: a morphometric MRI study. Am. J. Psychiatry 158, 494–496.
Waltz, J.A., Gold, J.M., 2007. Probabilistic reversal learning impairments in schizophrenia: further evidence of orbitofrontal dysfunction. Schizophr. Res. 93, 296–303.
Wicks, S., Hjern, A., Gunnell, D., Lewis, G., Dalman, C., 2005. Social adversity in childhood and the risk of developing psychosis: a national cohort study. Am. J. Psychiatry 162, 1652–1657.
Wiegand, L.C., Warfield, S.K., Levitt, J.J., Hirayasu, Y., Salisbury, D.F., Heckers, S., Bouix, S., Schwartz, D., Spencer, M., Dickey, C.C., Kikinis, R., Jolesz, F.A., McCarley, R.W., Shenton, M.E., 2005. An in vivo MRI study of prefrontal cortical complexity in first-episode psychosis. Am. J. Psychiatry 162, 65–70.
Witthaus, H., Kaufmann, C., Bohner, G., Ozgürdal, S., Gudlowski, Y., Gallinat, J., Ruhrmann, S., Brüne, M., Heinz, A., Klingebiel, R., Juckel, G., 2009. Gray matter abnormalities in subjects at ultra-high risk for schizophrenia and first-episode schizophrenic patients compared to healthy controls. Psychiatry Res. 173, 163–169.
Wood, S.J., Pantelis, C., Velakoulis, D., Yücel, M., Fornito, A., McGorry, P.D., 2008. Progressive changes in the development toward schizophrenia: studies in subjects at increased symptomatic risk. Schizophr. Bull. 34, 322–329.
World Health Organization, 1993. The ICD-10 Classification of Mental and Behavioral Disorders: Diagnostic Criteria for Research. Geneva, Switzerland.
Worthen, N.J., Gilbertson, V., Lau, C., 1986. Cortical sulcal development seen on sonography: relationship to gestational parameters. J. Ultrasound Med. 5, 153–156.
Yamasue, H., Iwanami, A., Hirayasu, Y., Yamada, H., Abe, O., Kuroki, N., Fukuda, R., Tsujii, K., Aoki, S., Ohtomo, K., Kato, N., Kasai, K., 2004. Localized volume reduction in prefrontal, temporolimbic, and paralimbic regions in schizophrenia: an MRI parcellation study. Psychiatry Res. 131, 195–207.
Yip, S.W., Sacco, K.A., George, T.P., Potenza, M.N., 2009. Risk/reward decision-making in schizophrenia: a preliminary examination of the influence of tobacco smoking and relationship to Wisconsin Card Sorting Task performance. Schizophr. Res. 110, 156–164.
Yücel, M., Stuart, G.W., Maruff, P., Wood, S.J., Savage, G.R., Smith, D.J., Crowe, S.F., Copolov, D.L., Velakoulis, D., Pantelis, C., 2002. Paracingulate morphologic differences in males with established schizophrenia: a magnetic resonance imaging morphometric study. Biol. Psychiatry 52, 15–23.
Yung, A.R., Phillips, L.J., Yuen, H., Francey, S., McFarlane, C.A., Hallgreen, M.A., McGorry, P.D., 2003. Psychosis prediction: a 12-month follow-up of a high-risk ('prodromal') group. Schizophr. Res. 60, 21–32.

島皮質と統合失調症

高橋 努　鈴木道雄

はじめに

統合失調症は，数年間の前駆状態を経て思春期・青年期に好発する精神疾患であり，幻覚・妄想などの陽性症状に加え，情動や思考の貧困などの陰性症状や認知機能障害といった様々な精神症状により特徴付けられる．しかし，その病因や病態生理学的メカニズムは十分に解明されていない．近年，磁気共鳴画像(magnetic resonance imaging, MRI)などの脳画像診断技術の進歩により，統合失調症患者の脳における軽微な構造異常の特徴が明らかとなりつつあり(図1)，特に前頭葉や側頭辺縁-傍辺縁系構造の体積減少が注目される[1]．

