2. Methods

2.1. Subjects

Thirty-seven schizotypal disorder patients (24 males and 13 females; mean age=25.8 years, SD=5.4, range=18–37) who met the ICD-10 criteria for research (World Health Organization, 1993) were examined. They were recruited from patients who visited the clinics of the Department of Neuropsychiatry, Toyama Medical and Pharmaceutical University Hospital, with schizotypal features accompanied by distress or associated problems in their lives and who needed to receive consistent clinical follow-up. Candidates who had a previous history of overt psychotic episode or met the ICD-10 criteria for schizophrenia during the follow-up period were excluded. The mental condition of each subject was assessed by well-trained psychiatrists approximately every 2 weeks to check for the emergence of overt psychotic symptoms as part of an early intervention program for psychoses, and none of the 37 patients have developed overt schizophrenia to date (mean follow-up period after MRI scanning=2.0 years, SD=1.7). All available clinical information and data obtained from a detailed review of the clinical records and structured interviews using the Comprehensive Assessment of Symptoms and History (CASH) including the chapter on premorbid or intermorbid personality (Andreasen et al., 1992) were stored in a database. The subjects were diagnosed by consensus reached by at least two experienced psychiatrists based on these data. Twenty-nine patients were outpatients, and the other eight underwent closer clinical and medical examinations including MRI during short-term admission. At the time of MRI scanning, 32 of the 37 patients were treated with low-dose antipsychotics, of which 11 patients were treated with typical neuroleptics and 21 patients received atypical neuroleptics. The remaining five patients were neuroleptic-naïve. Clinical symptoms were rated within 1 month of scanning using the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1984a) and the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984b). Their mean scores for the SANS and SAPS were 42.4 (SD=23.0, range=5–84) and 16.0 (SD=8.9, range=0–31), respectively. Thirty-three of the 37 patients with schizotypal disorder were also assessed using the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham, 1962). Their mean total BPRS score was 38.4 (SD=9.7, range=19–61).

The schizophrenic comparison group was composed of 62 patients with schizophrenia [32 males and 30 females, mean age=25.8±4.9 (SD) years, range=18–36], and this group contained 58 schizophrenia patients (31 males, 27 females) who were examined in our previous study of the whole insular cortex volume (Takahashi et al., 2004a). All patients fulfilled the ICD-10 diagnostic criteria for research on schizophrenia (World Health Organization, 1993). All but one of the schizophrenia patients were receiving neuroleptic medication; 30 patients were treated with typical neuroleptics and 31 patients with atypical neuroleptics. At the time of the MRI study, their mean scores on the SANS and SAPS were 46.8 (SD=23.4) and 25.2 (SD=20.4), respectively.

The control subjects consisted of 69 healthy volunteers [35 males and 34 females, mean age=24.0±6.5 (SD) years, range=18–38] recruited from among members of the community, hospital staff, and medical and pharmaceutical students, and included 61 subjects who participated in a previous study (Takahashi et al., 2004a). They were given a questionnaire consisting of 15 items concerning their family and past histories, as well as present illness. They did not have any personal or family history of psychiatric illness in their first-degree relatives. The control subjects were not screened with a standard measure such as the Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II; First et al., 1997) and this may be a possible limitation of the study. However, all control candidates were interviewed and administered the Minnesota Multiphasic Personality Inventory (MMPI) by experienced clinical psychologists to obtain a rather homogenous control group without eccentric profiles on the MMPI. Although the MMPI has not proved very sensitive for the detection of schizotypy (Walters, 1983), approximately 17% of the candidates for normal controls were excluded for having an abnormal profile with a T-score for the validity scales or the clinical scales exceeding 70.

All subjects were physically healthy at the time of the study, and none had a lifetime history of serious head trauma, neurological illness or substance abuse. A handedness inventory developed by

Kameyama et al. (1981) consisting of 14 questions about hand preference was used to assess handedness; the subjects were right-handed except for one female patient with schizotypal disorder of unknown handedness.

