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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 = $1.0\times1.0\times1.0$ 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

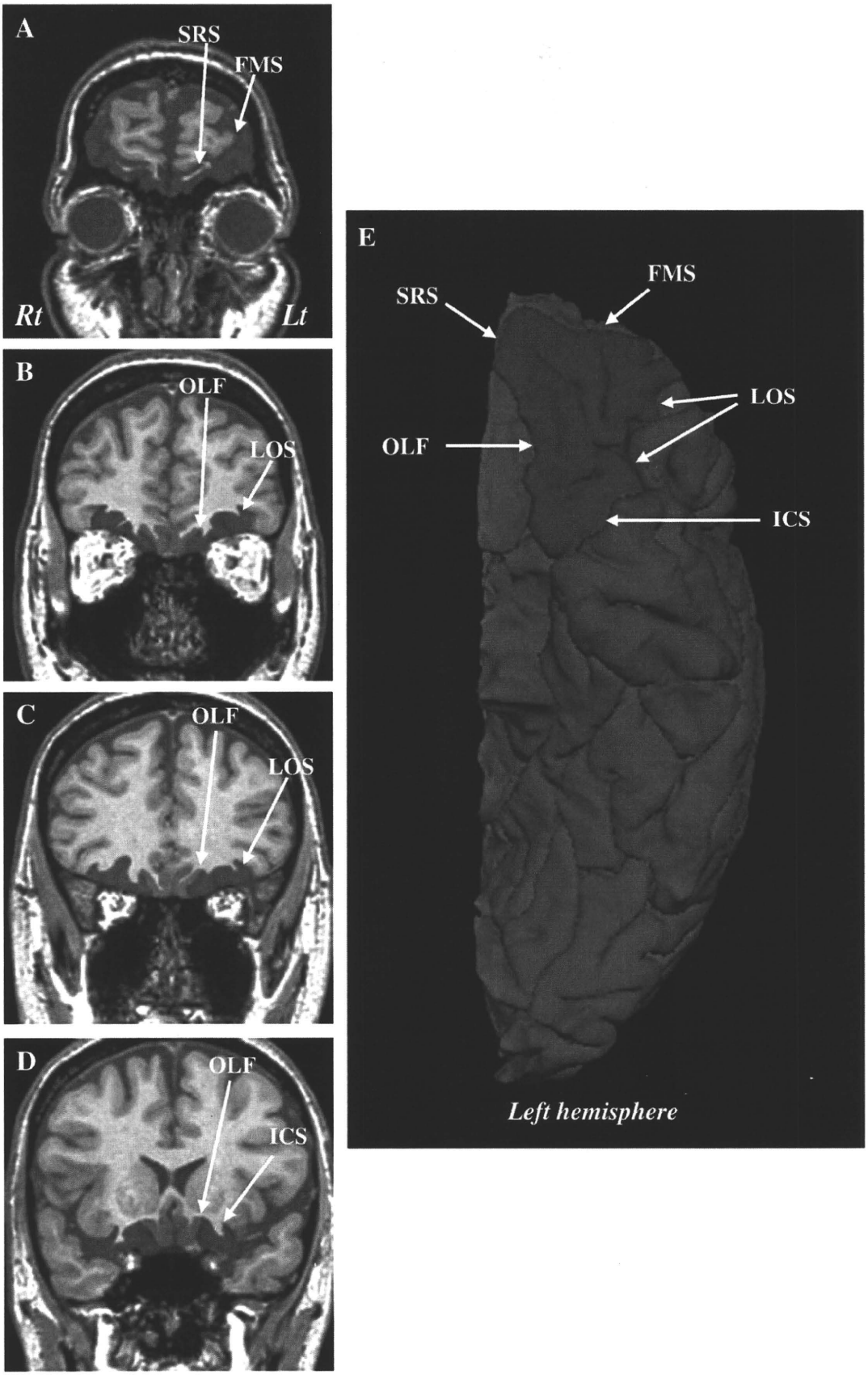

Fig. 1. Examples of regions of interest measured in this study on coronal view [(A) anterior part, (B) (C) intermediate part, and (D) posterior part] and ventral view (E). The OFC subregions are differentially colored in blue (orbital gyrus) and red (straight gyrus). Lt, left hemisphere; Rt, right hemisphere;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

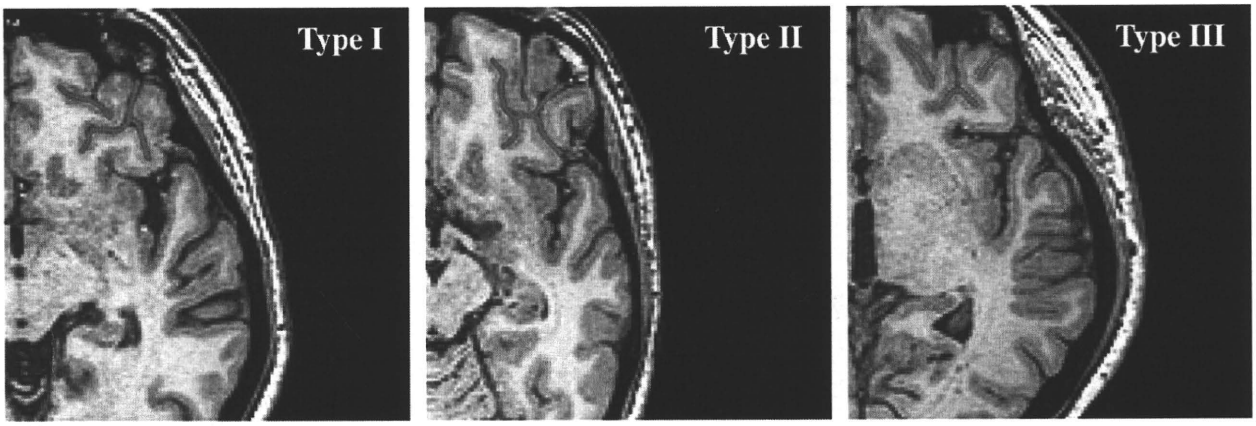

Fig. 2. Examples of the OFC sulco-gyral patterns (Types I, II, and III) from three left hemispheres on the axial view.