島皮質を中心とした神経回路網およびその諸機能に関しては永井らの総説[2]に詳しいが，島皮質は前頭葉，側頭葉，頭頂葉，大脳辺縁系，および視床などと密な線維連絡を持ち，情動や様々な認知機能に関連した大脳辺縁系における統合領域と考えられる．島皮質内の機能局在に関しては不明な点も多いが，前・中部島皮質が感情や痛みの知覚，言語に関連した情報処理などに関与するのに対し，後方部分は体性感覚や会話時の聴覚系情報処理に関連すると考えられる．

島皮質の形態および機能の異常は，統合失調症をはじめとする様々な精神疾患の病態に関与することが示唆されている．本稿では，統合失調症における島皮質異常についての知見を概観し，さらに，前駆期を含む各臨床病期における島皮質体積の変化に関する最近のMRI研究の成果を紹

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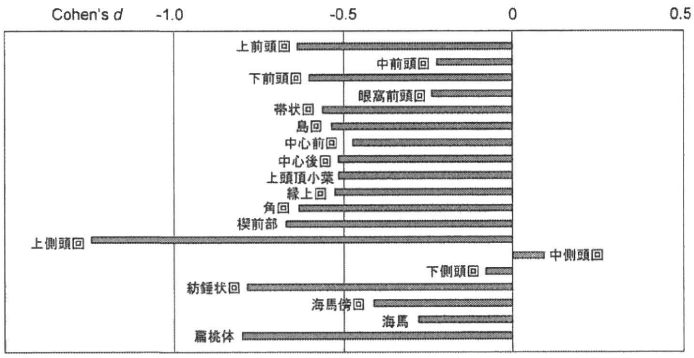

図1　健常者(63例)と比較した統合失調症患者(62例)における灰白質体積変化のeffect size(Cohen's *d*)
(当教室における関心領域法によるMRI研究の結果より作成)

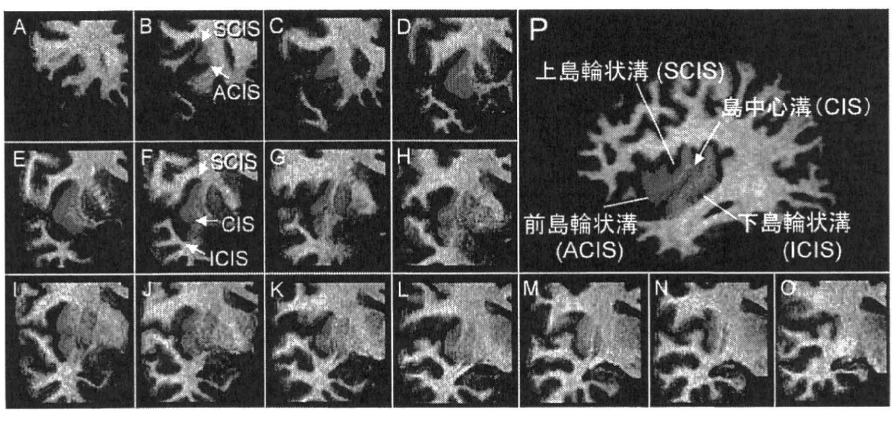

図2　島短回(青)および島長回(赤)のT1強調MRI画像
A～O：冠状断，P：矢状断
(Takahashiら[10]より一部改変)

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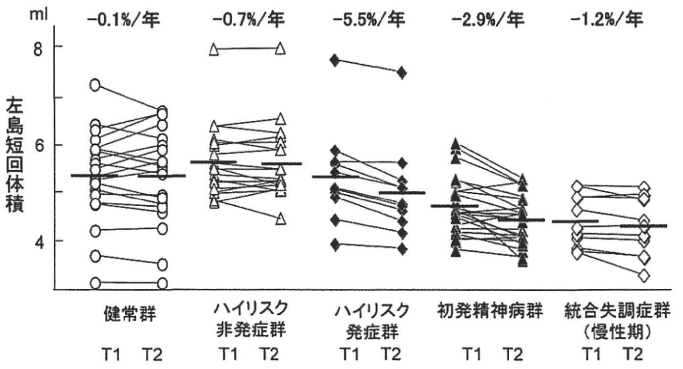