The demographic and clinical characteristics of the control subjects, patients with schizotypal disorder and patients with schizophrenia are summarized in Table 1. The three groups were matched on age, height or parental education. Although there were more male than female schizotypal patients, the difference in the gender ratios among the three diagnostic groups was not statistically significant (chi-square analysis, $\chi^2=2.20$, $P=0.333$). The control subjects had attained a higher mean level of education than had the patients with either disorder (control subjects, 15.7 ± 2.5 years; schizophrenia patients, 13.4 ± 1.9 years; schizotypal patients, 13.5 ± 1.9 years; ANOVA, $F=23.28$, $df=2,165$, $P<0.001$). The total SAPS score for the schizophrenia patients was significantly higher than that for the schizotypal patients (ANOVA, $F=6.60$, $df=1,96$, $P=0.012$), although there were no significant differences between patients with schizophrenia and schizotypal disorder for the total score for SANS. There were significant differences in medication dosage (ANOVA, $F=17.95$, $df=1,97$, $P<0.001$); the patients with schizotypal disorder took significantly smaller amounts of neuroleptics than did the patients with schizophrenia. This study was approved by the Committee on Medical Ethics of Toyama Medical and Pharmaceutical University. After a complete description of the study was given to the subjects, their written informed consent was obtained.

2.2. Magnetic resonance imaging procedures

Magnetic resonance images were obtained utilizing a 1.5-T Magnetom Vision (Siemens Medical System, Inc., Erlangen, Germany) with a three-dimensional gradient-echo sequence FLASH (fast low-angle shots) yielding 160–180 contiguous T1-weighted slices of 1.0-mm thickness in the sagittal plane. Imaging parameters were repetition time=24 ms, echo time=5 ms, flip angle=40°, field of view=256 mm, and matrix size=256×256 pixels. The voxel size was $1.0\times1.0\times1.0$ mm^3. Magnetic field inhomogeneities in our scanner were monitored with weekly phantom scanning and daily basic quality control, and had been stable over the MR acquisition time for this study.

Table 1
Clinical and demographic characteristics of normal control subjects, patients with schizotypal disorder, and patients with schizophrenia

Variable	Control subjects		Schizotypal patients		Schizophrenia patients	
	Male ($N=35$)	Female ($N=34$)	Male ($N=24$)	Female ($N=13$)	Male ($N=32$)	Female ($N=30$)
Age (years)	24.1 ± 5.1	23.8 ± 5.8	25.7 ± 5.8	25.9 ± 4.6	25.6 ± 4.8	26.0 ± 5.1
Height (cm)	171.9[a] ± 4.3	159.2 ± 4.5	170.8[a] ± 5.9	156.2 ± 4.6	170.7[a] ± 5.1	158.5 ± 4.0
Education (years)	16.6[b] ± 2.8	14.8 ± 1.6	13.4 ± 1.9	13.5 ± 2.0	13.5 ± 1.9	13.3 ± 1.9
Parental education (years)	13.0 ± 2.3	12.5 ± 2.3	12.1 ± 1.5	12.1 ± 2.3	12.2 ± 1.9	11.9 ± 2.4
Age at onset (years)	–	–	–	–	22.1 ± 4.5	21.9 ± 4.2
Duration of illness (years)	–	–	–	–	3.5 ± 3.9	4.4 ± 4.3
Duration of medication (years)	–	–	2.1 ± 3.8	0.9 ± 1.5	2.4 ± 2.9	3.3 ± 3.7
Drug (mg/day, haloperidol equiv.)[c]	–	–	5.1 ± 5.5	2.5 ± 1.6	11.7[d] ± 8.6	10.8[d] ± 10.4
Total SAPS score	–	–	15.8 ± 8.7	16.3 ± 10.1	23.0[e] ± 21.1	27.7[e] ± 19.8
Total SANS score	–	–	40.4 ± 23.4	46.5 ± 23.4	50.0 ± 22.4	43.4 ± 24.4

This values represent means ± SDs. SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms.

ANOVA followed by Scheffé's test was used.

[a] $P<0.01$: compared with females.

[b] $P<0.01$: compared with female schizophrenia patients, male schizotypal patients, and female schizotypal patients; $P<0.05$: compared with female controls and male schizophrenia patients.

[c] The different typical and atypical neuroleptic dosages were converted into haloperidol equivalents according to Toru (2001).

[d] $P<0.01$: compared with schizotypal patients.

[e] $P<0.05$: compared with schizotypal patients.