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

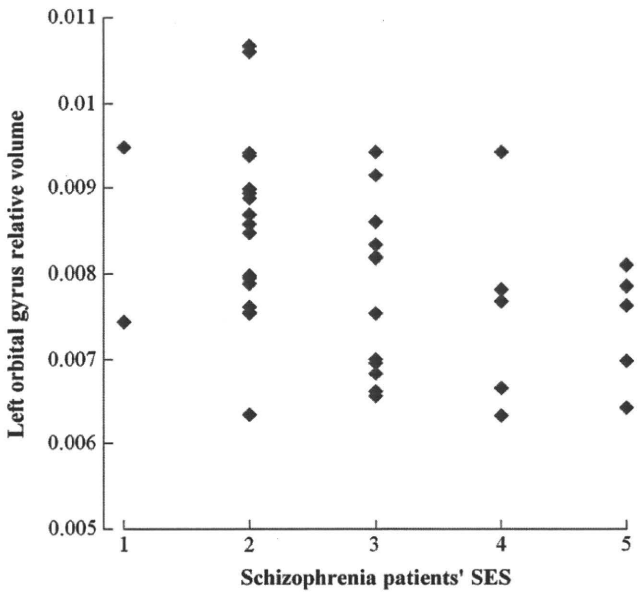

Fig. 3. Correlation between schizophrenia patients' SES and the relative volume of the left orbital gyrus. A smaller left orbital gyrus volume was negatively associated with the patients' SES (rho = −0.395, $p = 0.010$). Note that a smaller numerical value of SES indicates a higher social position.

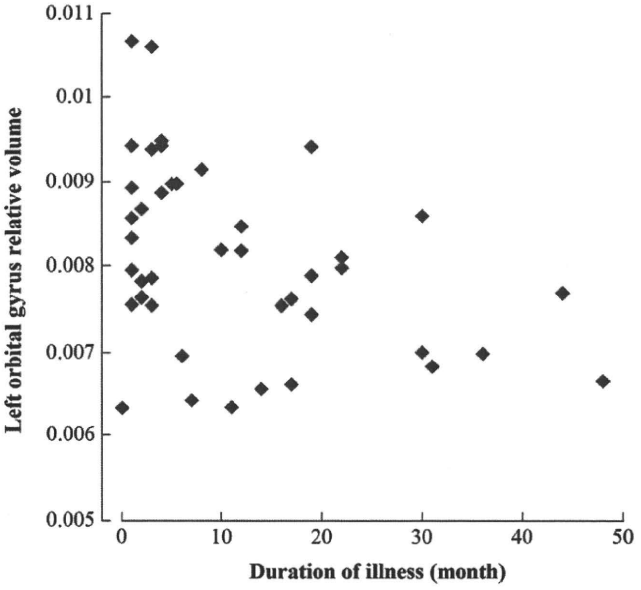

Fig. 4. Correlation between duration of illness and relative volume of the left orbital gyrus. There was a significant inverse correlation between the illness duration and the volume of the left orbital gyrus (rho = −0.347, $p = 0.024$).

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

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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Differentiation of first-episode schizophrenia patients from healthy controls using ROI-based multiple structural brain variables

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ABSTRACT

Background: Brain morphometric measures from magnetic resonance imaging (MRI) have not been used to discriminate between first-episode patients with schizophrenia and healthy subjects.
Methods: Magnetic resonance images were acquired from 34 (17 males, 17 females) first-episode schizophrenia patients and 48 (24 males, 24 females) age- and parental socio-economic status-matched healthy subjects. Twenty-nine regions of interest (ROI) were measured on 1-mm-thick coronal slices from the prefrontal and central parts of the brain. Linear discriminant function analysis was conducted using standardized *z* scores of the volumes of each ROI.
Results: Discriminant function analysis with cross-validation procedures revealed that brain anatomical variables correctly classified 75.6% of male subjects and 82.9% of female subjects, respectively. The results of the volumetric comparisons of each ROI between patients and controls were generally consistent with those of the previous literature.
Conclusions: To our knowledge, this study provides the first evidence of MRI-based successful classification between first-episode patients with schizophrenia and healthy controls. The potential of these methods for early detection of schizophrenia should be further explored.

1. Introduction

A number of neuroimaging studies have demonstrated subtle but significant structural changes in multiple brain regions in schizophrenia (McCarley et al., 1999; Wright et al., 2000; Shenton et al., 2001; Honea et al., 2005). Although magnetic resonance imaging (MRI), which provides stable and reliable information of brain structure, has brought about increasing understanding of the pathophysiology of schizophrenia, relatively few efforts have been made in the clinical application of MRI. Several studies have attempted to discriminate between schizophrenia patients and healthy subjects using brain anatomical structures obtained by MRI (Suddath et al., 1990; Leonard et al., 1999; Nakamura et al., 2004). Recently, some studies reported voxel-based morphometry (VBM)-based classification approaches (Davatzikos et al., 2005; Kawasaki et al., 2007; Fan et al., 2007). Although VBM is an unbiased, rater-independent technique, there are several criticisms of VBM and discrepancies between VBM and manually-traced region of interest (ROI) measurements (Bookstein 2001; Gitelman et al., 2001; Good et al., 2002; Mehta et al., 2003).