図 3　各群における左島短回体積の縦断的変化
（Takahashi ら[19,20]より作成）

T 1 は初回撮像時，T 2 は follow 時（1〜4 年後）を示す．経過中に精神病を発症したハイリスク群（ハイリスク発症群）の発症前後において，最も顕著な縦断的変化がみられた．他の部位（右短回および両側長回）にもほぼ同様の変化を認めた．

介する．

統合失調症における島皮質異常

X 線 CT を用いた初期の脳画像研究において，Sylvius 裂の開大は統合失調症にみられる主要な所見のひとつであったが[1]，この所見は少なくとも一部は島皮質体積の減少を反映した変化と考えられる．統合失調症の死後脳研究において，Jakob と Beckmann[3]は内嗅皮質および腹側島皮質における細胞構築の異常を報告し，これらの脳部位における胎生期の神経発達障害を示唆した．近年の MRI 研究では voxel-based morphometry（VBM）法，すなわち個々の画像データを標準脳座標系に合わせて変換した後にボクセル単位で全脳レベルの比較を行う方法が一般的となりつつある．Glahn ら[4]は 31 編の VBM 研究からなるメタ解析を行い，1195 例の統合失調症患者の灰白質は 1262 例の健常対照者と比較して，両側島皮質，前部帯状回，左海馬傍回，左中前頭回，中心後回，および視床などで有意に減少しており，特に左島皮質を中心とした下前頭回，上側頭回，および中心前回を含む領域で最も変化が大きいことを報告した．統合失調症患者における両側性[5]ないし左優位[6,7]の島皮質体積減少は関心領域法による MRI 研究でも報告されており，これらの体積減少は陰性[8]および陽性[6,9]症状の重症度とも相関するようである．一方，島皮質体積を島中心溝により前後（短回および長回；図 2）に分割して測定した MRI 研究は少なく，結果の不一致もみられる．統合失調症群において健常群と比較して島短回，島長回ともに両側性の体積減少を認めたわれわれの報告[10]に対し，Makris ら[11]は島短回のみ（左優位），Saze ら[12]は右長回優位の体積減少を報告した．統合失調症における島皮質の異常は脳機能画像研究からも示唆され，安静時の糖代謝低下[13]や幻聴時の賦活[14]に加え，不快な嗅覚刺激[15]や言語記憶課題[16]，言語流暢性課題[17]といった賦活課題時の活性化の障害が報告されている．

以上の所見より，統合失調症の病的過程に島皮質が関与し，特に幻聴をはじめとする精神病症状や種々の認知機能障害の少なくとも一部については，島皮質を含む神経回路の異常が中心的な役割を果たすことが示唆される．また，自己意識の形成における島皮質の重要な役割が示唆されており[18]，今後，島皮質の機能がさらに明らかになることにより，統合失調症の病態生理においてもその重要性が増すものと考えられる．

精神病前駆期における島皮質体積の変化

統合失調症患者では発病初期にすでに島皮質体積の減少が報告されていたが[5,6]，この形態学的変化の生じる時期や疾患経過中の進行性変化については不明な点が多かった．最近の MRI 研究において，島皮質の体積減少は後に統合失調症などの精神病を発症したハイリスク者にすでに認められ[19]，その発症の前後および統合失調症の初回エピソード中において進行すること，また，島皮質の進行性体積減少の程度が臨床症状の重症度と関連することが示された[20]．しかし，慢性期の統合失調症患者には健常者と比較して有意な島皮質の進行性変化はみられず（図 3）[20]，統合失調症における脳の病的過程が病初期により顕著に生じることが示唆される．これらの脳画像所見は，多くの統合失調症患者で臨床症状や社会的機能などの悪化が発病早期に生じ，発症後数年の間に安定化するという臨床的観察を支持するものである[21]．このような進行性脳構造変化の機序は明らかではないが，前駆期を含む病初期における島皮質体積の変化は，将来の精神病発症の予測因子あるいは早期治療における治療標的としての役割が期待できるかもしれない．