The images were transferred to a Unix workstation (Silicon Graphics, Inc, Mountain View, CA., USA), and the data were randomly coded and analyzed using the software package Dr View 5.3 (Asahi Kasei Joho System Co, Ltd, Tokyo, Japan) without knowledge of the subjects' gender and diagnosis. Details of the data analyses have been previously described (Takahashi et al., 2002a). Briefly, the scans were realigned in three dimensions to standardize for differences in head tilt during image acquisition and were then reconstructed into entire contiguous coronal images, with a 1-mm thickness, perpendicular to the anterior commissure–posterior commissure (AC-PC) line on the workstation. 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). Although the images were not corrected for the magnetic field inhomogeneities, no visible effect on the quality of the segmentation was detected for any case. Before the volumetric analysis of the insular cortex, masks were semi-automatically created to demarcate the outer extent of the intracranial contents with the skull, scalp, and neck tissues removed, and therefore minimal manual editing of the masks was required.

2.3. Intracranial volume (ICV) measurements

Intracranial volume (ICV) was measured to correct for differences in head size. Before creation of the mask images, the 1-mm-thick coronal slices which had been corrected for head tilt were reformatted into consecutive 5-mm-thick sagittal slices with each voxel as $1 \times 1 \times 5$ mm^3. The intracranial cavity was manually traced for each slice using anatomical landmarks according to a study by Eritaia et al. (2000), and the ICV was calculated by summing the measured volumes of all slices.

2.4. Insular cortex measurements

First, based on the segmented gray matter images, the whole (short and long) insular cortex was traced on 1-mm consecutive coronal slices as described elsewhere (Takahashi et al., 2004a). Specifically, the most rostral coronal plane containing the insular cortex and the coronal plane containing the fusion of the superior and inferior circular insular sulci were chosen as anterior and posterior boundaries, respectively. On each coronal slice, the insular cortex was bounded superiorly by the superior circular insular sulcus and inferiorly by the inferior circular insular sulcus or the orbitoinsular sulcus.

Next, we followed the course of the central insular sulcus in three dimensions from the limen insulae and distinguished between the short and long insular cortex on coronal 1-mm slices (Fig. 1). The insular cortex rostral to the slice showing the limen insulae was regarded as the short insular cortex. On more caudal coronal slices, the short and long insular cortices were divided in a superior–inferior direction by the central insular sulcus, which was readily identified on the coronal slices in most cases. As previously noted by Naidich et al. (2004), the central insular sulcus provided a prominent landmark on conventional sagittal images, even when it was not clearly seen on coronal slices.

All volumetric data reported in this study were measured by one rater (TT) who was unaware of the subjects' identity, gender, and diagnosis. To determine the reliability of the measurements, five subjects were randomly selected for a total of approximately 275 slices (approximately 55 slices per brain). The short and long insular cortices in a subset of these five subjects were measured independently by two raters (TT and RT), and intraclass correlation coefficients (ICCs) were calculated. The inter-rater ICCs of the short and long insular cortex measurements were greater than 0.93. Each volume was then remeasured after at least 4 weeks by the first rater; the intra-rater ICCs of the short and long insular cortex measurements were greater than 0.98.

2.5. Statistical analysis

The absolute insular cortex volume was analyzed using repeated measures multivariate analysis of variance (MANCOVA) with age, ICV, and dosage of neuroleptic medication as covariates, diagnosis and gender as between-subject factors, and hemisphere (left, right) and subregion (short, long) as within-subject variables. Since a significant main effect for the subregion was observed ($F=2469.84$; $df=1,162$;