In our previous classification study, we investigated how brain anatomical measures based on ROI methods could distinguish mostly chronic schizophrenia patients from control subjects (Nakamura et al., 2004). Discriminant function analysis of 14 anatomical variables measured in a small number of coronal slices at the level of the mammillary body correctly classified 80% of male schizophrenia patients, 77.8% of female patients, 80% of male controls, and 86.4% of female controls. The relatively high specificity and sensitivity of the

Abbreviations: ANOVA, Analysis of variance; AZ, Area under the receiver operating characteristics curve; BPRS, Brief Psychiatric Rating Scale; DTI, Diffusion tensor imaging; DUP, Duration of untreated psychosis; ICC, Intraclass correlation coefficients; ICD-10, International Classification of Diseases, 10th edition; JART, Japanese version of the National Adult Reading Test; MRI, Magnetic resonance imaging; ROC, Receiver operating characteristics curve; ROI, Region of interest; SD, Standard deviation; VBM, Voxel-based morphometry.

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obtained classifiers revealed the validity of the use of anatomical measures from limited slices of MRI in discriminant function analysis. In the study, however, the medial temporal and prefrontal structures were not included as ROI, despite the fact that volume reduction of these structures has been repeatedly demonstrated in schizophrenia patients and these regions have been strongly implicated in the pathophysiology of schizophrenia (McCarley et al., 1999; Wright et al., 2000; Shenton et al., 2001; Suzuki et al., 2005b). Involvement of the hippocampal formation has been related to psychotic symptoms and verbal memory deficits in schizophrenia patients (Friston et al., 1992; Liddle et al., 1992; Goldberg et al., 1994), while prefrontal abnormalities have been implicated in negative symptoms and cognitive impairments such as deficits in working memory, executive and problem solving functions (Goldman-Rakic and Selemon, 1997). Thus, inclusion of medial temporal and prefrontal measures would enhance the accuracy of the classifiers.

A shorter duration of untreated psychosis (DUP) has consistently been associated with greater therapeutic outcome and better prognosis in schizophrenia (Marshall et al., 2005; Perkins et al., 2005). Given the chronic and disabling nature of schizophrenia for most affected individuals, the link between shorter DUP and better outcome suggests the critical importance of early detection and intervention. Accurate diagnosis of schizophrenia in the early stage is important for specific early intervention, although some instability of the clinical diagnosis over time has been demonstrated in patients with first-episode psychosis (Haahr et al., 2008; Salvatore et al., 2008). There have been replicated findings of structural brain changes in first-episode patients with schizophrenia, which may be less marked than those in chronic patients (Steen et al., 2006; Vita et al., 2006; Ellison-Wright et al., 2008). For the early detection of schizophrenia, structural neuroimaging techniques might be useful as a biological marker adjunct to clinical diagnosis. However previous classification studies were conducted in mixed samples of chronic and first-episode patients (Nakamura et al., 2004; Davatzikos et al., 2005; Kawasaki et al., 2007; Fan et al., 2007). To our knowledge, no MRI-based study has ever attempted to discriminate between first-episode schizophrenia patients and healthy subjects.

In the present study, we primarily intended to distinguish between first-episode patients with schizophrenia and healthy subjects by MRI-based structural measures. The secondary aim was to investigate regional brain volumetric differences between patients and controls to compare our results with those of previous studies. We generally followed the method of our previous classification study, in which ROI were taken from the central part of MRI images (Nakamura et al., 2004). Additionally, we included eight prefrontal lobe ROI and four medial temporal lobe ROI for use in discriminant function analysis. We predicted that the inclusion of the additional variables from these regions would enhance the potency of the classifiers to yield good classification rates, even in first-episode patients.

2. Methods

2.1. Subjects

Table 1 presents the demographic and clinical characteristics of the subjects. Thirty-four patients (17 males, 17 females) with first-episode schizophrenia (characterized as the first hospitalization for psychiatric illness) were recruited from the inpatient population at the Tokyo Metropolitan Matsuzawa Hospital. All but four males were right-handed. All patients fulfilled the ICD-10 research criteria for schizophrenia (World Health Organization, 1993) and were diagnosed by a consensus of at least two experienced psychiatrists based on a direct interview as well as a chart review. All patients had already been treated with neuroleptics at the time of scanning. Sixteen patients were treated with only atypical antipsychotics, and 18 patients received both typical and atypical antipsychotics. Clinical symptoms were assessed using the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962).

The age- and gender-matched control subjects consisted of forty-eight healthy volunteers (24 males, 24 females) recruited from the hospital staff and college students (Table 1). All of the controls except one female were right-handed. Control subjects with a personal or family history of psychiatric illness were excluded.

Premorbid IQ for schizophrenia patients and 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; Uetsuki et al., 2007). Socio-economic status as well as parental socio-economic status was assessed (Hollingshead, 1965).

All participants were physically healthy, 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

Magnetic resonance 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.

Table 1
Demographic and clinical characteristics of the subjects.

	Schizophrenia patients		Control subjects		Analysis of variance[a]			
					Diagnosis		Gender	
	Male (n = 17)	Female (n = 17)	Male (n = 24)	Female (n = 24)	F	p	F	p
Age (years)	29.3 ± 6.6	28.8 ± 6.1	30.8 ± 5.4	29.8 ± 5.8	0.89	0.344	0.32	0.572
Handedness (number of right-handed subjects)	14	17	24	23				
Socio-economic status	2.3 ± 0.9	3.1 ± 1.2	1.7 ± 0.5	1.6 ± 0.5	34.20	<0.001	3.90	0.051
Parental socio-economic status	2.3 ± 0.8	2.7 ± 0.7	2.4 ± 0.6	2.3 ± 0.5	1.47	0.230	0.41	0.520
Estimated IQ[b]	102.4 ± 9.7	102.1 ± 7.6	109.6 ± 7.2	108.6 ± 7.9	13.50	<0.001	0.12	0.734
Duration of untreated psychosis (month)	7.8 ± 8.7	12.2 ± 15.5						
Duration of illness (month)	10.1 ± 10.4	14.6 ± 15.5						
Duration of medication (days)	49.0 ± 73.0	75.4 ± 69.1						
Medication (mg/day, chlorpromazine equiv.)	1055.6 ± 472.4	864.6 ± 431.0						
Total BPRS score	40.1 ± 9.3	37.9 ± 9.4						

BPRS, Brief Psychiatric Rating Scale.
[a] For the results of the post hoc tests, see the text.
[b] 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).