むすび

統合失調症における島皮質の形態および機能の異常に関する報告を概観し，さらに，精神病前駆期の島皮質体積変化に関するMRI研究の成果を紹介した．様々な精神疾患における島皮質異常の疾患特異性や島皮質体積変化に対する投薬(抗精神病薬など)の影響については，今後さらに検討が必要と思われる．

文献

1) 鈴木道雄，高橋 努，川崎康弘，他．統合失調症脳の構造的変化．臨床精神薬理．2004；7：321-30.
2) 永井道明，岸 浩一郎，加藤 敏．大脳皮質島葉の構造と諸機能—最近の研究の展望．神経進歩．2001；46：157-74.
3) Jakob H, Beckmann H. Prenatal developmental disturbances in the limbic allocortex in schizophrenics. J Neural Transm. 1986；65：303-26.
4) Glahn DC, Laird AR, Ellison-Wright I, et al. Meta-analysis of gray matter anomalies in schizophrenia：application of anatomic likelihood estimation and network analysis. Biol Psychiatry. 2008；64：774-81.
5) Kasai K, Shenton ME, Salisbury DF, et al. Differences and similarities in insular and temporal pole MRI gray matter volume abnormalities in first-episode schizophrenia and affective psychosis. Arch Gen Psychiatry. 2003；60：1069-77.
6) Crespo-Facorro B, Kim J, Andreasen NC, et al. Insular cortex abnormalities in schizophrenia：a structural magnetic resonance imaging study of first-episode patients. Schizoph Res. 2000；46：35-43.
7) Kim JJ, Youn T, Lee JM, et al. Morphometric abnormality of the insula in schizophrenia：a comparison with obsessive-compulsive disorder and normal control using MRI. Schizoph Res. 2003；60：191-8.
8) Sigmundsson T, Suckling J, Maier M, et al. Structural abnormalities in frontal, temporal, and limbic regions and interconnecting white matter tracts in schizophrenic patients with prominent negative symptoms. Am J Psychiatry. 2001；158：234-43.
9) Shapleske J, Rossell SL, Chitnis XA, et al. A computational morphometric MRI study of schizophrenia：effects of hallucinations. Cerebral Cortex. 2002；12：1331-41.
10) Takahashi T, Suzuki M, Zhou SY, et al. Volumetric MRI study of the short and long insular cortices in schizophrenia spectrum disorders. Psychiatry Res. 2005；138：209-20.
11) Makris N, Goldstein JM, Kennedy D, et al. Decreased volume of left and total anterior insular lobule in schizophrenia. Schizoph Res. 2006；83：155-71.
12) Saze T, Hirao K, Namiki C, et al. Insular volume reduction in schizophrenia. Eur Arch Psychiatry Clin Neurosci. 2007；257：473-9.
13) Desco M, Gispert JD, Reig S, et al. Cerebral metabolic patterns in chronic and recent-onset schizophrenia. Psychiatry Res. 2003；122：125-35.
14) Shergill SS, Brammer MJ, Williams SC, et al. Mapping auditory hallucinations in schizophrenia using functional magnetic resonance imaging. Arch Gen Psychiatry. 2000；57：1033-8.
15) Crespo-Facorro B, Paradiso S, Andreasen NC, et al. Neural mechanisms of anhedonia in schizophrenia：a PET study of response to unpleasant and pleasant odors. JAMA. 2001；286：427-35.
16) Crespo-Facorro B, Wiser AK, Andreasen NC, et al. Neural basis of novel and well-learned recognition memory in schizophrenia：a positron emission tomography study. Human Brain Mapping. 2001；12：219-31.
17) Curtis VA, Bullmore ET, Brammer MJ, et al. Attenuated frontal activation during a verbal fluency task in patients with schizophrenia. Am J Psychiatry. 1998；155：1056-63.
18) Craig AD. How do you feel—now？The anterior insula and human awareness. Nat Rev Neurosci. 2009；10：59-70.
19) Takahashi T, Wood SJ, Yung AR, et al. Insular cortex gray matter changes in individuals at ultra-high-risk of developing psychosis. Schizoph Res. 2009 a；111：94-102.
20) Takahashi T, Wood SJ, Soulsby B, et al. Follow-up MRI study of the insular cortex in first-episode psychosis and chronic schizophrenia. Schizoph Res. 2009 b；108：48-55.
21) 鈴木道雄，高橋 努，田仲耕大．統合失調症の早期介入・初期治療と予後．Schizoph Front. 2009；10：18-23.