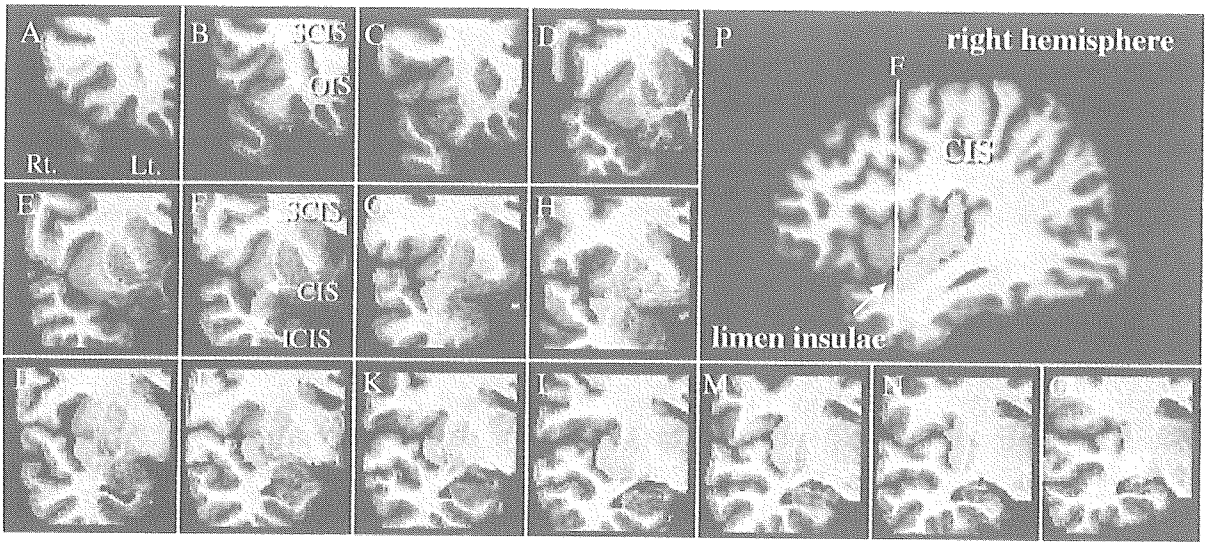

Fig. 1. Regions of interest manually traced in this study. The sample coronal slices (panels A-O) show delineations of the right short insular cortex (blue) and right long insular cortex (red), and panel P shows a sagittal view of the insular cortex in the right hemisphere. The coronal line F corresponds to panel F, a coronal slice showing the limen insulae. Abbreviations: CIS=central insular sulcus; ICIS=inferior circular insular sulcus; OIS=orbitoinsular sulcus; SCIS=superior circular insular sulcus.

$P<0.001$), the absolute volumes for the short and long insular cortex were then separately analyzed using the same model but with only hemisphere as a within-subject variable. As the schizotypal disorder patients took significantly smaller amounts of neuroleptics than the schizophrenia patients, the dosage of neuroleptic medication was used as the covariate for these analyses. For the comparison of the ICV, height was treated as covariate; groups did not significantly differ in ICV volume (Table 2). Post hoc Spjotvoll and Stoline tests, modified Tukey's tests for unequal sample size, were carried out to follow up the significant main effects or interactions yielded by these analyses (Fig. 2).

To analyze volume changes in relation to clinical symptoms, Spearman's rank correlation was calculated between the relative volumes for the long and short insular cortex and scores for the subscales of SAPS and SANS. The relative insular cortex volume, used to control for differences in head size, was obtained by dividing the absolute volume of the insular cortex by ICV and multiplying the result by 100. To examine the

Table 2
Intracranial volume (ICV) and absolute insular cortex volume in control subjects, patients with schizotypal disorder, and patients with schizophrenia

Brain region	Control subjects				Schizotypal patients				Schizophrenia patients				Analysis of covariance		
	Male (N=35)		Female (N=34)		Male (N=24)		Female (N=13)		Male (N=32)		Female (N=30)		Diagnosis effect[a]		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	df	P
ICV (cm^3)	1579	99	1384	108	1584	108	1420	154	1567	136	1391	101	1.13	2, 161	0.325[b]
Short insular cortex (mm^3)													3.19	2, 159	0.044[c]
Left	5588	601	4808	686	5347	652	4981	542	5095	661	4689	695			
Right	5349	637	4695	588	5261	699	5112	807	4855	556	4458	639			
Long insular cortex (mm^3)													5.26	2, 159	0.006[c]
Left	2795	493	2649	449	2911	628	2899	481	2763	500	2357	550			
Right	2678	429	2627	336	2906	377	2650	405	2676	448	2372	474			

[a] For the other main effects and interactions, and the results of post hoc tests, see the text.
[b] Height was used as covariate.
[c] Age, ICV, and dosage of neuroleptic medication were used as covariates.