The MRI data were transferred to a UNIX work station (Silicon Graphics, Inc., Mountain View, CA) and were randomly coded and analyzed with the software package Dr.View 5.0 (Asahi Kasei Joho System, Tokyo, Japan). Before reconstruction of the MR images, they were realigned in three dimensions to standardize for differences in head tilt during MR image acquisition. Head tilt in the sagittal plane was corrected by aligning the anterior commissure–posterior commissure (AC–PC) plane. Correction in the axial and coronal planes was achieved by aligning the longitudinal third ventricle and the interhemispheric fissure by reference to the symmetry of the eyeballs and optic nerves. After correction, the entire contiguous coronal images of 1-mm thickness vertical to the AC–PC line were reconstructed. 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 brain tissue and cerebrospinal fluid (CSF) according to the Alpert algorithm (Alpert et al., 1996). The gray and white matter of each ROI were manually separated because of the slight non-uniformity of intensity observed in most of the cases.

2.3. Volumetric measurements of ROI

The ROI were measured in the following two regions as presented in Fig. 1.

2.3.1. Prefrontal region

The delineation of the ROI of the prefrontal region was based on the work of Crespo-Facorro et al. (1999) and Ballmaier et al. (2004). The three contiguous coronal slices posterior to the first appearance of the genu of the corpus callosum were chosen for measurement. The genu of the corpus callosum was used as a landmark for the following reasons. First, the present delineation methods can be easily reproduced among different subjects using this procedure. Second, the inferior frontal gyrus, which is a relatively short structure, can be observed adequately within these slices. Third, the anatomical boundary of the anterior cingulate gyrus can be readily determined posterior to the genu of the corpus callosum.

In the prefrontal slices, the areas of the following structures were measured in each slice and summed to obtain volumes: the prefrontal part of the whole cerebrum; the anterior interhemispheric fissure; and the gray matter of the anterior cingulate gyrus, superior frontal gyrus, middle frontal gyrus, inferior frontal gyrus, and orbitofrontal gyrus. The prefrontal part of the whole cerebrum included all the brain tissue of the three chosen slices and was used in the following regression analysis. The boundaries of each ROI were defined as described in Table 2.

2.3.2. Central region

The three contiguous coronal slices in which the mammillary body was most clearly seen were chosen for measurement. The central part of the whole cerebrum and the following ROI were measured: the body and inferior horn of the lateral ventricle, third ventricle, Sylvian fissure, central interhemispheric fissure, whole temporal lobe, gray and white matter of the superior temporal gyrus, amygdala–hippocampal complex, and parahippocampal gyrus. The central part of the whole cerebrum included all the brain tissue of the three chosen slices and was used in the subsequent regression analysis. The detailed delineation of these ROI was based on the method of our previous studies (Nakamura et al., 2004; Niu et al., 2004; Suzuki et al., 2005a). The boundaries of each ROI were defined as described in Table 2.

2.4. Reliability

All measurements were performed by one rater (Y.T.) who was blind to the subjects' gender and diagnosis. The intrarater reliability was established by remeasuring all regions in five randomly selected subjects. The intraclass correlation coefficient (ICC) ranged from 0.91 to 0.99 for all ROI. A second rater (E.T.) blinded to the subjects' identity measured all regions in five randomly selected samples to evaluate the interrater reliability. The interrater ICC was 0.83 for the left parahippocampal gyrus, 0.86 for the right amygdala–hippocampal complex, 0.88 for white matter of the right superior temporal gyrus, and between 0.90 and 0.99 for all other ROI.

2.5. Statistical analysis

All statistical analyses were performed using the software package SPSS 11.01J (SPSS, Chicago, IL, USA).

Demographic and clinical variables were compared by analysis of variance (ANOVA).

The volumes of each ROI were expressed as standardized z scores corrected by regression analysis for the variations in head size and age of the control subjects (Zipursky et al., 1992; Pfefferbaum et al., 1993; Mathalon et al., 1993; Sullivan et al., 2000). Briefly, the prefrontal ROI value for the control group was regressed against prefrontal whole cerebral volume and age, yielding a residual value for each control subject. The prefrontal ROI value for the patient group was entered into the same equation as for the control group to calculate the residual value for each patient. The mean residual values and standard deviation (SD) derived from the control subjects were used to calculate z scores (z=[residual value − mean residual value for control subjects]/SD). For the control subjects, the expected mean z

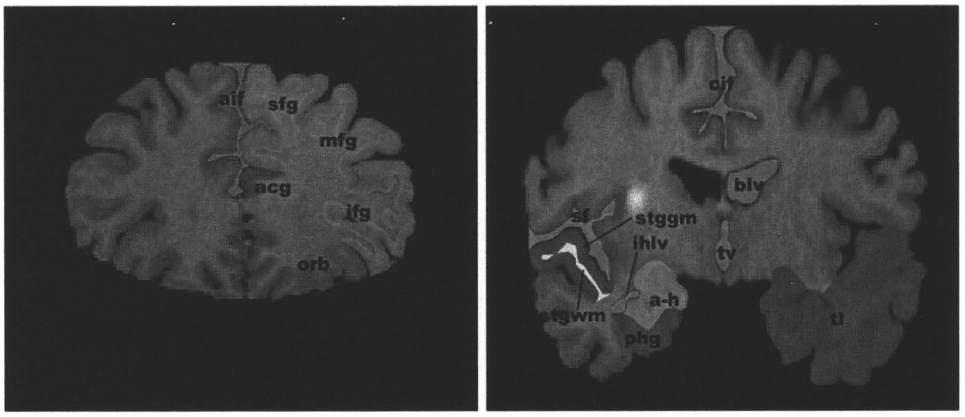

Fig. 1. Examples of the prefrontal regions of interest (left) and central regions of interest (right) traced manually in this study. acg: anterior cingulate gyrus; a–h: amygdala–hippocampal complex; aif: anterior interhemispheric fissure; blv: body of the lateral ventricle; cif: central interhemispheric fissure; ifg: inferior frontal gyrus; ihlv: inferior horn of the lateral ventricle; mfg: middle frontal gyrus; orb: orbitofrontal gyrus; phg: parahippocampal gyrus; sf: Sylvian fissure; sfg: superior frontal gyrus; stggm: gray matter of the superior temporal gyrus; stgwm: white matter of the superior temporal gyrus; tl: temporal lobe; tv: third ventricle.