第105回日本精神神経学会総会

シンポジウム

サイコーシス早期段階における生物学的所見

住吉 太幹[1,2]，川崎 康弘[1,2]，高橋 努[1,2]，中村 主計[1]，樋口 悠子[1]，瀬尾 友徳[1]，伊東 徹[1]，古市 厚志[1]，西山 志満子[1]，倉知 正佳[1,2]，鈴木 道雄[1,2]
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患者の長期予後の改善などを目的とした，統合失調症を含む“サイコーシス”への早期介入が注目されつつある．特に，発症脆弱性を内包しつつ，精神病症状（主に陽性症状）が未だ顕在化しない“（統合失調症）前駆期”の同定のための鋭敏な指標の開発などが求められている．その際，統合失調症圏疾患に特徴的な生物学的所見を理解することは，早期診断の促進などに重要と思われる．

脳構造画像研究からは，1）扁桃体および海馬の体積減少を統合失調症患者および統合失調症型障害患者に共通して認めるが，統合失調症患者ではさらに前頭前野における広範囲な灰白質体積減少を認める，2）精神病発症高危険状態（at risk mental state：ARMS）にあり，後に統合失調症に移行する患者では，発病後に上側頭回や前頭前野の灰白質体積減少を認める，3）発病初期の統合失調症患者において，左上側頭回の一部である側頭平面の灰白質体積と精神病未治療期間（duration of untreated psychosis：DUP）の間に負の相関を認める，4）前頭前野皮質の体積減少率は，健常者に比べ統合失調症患者でより大きい，などの所見が報告されている．

事象関連電位などを対象とした神経生理学的研究において，構造画像研究で同定された脳領域における機能異常が示唆されている．すなわち，P300成分の発生源電流密度分布をLow Resolution Electromagnetic Tomography（LORETA）を用いて三次元的に解析した結果，左上側頭回や左前頭前野における電流密度が統合失調症患者で低下していることが見出された．これらの脳部位におけるP300電流密度の減少の程度は，それぞれ陽性症状や陰性症状の重症度と相関する．さらに，各種セロトニン受容体サブタイプへの作用が強い第二世代抗精神病薬による治療により，これらの電気生理学的異常が改善され，その変化は認知機能，QOL，社会機能などの改善と相関することも明らかにされつつある．また，比較的高い鋭敏性と低い侵襲性を特徴とする神経心理学的指標として，言語記憶などの認知機能領域の精神病前駆期～早期における障害など（図）が，これまで多く報告されている．

精神病の発症脆弱性を有すると考えられる若年者を対象としたケアシステムの地域への導入は，精神病への早期介入を促進する．富山県においても精神保健福祉センターと協同で，Consultation and Support Service in Toyama（CAST）が2006年に開始されている．これらの取組みが，サイコーシス早期段階に対する介入の促進や統合失調症の発症予防につながることが期待される．