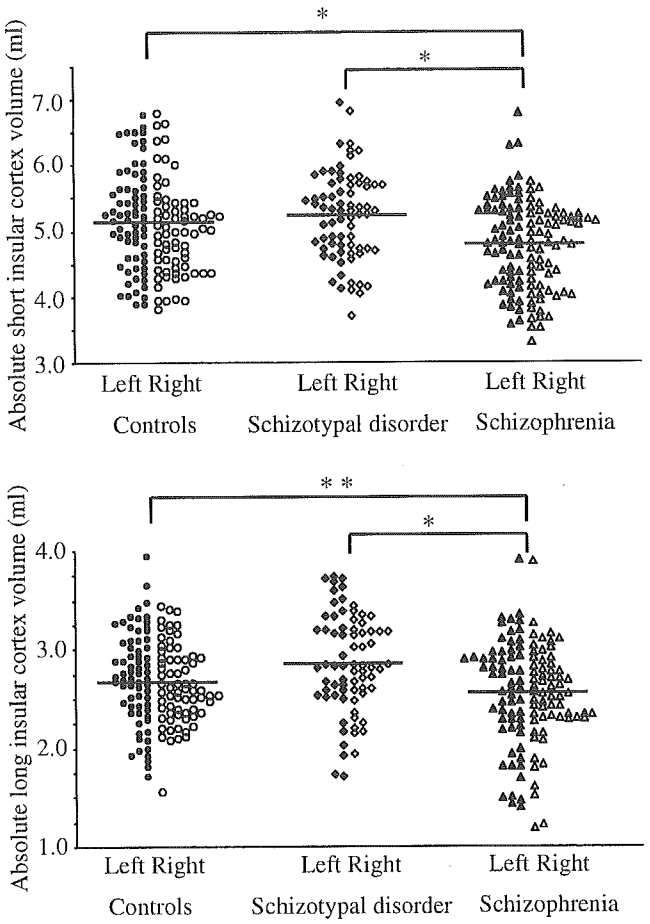

Fig. 2. Absolute volumes of the short and long insular cortex in control subjects (35 males, 34 females), schizotypal disorder patients (24 males, 13 females), and schizophrenia patients (32 males, 30 females). Horizontal lines indicate means. Post hoc Spjotvoll and Stoline tests: $^{*}P<0.01$, $^{**}P<0.05$.

effects of neuroleptic medication, correlations between the relative volumes for the long and short insular cortices and daily medication dosage and duration of neuroleptic medication were analyzed using Spearman's rank correlation coefficients. For the patients with schizophrenia, the correlation between the relative insular cortex volume and illness duration or age of onset was also analyzed. For these analyses, statistical significance was defined as $P<0.05$.

3. Results

3.1. Insular cortex measurements

Table 2 summarizes the short and long insular cortex measurements in schizophrenia patients, schizotypal disorder patients, and control subjects. Repeated measures MANCOVA revealed significant main effects for diagnosis ($F=6.06$; $df=2,159$; $P=0.003$), hemisphere ($F=23.55$; $df=1,162$; $P<0.001$), and subregion ($F=2469.84$; $df=1,162$; $P<0.001$). However, there was no significant diagnosis × subregion interaction ($F=1.80$; $df=2,162$; $P=0.169$). This indicates that the between-group difference in insular cortex volume was not specific for one subregion.

Lower order MANCOVA of the short insular cortex revealed significant main effects for diagnosis ($F=3.19$; $df=2,159$; $P=0.044$) and hemisphere ($F=8.91$; $df=1,162$; $P=0.003$), where patients with schizophrenia had a significantly smaller short insular cortex than schizotypal patients (post hoc test, $P=0.001$) and control subjects (post hoc test, $P=0.001$) bilaterally, and the short insular cortex volume was larger for the left than the right hemisphere for all diagnostic groups (post hoc test, $P=0.002$). There was no significant difference in short insular cortex volume between schizotypal disorder patients and control subjects (post hoc test, $P=0.827$), and no main effect for gender ($F=2.35$; $df=1,159$; $P=0.127$) or interaction among the factors was observed.

Lower order MANCOVA of the long insular cortex revealed significant main effects for diagnosis ($F=5.26$; $df=2,159$; $P=0.006$). Post hoc analyses showed the long insular cortex to be significantly reduced in the schizophrenia patients compared with the schizotypal disorder patients ($P<0.001$) and with the controls ($P=0.044$). No significant difference in the long insular cortex volume emerged between the schizotypal disorder patients and control subjects ($P=0.074$). There was no significant main effect for gender ($F=1.73$; $df=1,159$; $P=0.190$) or hemisphere ($F=3.79$; $df=1,162$; $P=0.053$), and no interaction among the factors was found.