Table 2
Anatomical boundaries of the regions of interest.

Region	Anatomical landmark
Prefrontal region	
Anterior cingulate gyrus	Superior border: cingulate sulcus Inferior border: callosal sulcus
Superior frontal gyrus[a]	Lateral inferior border: superior frontal sulcus Medial inferior border: cingulate sulcus
Middle frontal gyrus	Superior border: superior frontal sulcus Inferior border: inferior frontal sulcus
Inferior frontal gyrus	Superior border: inferior frontal sulcus Inferior border: lateral orbital sulcus or superior circular sulcus
Orbitofrontal gyrus	Lateral border: lateral orbital sulcus or inferior circular sulcus Medial border: olfactory sulcus
Anterior interhemispheric fissure	Superior border: a line connecting the outer limb of the left superior frontal gyrus with the right one
Central region	
Temporal lobe	Demarcated by a line perpendicular to the axis of the temporal stem from the inferior aspect of the insula
Superior temporal gyrus	Superior border: Sylvian fissure Inferior border: superior temporal sulcus
Amygdala–hippocampal complex	Superior border: cerebrospinal fluid overlying the semilunar gyrus and its medial extension Lateral border: temporal lobe white matter and extension of the inferior horn of the lateral ventricle Inferior border: white matter of the parahippocampal gyrus
Parahippocampal gyrus	Superior border: inferior gray border of the hippocampal formation Inferior border: a line drawn from the most lateral border of the hippocampal flexure to the collateral sulcus
Central interhemispheric fissure	Superior border: a line connecting the outer limb of the left superior frontal gyrus with the right one
Sylvian fissure	Lateral border: a line connecting the outer limb of the postcentral gyrus with the outer limb of the superior temporal gyrus

[a] The paracingulate gyrus was included in the superior frontal gyrus when present (Takahashi et al., 2002; Suzuki et al., 2005a; Zhou et al., 2005).

score was 0 with an SD of 1. The use of standardized z scores allows analysis of disease-related changes independent of head size and normal aging. The central ROI value was also processed in the same way as the prefrontal ROI.

In order to see whether volumetric changes in our sample were comparable with those in previous literature, the volumes of each ROI were compared across the diagnostic groups. The z scores of each ROI were analyzed by repeated measures ANOVA with diagnosis as a between-subject factor and hemisphere (left, right) as a within-subject factor. The one-way ANOVA for the z scores of the third ventricle and the anterior and central interhemispheric fissures was carried out without using the within-subject factors. For post hoc pairwise comparisons, Fisher's Least Significant Difference (LSD) tests were employed.

Discriminant function analysis was conducted using z scores as independent variables to assess the possibility of differentiating the schizophrenia patients from the control subjects by a combination of brain anatomical variables. The variables were entered in a stepwise manner using the Wilks method. For the stepwise selection, the inclusion criterion was set at $p \leq 0.25$ according to the recommendation by Costanza and Afifi (1979). This liberal cutoff p value for entry was chosen to avoid the exclusion of potentially important variables (Bendel and Afifi, 1977; Costanza and Afifi, 1979). Such liberal criteria have been employed in a number of previous studies (Carter et al., 1999; Shaw et al., 2000; Nakamura et al., 2004).

To validate the present discriminant function, we used the Jackknife (leave-one-out) approach. Using this, we were able to estimate the potency of the obtained classifier when it was adopted for new subjects. We also performed a receiver operating characteristic curve (ROC) analysis and calculated the area under the ROC curve (Az).

Pearson's correlation coefficients were calculated to examine relationships between z scores of each ROI and DUP, duration of illness, daily medication dosage, duration of neuroleptic medication, total BPRS score, and estimated IQ. To prevent a possible type I error due to multiple tests, a Bonferroni correction was applied for correlation analyses.

Transformation of ROI volumes into z scores, ANOVA comparisons, discriminant function analyses and correlation analyses were carried out separately for each gender because of the evidence for gender differences in brain morphology among healthy subjects (Cosgrove et al., 2007) and gender-specific brain structural changes in schizophrenia patients (Goldstein et al., 2002; Takahashi et al., 2002).

Statistical significance was defined as $p < 0.05$ (two-tailed).

3. Results

3.1. Demographic and clinical characteristics

There were no significant group differences in age or parental socio-economic status. There were significant main effects on diagnosis of socio-economic status (ANOVA, $F = 34.20$, df = 1,79, $p < 0.001$) and estimated IQ (ANOVA, $F = 13.50$, df = 1,74, $p < 0.001$). Post hoc tests showed that the schizophrenia patients had a significantly lower socio-economic status ($p < 0.001$) and estimated premorbid IQ ($p < 0.001$) (Table 1).

3.2.1. Comparison of the ROI volumes in male subjects

One-way ANOVA revealed a significant main effect of diagnosis for the third ventricle ($F = 5.63$, df = 1,39, $p = 0.023$). The post hoc test showed that the third ventricle was significantly larger in the schizophrenia patients than in the controls ($p = 0.023$).