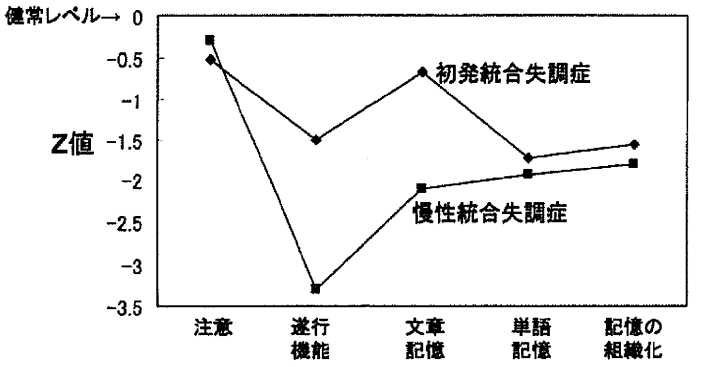

図　統合失調症早期における認知機能障害
単語記憶や記憶の組織化などの言語記憶に関係する認知機能領域は，初発統合失調症患者において慢性統合失調症患者と同程度に障害されている（Sumiyoshi, T.: Neurocognitive assessment and pharmacotherapy: Towards prevention of psychosis. Workshop "First Episode Psychosis: Integrating Neurobiological and Psychosocial determinants of outcome"; Society of Biological Psychiatry—62nd Annual Meeting, 2007, San Diego）

文　献

1）鈴木道雄，川崎康弘，高橋　努ほか：精神病への早期介入と脳構造画像研究．脳と精神の医学，19；203-10, 2008

2）鈴木道雄，高橋　努：統合失調症前駆期および初回エピソードにおける脳構造画像所見の特徴．臨床精神薬理，13；13-21, 2010

3）Sumiyoshi, T., Kawasaki, Y., Suzuki, M., et al.: Neurocognitive assessment and pharmacotherapy towards prevention of schizophrenia: What can we learn from first episode psychosis? Clin Psychopharmacol Neurosci, 6；57-64, 2008

4）住吉太幹：統合失調症前駆期における薬物療法．臨床精神薬理，13；37-46, 2010

特集
臨床精神薬理 13：13-21, 2010
統合失調症発症前における予防的薬物療法の可能性

統合失調症前駆期および初回エピソードにおける脳構造画像所見の特徴

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抄録：脳画像研究の進展により，統合失調症における軽度の脳灰白質体積減少などの構造変化についての知見が集積されてきた。また近年では，統合失調症を含む精神病性障害に対する早期介入活動の新しい試みと軌を一にして，初回エピソード，さらに遡って前駆期における構造変化に関する研究報告も増加しつつある。それとともに，顕在発症が切迫した時期から初回エピソードにかけて，活発な進行性の脳体積減少が生じていることが明らかになってきた。本稿では，そのような病初期における脳構造画像研究の選択的なレビューを行い，特に進行性変化の特徴を明らかにするとともに，今後の課題について考察する。
臨床精神薬理 13：13-21, 2010

Key words：*schizophrenia, at risk mental state, first episode, magnetic resonance imaging, progressive brain change*

Ⅰ．はじめに

1970年代におけるX線CTの登場によって脳構造の低侵襲的評価が可能となり，統合失調症の脳構造画像研究が行われるようになった。多様な所見が報告されるようになったのは，1990年代に磁気共鳴画像（MRI）が普及し，脳実質を解剖学的領域に細分化して評価・計測することが可能となってからである。特に2000年以降は，MRIの高解像度化と，関心領域（region of interest：ROI）法に加えて，比較的簡便に多数データの処理と全脳の検討ができるvoxel-based morphometry（VBM）の普及により，研究が活発化している。初期の研究は慢性例を対象にしたものが多かったが，その後初回エピソード統合失調症，さらに近年では前駆期の患者を対象とするようになり，病期を遡る形で研究が進展している。このような研究の進展は，統合失調症に対する早期介入活動の新しい試みと軌を一にするものであり，統合失調症早期の病態生理や脳構造変化の臨床的意義が徐々に明らかになるとともに，病期に即した治療法の開発が重要課題となりつつある。

Ⅱ．病前における脳構造変化

統合失調症患者では，明らかな精神病症状（陽性症状）が出現する前に非特異的な前駆症状が認められる場合が多いが，精神病性障害として診断が可能になるのは陽性症状が顕在化してからである。本稿ではこの時点を「発症」と呼び，疾患としては一連のものである前駆症状の始まりは「発病」と呼んで区別する。後述のように，統合失調症に認められる脳構造変化は，神経発達障害仮説が提唱された当時に考えられていたように固定的

Findings of structural brain imaging in prodromal and first-episode schizophrenia.

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なものばかりではなく，ある程度進行性であることが明らかになっている。そのような病態を理解するためにも，病前の状態を知ることは重要である。しかし病前（発病前）は脳画像検査の対象となりえないので，直接の知見はほとんどない。

1．固定的な脳構造変化

統合失調症をすでに発症している患者で報告されている脳構造の変化の中に，病前からの存在が推定されるものがある。脳の左右差は出生時にはすでに明瞭に認められるので，側頭平面体積の左半球優位性の減退あるいは逆転などの所見[18]は病前から存在することが示唆されるが，後述の上側頭回における左側優位の進行性変化を考慮すると単純には結論できない。透明中隔腔の拡大，視床間橋の短縮・欠損などの大脳正中構造の異常[38,39]も胎生期の発達異常を示唆する所見であるが，視床間橋についても最近，慢性例でより顕著な短縮が報告されており[40]，進行性の部分を含むと考えられる。大脳脳回の褶曲パターンは発達早期にほぼ決定されるので，gyrification index増大（hypergyria）の所見[49]や，左前部帯状回の脳溝の分枝（傍帯状溝）が減少し，左半球優位性が失われているという所見[53]は，比較的早期の神経発達障害を示唆する固定的変化と考えられるであろう。以上の所見は，早期神経発達障害による大脳半球間あるいは半球内の機能的結合の変化が脆弱性に関与していることを示唆する。

2．遺伝的ハイリスク

病前の状態をうかがい知るには，統合失調症患者の親族，すなわち遺伝的ハイリスクの状態にある人を対象とした研究が参考になる。第一～二度親族に少なくとも2名の罹患者を持つ青年を前方視的に追跡するエジンバラ・ハイリスク研究は，この集団における統合失調症の発症率が10年間で約10%と推定されるので，従来の遺伝的ハイリスク研究に比較して，病前の状態にある人を多く含むといえる。ROI法による100名のハイリスク者の検討では左側の扁桃体-海馬複合体および両側視床の体積減少[21]，VBMでは146名のハイリスク者における両側の前部帯状回の灰白質減少が報告されている[13]。しかし遺伝負因の強いサンプルは，一般の統合失調症患者とは異なった特徴を有する可能性がある。親族を対象としたROI法による体積測定研究のメタ解析[2]では，海馬あるいは扁桃体-海馬複合体の体積減少がもっとも一致した所見とされている。

Ⅲ．前駆期における脳構造変化

統合失調症前駆期の脳構造画像については，近年知見が増加している。前駆症状を示す段階で確定診断はできないので，近年の臨床的ハイリスク研究では，特定の徴候を有する者を精神病発症リスクの高い状態at risk mental state（ARMS）あるいは前駆状態の疑いとして，操作的に診断して検査や介入の対象としている[54]。ARMSと診断された者が1～2年以内に精神病に移行する率は30～40%という報告が多い。すなわち，かなりの率で偽陽性（前駆症状類似の症状を示すが，実際には精神病を発症することのない1群）が存在すると考えられる[34]。真の前駆期の特徴を知るためには，ARMSと診断された者を追跡し，発症に至った者の所見を吟味しなければならない。また注意すべき点として，ARMSから精神病に移行する場合，必ずしも統合失調症を発症するとは限らず，精神病症状を伴う気分障害など多様な疾患を発症しうる。現時点では，ARMSから統合失調症を発症した者を十分な数だけそろえた研究はほとんどない。

1．後に精神病を発症したARMSにおける所見

この分野において先進的な研究を推進しているメルボルン大学のグループは，VBMにより，ARMSのうち2年以内に精神病を発症した23名（8名が統合失調症）では，発症していない52名と比較して，ARMSの時点で右の海馬・海馬傍回，上側頭回，下前頭回および両側帯状回の灰白質が減少していることを報告した[26]。

バーゼル大学からのVBMによる検討[3]では，36名のARMSにおいて，後部帯状回，楔前部，左の島回，上側頭回，海馬，扁桃体，右の側頭葉前方部の灰白質が健常対照群より減少していた。