Repeated measures ANOVA revealed significant main effects of diagnosis for the middle frontal gyrus ($F = 4.65$, df = 1,39, $p = 0.037$), the amygdala–hippocampal complex ($F = 4.10$, df = 1,39, $p = 0.049$), and the inferior horn of the lateral ventricle ($F = 4.07$, df = 1,39, $p = 0.049$). Post hoc tests showed that the left amygdala–hippocampal complex volume was significantly reduced ($p = 0.038$) and the left inferior horn of the lateral ventricle was significantly enlarged in the schizophrenia patients ($p = 0.019$). The difference in the volume of the middle frontal gyrus did not reach statistical significance.

There were significant main effects of hemisphere ($F = 4.46$, df = 1,39, $p = 0.041$) and diagnosis × hemisphere interaction ($F = 4.46$, df = 1,39, $p = 0.041$) for the parahippocampal gyrus. Post hoc tests showed that the parahippocampal gyrus was significantly smaller in the left hemisphere ($p = 0.041$) than in the right and that the parahippocampal gyrus was significantly unilaterally reduced in the schizophrenia patients ($p = 0.039$ for the left hemisphere) (Fig. 2).

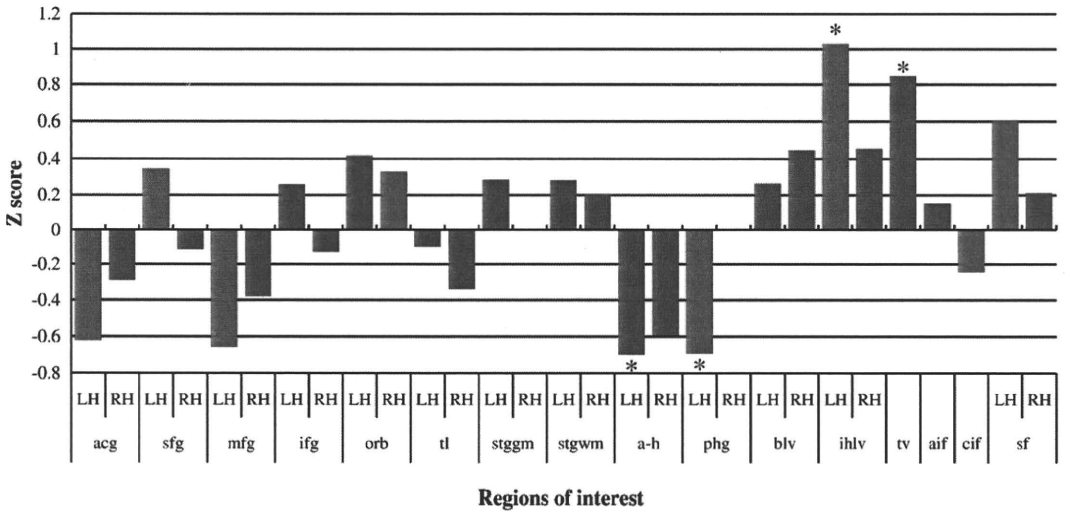

Fig. 2. Standardized *z* scores for each ROI of male patients with schizophrenia. For the control subjects, the expected mean *z* score was 0. LH: left hemisphere; RH: right hemisphere; acg: anterior cingulate gyrus; a–h: amygdala–hippocampal complex; aif: anterior interhemispheric fissure; blv: body of the lateral ventricle; cif: central interhemispheric fissure; ifg: inferior frontal gyrus; ihlv: inferior horn of the lateral ventricle; mfg: middle frontal gyrus; orb: orbitofrontal gyrus; phg: parahippocampal gyrus; sf: Sylvian fissure; sfg: superior frontal gyrus; stggm: gray matter of the superior temporal gyrus; stgwm: white matter of the superior temporal gyrus; tl: temporal lobe; tv: third ventricle. $^{*}p<0.05$, post hoc analysis. Red bar indicates inclusion in the discriminant model.

There were no significant differences in any ROI volume between patients receiving only atypical antipsychotics and those treated with both typical and atypical antipsychotics.

3.2.2. Comparison of the ROI volumes in female subjects

One-way ANOVA revealed a significant main effect of diagnosis for the third ventricle ($F=5.03$, df = 1,39, $p=0.030$). The post hoc test showed that the third ventricle was significantly enlarged in the schizophrenia patients ($p=0.030$).

Repeated measures ANOVA revealed significant main effects of diagnosis for the body of the lateral ventricle ($F=6.45$, df = 1,39, $p=0.015$) and the Sylvian fissure ($F=8.03$, df = 1,39, $p=0.007$). Post hoc tests showed that the body of the lateral ventricle ($p=0.022$ for the left hemisphere, $p=0.016$ for the right hemisphere) and the Sylvian fissure ($p=0.013$ for the left hemisphere, $p=0.025$ for the right hemisphere) were significantly bilaterally enlarged in the schizophrenia patients (Fig. 3).

No ROI volumes differed between the patients treated with only atypical antipsychotics and those treated with both typical and atypical antipsychotics.

3.3. Discriminant function analysis

Among the male subjects, the following eight variables were entered in a stepwise manner: the left anterior cingulate gyrus, the left superior frontal gyrus, the left middle frontal gyrus, the right orbitofrontal gyrus, the left parahippocampal gyrus, the left inferior horn of the lateral ventricle, the central interhemispheric fissure, and the left Sylvian fissure. The use of these variables resulted in correct classification rates of 95.8% in the control subjects, 76.5% in the

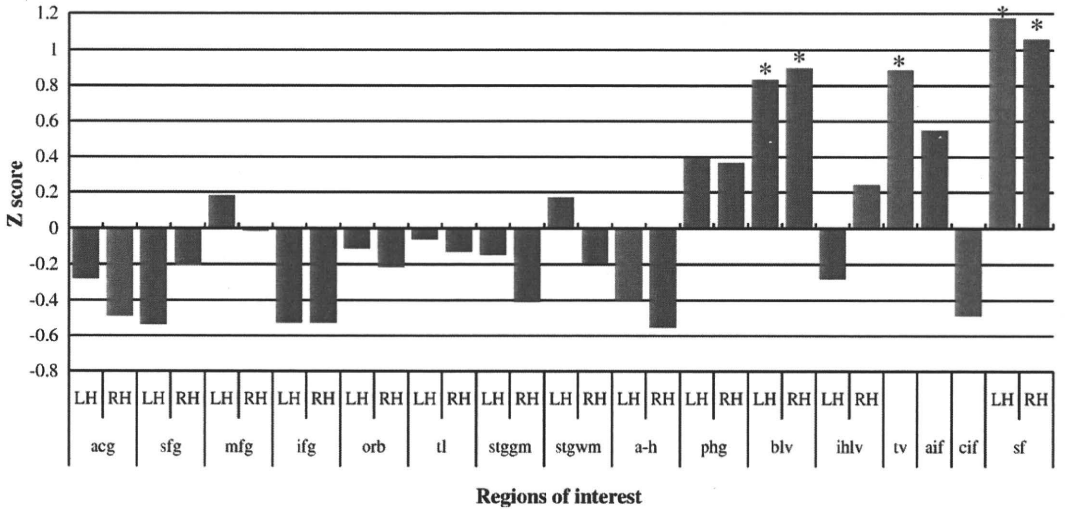

Fig. 3. Standardized *z* scores for each ROI of female patients with schizophrenia. For the control subjects, the expected mean *z* score was 0. LH: left hemisphere; RH: right hemisphere; acg: anterior cingulate gyrus; a–h: amygdala–hippocampal complex; aif: anterior interhemispheric fissure; blv: body of the lateral ventricle; cif: central interhemispheric fissure; ifg: inferior frontal gyrus; ihlv: inferior horn of the lateral ventricle; mfg: middle frontal gyrus; orb: orbitofrontal gyrus; phg: parahippocampal gyrus; sf: Sylvian fissure; sfg: superior frontal gyrus; stggm: gray matter of the superior temporal gyrus; stgwm: white matter of the superior temporal gyrus; tl: temporal lobe; tv: third ventricle. $^{*}p<0.05$, post hoc analysis. Red bar indicates inclusion in the discriminant model.

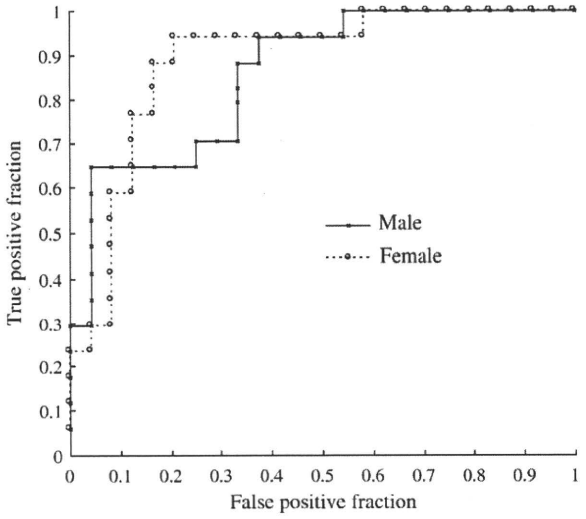

Fig. 4. Receiver operating characteristic (ROC) curves for male and female subjects. The area under the ROC curve (Az) was 0.858 for male subjects and 0.885 for female subjects. Greater Az value indicates better diagnostic performance of the classifier. True positive fraction and false positive fraction indicate sensitivity and 1 − specificity, respectively.

schizophrenia patients, and 87.8% in all male subjects ($F=4.53$; df = 8,32; $p=0.001$; Wilks lambda = 0.469).

Among the female subjects, the following six variables were entered in a stepwise manner: the right anterior cingulate gyrus, the left amygdala–hippocampal complex, the third ventricle, the right inferior horn of the lateral ventricle, the central interhemispheric fissure, and the left Sylvian fissure. By using these variables, 83.3% of the control subjects, 94.1% of the schizophrenia patients, and 87.8% of all female subjects were correctly classified ($F=6.11$; df = 6,34; $p<0.001$; Wilks lambda = 0.481).

After a cross-validation procedure using the Jackknife approach, the correct classification rates were 75.6% in the male subjects (83.3% specificity and 64.7% sensitivity) and 82.9% in the female subjects (83.3% specificity and 82.4% sensitivity). The area under the ROC curve (Az) was 0.858 for the male subjects and 0.885 for the female subjects, respectively (Fig. 4).

3.4. Correlation analysis

Pearson's correlation coefficients did not reveal any significant correlation between ROI volumes and clinical variables after the Bonferroni correction [Twenty-nine ROI; $p<0.0017$ (0.05/29)].

4. Discussion

To our knowledge, this study is the first that differentiated first-episode schizophrenia patients from healthy subjects by the discriminant function analysis using ROI-based brain structural variables from MRI. The stepwise discriminant function analysis identified the combinations of ROI that characterized brain anatomical features distinguishing first-episode patients from healthy controls with fairly good sensitivity and specificity. As to the correct classification rates, our results were comparable to those of previous MRI-based classification studies conducted among mainly chronic patients (Leonard et al., 1999; Nakamura et al., 2004; Davatzikos et al., 2005; Kawasaki et al., 2007; Fan et al., 2007). Considering the smaller magnitude of brain volume changes observed in first-episode schizophrenia patients relative to chronic patients (Steen et al., 2006; Vita et al., 2006; Ellison-Wright et al., 2008), the classification accuracy in the present study comparable to that obtained in our previous study (Nakamura et al., 2004) may be accounted by the additional inclusion of the prefrontal and medial temporal components in the analyses.