また平均306日後に統合失調症を発症した12名では，発症しなかった23名より，右の島回，上側頭回前方部，前部帯状回の灰白質が減少していた。

ミュンヘン大学のサンプルでは，後の発症の有無については検討されていないが，VBMにより，40名のARMSにおける前頭，側頭葉外側および内側領域の灰白質減少が認められている[25]。

これら複数のサンプルによる研究結果は，前駆状態においてすでに脳灰白質の減少がある程度存在すること，それは同様の前駆症的症状を示しながら発症しない，あるいは発症までより長期間を要する者に比較して顕著であることを示している。

ところでメルボルングループからの報告[9]によると，94名のARMSのうち，後に精神病に移行した31名（17名が統合失調症）では下垂体体積が有意に大きかったという。この所見の発症予測性が示唆されているが，この結果には気分障害に移行した患者の寄与が大きいという問題がある。

2．統合失調型障害

統合失調型障害は，軽度なあるいは萌芽的な統合失調症様症状を特徴とするが，その状態はARMSと共通する部分もあり，一部は統合失調症の前駆状態と考えられる。筆者らのグループは，VBMとROI法により，統合失調型障害における大脳領域の構造変化について包括的な検討を行った。全体のまとめはすでに報告済み[33]なのでごく概略を記すと，まず扁桃体，海馬，上側頭回（特に後方部分）などの体積減少は，統合失調型障害と統合失調症に共通して認められた[17,32,37]。一方，前頭前野は，統合失調症では広範囲に体積減少が認められた[17,32]のに対し，統合失調型障害ではむしろ体積の増大を示した[32]ことから，特に前頭前野における発症前後の変化を検討する必要性が示された。

3．精神病発症前後の縦断的所見

まだ少数の研究グループによる成果であるが，ARMSから精神病に移行した患者における，発症前後の縦断的変化に関する知見が集積されつつある（表1）。メルボルングループによる最初のVBMによる検討[26]では，後に精神病に移行した10名（5名が統合失調症）において，1回目（発症の平均172日前）と2回目（発症の平均202日後）の比較により，左の海馬傍回・紡錘状回，眼窩前頭葉，小脳，両側の帯状回に進行性の灰白質減少がみられた。移行しなかった11名では，右小脳に灰白質減少がみられたのみであった。

バーゼルのサンプルでは，統合失調症を発症したARMSの10症例において，1回目（発症の平均232日前）と2回目（発症の平均802日後）のVBMを用いた比較により，右の眼窩回，左の直回，右の下側頭回，上前頭回，上頭頂小葉，左の楔前部，右の小脳の灰白質体積減少が報告されている[4]。

またARMS基準を用いた研究ではないが，前述のエジンバラ・ハイリスク研究において，一過性の精神病症状を示した遺伝的ハイリスク者のうち8名が経過観察中に統合失調症を発症し，1回目（発症の平均2.3年前）と2回目（発症の平均0.8年前）に撮像されたMRIをVBMにより比較すると，左の下側頭回，鈎回，右の小脳において灰白質の進行性減少が認められた[14]。

上記の所見は，前駆期においてすでに進行性の脳構造変化が生じていることを一致して示している。なお，上側頭回，前頭前野，内側側頭葉などにおける縦断的変化については改めて後述する。

Ⅳ．初回エピソード統合失調症における脳構造変化

これまでに発表された初回エピソード統合失調症患者のMRI研究は相当な数に上る。Steenら[29]のメタ解析では，ROI法を用いた研究のうち，52編の横断的研究と16編の縦断的研究が対象とされている。選択基準がより厳格なVitaら[48]のメタ解析では21編の研究が対象である。これらのメタ解析によって確認されたのは，脳室系の拡大と全脳および海馬の体積減少である。

ROI法の場合，個々の脳部位については研究数が少なくメタ解析の対象とならない場合が多いが，全脳の情報が得られるVBMはその点で有利である。Ellison-Wrightら[7]は，anatomical likeli-