The results of the present study suggest that the combinations of brain structural measures may provide objective biological information adjunct to the clinical diagnosis of schizophrenia even in the early stage. However it is too early to draw a conclusion that the MRI-based classification methods can be applied directly to the diagnosis of first-episode schizophrenia, since we have not included patients with other types of psychosis such as first-episode affective psychosis in the analyses. Further studies are needed to examine whether first-episode patients who later become clearly diagnosed with schizophrenia would be discriminated from those with some other types of psychosis. For the detection at the earliest stage, it must be tested if our methods would help to predict whether subjects in a prodromal phase will later go on to develop schizophrenia.

Among male patients, the volumes of the third ventricle and the left inferior horn of the lateral ventricle were significantly enlarged, and the left amygdala–hippocampal complex and the left parahippocampal gyrus were significantly reduced compared to those of the controls. Significant enlargements of the third ventricle, the bilateral body of the lateral ventricle, and the bilateral Sylvian fissure were observed in female patients. These results are consistent with those of a number of previous studies (McCarley et al., 1999; Wright et al., 2000; Shenton et al., 2001; Honea et al., 2005). Gray matter volume reduction of the superior temporal gyrus is one of the most consistently reported abnormalities in the brain structure of schizophrenia patients (Shenton et al., 2001). Moreover, the smaller gray matter volume of the superior temporal gyrus and its progressive volume reduction were demonstrated in first-episode schizophrenia patients (Hirayasu et al., 1998, 2000; Gur et al., 2000; Kasai et al., 2003; Sumich et al., 2005; Takahashi et al., 2009). However, no significant volume differences in the superior temporal gyrus were observed in the present study. Although the validity of using a limited number of slices was demonstrated in our previous studies (Kurokawa et al., 2000; Nakamura et al., 2004), a larger number of slices for measurement may be required to detect significant volume changes in the superior temporal gyrus in patients.

In the stepwise discriminant function analyses, eight ROI were entered among the male subjects whereas six ROI were selected for entry among the female subjects. Some of ROI which showed volume differences between diagnostic groups in ANOVA were not included in the discriminant model because their p values for entry varied during the stepwise processes and consequently exceeded the criterion for inclusion. ROI included in the discriminant function analysis in the male subjects appeared more lateralized to the left hemisphere relative to those in the female subjects, as were similarly seen in the volume changes of many ROI (see Figs. 2 and 3). Several previous studies demonstrated more left-lateralized volume reductions specific to male schizophrenia patients in the whole temporal lobe (Bryant et al., 1999), planum temporale (Goldstein et al., 2002), hippocampus (Bogerts et al., 1990) and amygdala (Niu et al., 2004), while right-sided abnormalities such as the lack of normal leftward asymmetry of the planum temporale (Goldstein et al., 2002) and smaller right anterior cingulate gyrus (Takahashi et al., 2002) were reported in female patients. Although our results were not fully consistent with those of the previous studies, gender differences in lateralization of selected ROI for the discriminant function analyses might reflect such sexually dimorphic changes in schizophrenia patients.

The lack of significant correlations between brain structural measures and clinical variables in the patients might be explained from several aspects. Structural changes associated with schizophrenia may probably consist of the consequences of multiple processes including premorbid vulnerability, progressive changes during and/or after onset, effects of antipsychotic medication, and influence of other non-specific factors (Pantelis et al., 2005; Lieberman et al., 2005). Meanwhile, severity of clinical symptoms can be variable, in particular, under the influence of pharmacotherapy. These complexities may

make it difficult to see simple correlations of brain measures with clinical variables. Furthermore the volumes of ROI measured from the limited number of slices may not necessarily have represented those of the whole structures. The conservative Bonferroni correction taking account of the multiple measured ROI (29 ROI) might have also affected the results.

Discrimination of schizophrenia patients from healthy subjects has been attempted by several studies employing variables derived from positron emission tomography (Levy et al., 1992), neuropsychological tests (Arango et al., 1999; Fleck et al., 2001), MMPI scales (Carter et al., 1999), and neurophysiological measures (Gerez and Tello, 1995; Knott et al., 1999; Kojima et al., 2001). These functional measures have been reported to successfully distinguish between schizophrenia patients and controls, although they are considered more susceptible to the subjects' condition than brain structural measures, which provide stable biological information. Pardo et al. (2006) demonstrated successful classification of the three diagnostic groups (schizophrenia, bipolar disorder, and controls) by employing discriminant function analysis with variables obtained by structural brain measures and neuropsychological tests. Combinations of different modalities would contribute to the enhancement of classification accuracy.

There are several limitations of this study that should be taken into account. First, the sample size was not so large, although fairly good correct classification rates were obtained between the patients and controls. Second, the effects of lower premorbid intelligence in the patients on brain morphometric changes were not fully investigated in the present study, although treating the premorbid IQ as a covariate in the statistical analysis did not essentially affect the results (data not shown). Third, the structured interview such as SCID was not used for diagnosis in this study. However we have confirmed the diagnostic stability of all the patients included in the present study during the follow-up periods (1 to 4 years) after the scans. Fourth, all patients were exposed to antipsychotic medications before scanning even for a short period. In a recent study, schizophrenia patients treated with the typical antipsychotic drug haloperidol showed gray matter volume reduction over time, while olanzapine-treated patients did not (Lieberman et al., 2005). Although there were no significant differences in all ROI volumes between the patients receiving typical antipsychotics and those treated with both typical and atypical antipsychotics, future research should be designed to analyze drug-naïve patients to exclude the influence of antipsychotic medication. Finally, as discussed above, since other psychiatric disorders such as mood disorder were not included in the present study, the current classification methods cannot be applied to separate patients with schizophrenia from those with different psychiatric diagnoses.

In conclusion, our results showed that the discriminant function analysis using brain structural variables successfully distinguished between first-episode schizophrenia patients and healthy subjects with good accuracy. Such techniques may provide objective biological information adjunct to the clinical diagnosis of schizophrenia, although further studies are needed to see if they could contribute to early detection.

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