3.2. Clinical correlations

For both patient groups, there were no significant correlations between the volumes for the short and long insular cortex and the scores for the subscales of the SAPS or SANS. For schizotypal disorder patients, the short and long insular cortex volumes were not correlated with the medication dosage or duration of

neuroleptic medication. For schizophrenia patients, insular cortex volume was negatively correlated with illness duration (right short insular cortex, Spearman's rho=0.39, $P=0.002$; left long insular cortex, Spearman's rho=0.47, $P<0.001$) and duration of neuroleptic medication (right short insular cortex, Spearman's rho=0.38, $P=0.002$) even after Bonferroni correction for multiple comparisons was made [i.e. $P<0.003$ (0.05/16)]. However, insular cortex volume was not correlated with age at onset of illness or dosage of neuroleptic medication.

4. Discussion

To our knowledge, this is the first volumetric MRI study to separately investigate sulcally defined short and long insular cortex volumes in schizophrenia spectrum disorders. The primary positive finding of this study was a significant volume reduction in the short and long insular cortices without a pattern of topographically specific localization for schizophrenia patients compared with schizotypal disorder patients and control subjects. In contrast, we found no volume differences in the short or long insular cortices between schizotypal disorder patients and normal controls.

The anterior and posterior portions of the insular cortex have been reported to have cytoarchitectural, connectional, and functional differences (Augustine, 1996; Duvernoy, 1999; Türe et al., 1999). The anterior portion, which is divided into three short insular gyri, has extensive connections with the frontal lobe. In contrast, the posterior portion of the insular cortex is formed by one or two long insular gyri and is seen to connect with both the parietal and temporal lobes. Functional neuroimaging studies have suggested that the short insular cortex is more involved in emotional and language-related functions, whereas the long insular cortex includes somatosensory and auditory processing areas [as reviewed by Augustine (1996), Nagai et al. (2001), Bamiou et al. (2003), and Naidich et al. (2004)]. Our findings are consistent with a recent MRI study by Kasai et al. (2003), who reported that both anterior and posterior insulae were significantly reduced in schizophrenia patients compared with control subjects and that group differences were not localized to a particular subregion. For the present study, we used the central insular sulcus as an anatomical boundary between the short and long insular cortex, whereas Kasai et al. (2003) used an alternative extrinsic landmark (mamillary body). Disruption of the paralimbic neural network including the insula has been proposed to contribute to the pathophysiology of schizophrenia by previous structural MRI studies (Goldstein et al., 1999; Shapleske et al., 2002). More specifically, functional neuroimaging studies have reported that various cognitive dysfunctions in schizophrenia such as emotional deficit (Crespo-Facorro et al., 2001a), recognition memory impairment (Crespo-Facorro et al., 2001b) or abnormal audiovisual speech perception (Surguladze et al., 2001) are mediated at least in part by the insular cortex. The insular cortex is engaged in a variety of cognitive functions, but its topographical localization has not been fully established. From the present and previous studies, it appears that the involvement of the insular cortex in schizophrenia is widespread and diffusely distributed rather than being specifically located in the anterior or posterior portion.

The sample characteristics of the clinic-based schizotypal disorder patients in our laboratory have been described in previous publications (Takahashi et al., 2002b, 2004b; Yoneyama et al., 2003; Kawasaki et al., 2004; Suzuki et al., 2004). The present study may not have been completely framed for direct comparisons with several previous studies in subjects with SPD since there are subtle but distinct differences between the diagnostic categories of schizotypal disorder (ICD-10) and SPD (DSM-IV). SPD is a stable personality, but schizotypal disorder in contrast requires a period of at least 2 years and the criteria include occasional transient quasi-psychotic episodes. Although all of the schizotypal subjects in this study also fulfilled DSM-IV criteria for SPD on Axis II, an additional diagnosis of brief psychotic disorder on Axis I was considered in eight subjects who experienced occasional transient quasi-psychotic episodes. In addition, schizotypal disorder "occasionally evolves into overt schizophrenia." Thus, schizotypal disorder in ICD-10 includes prodromal schizophrenia in addition to SPD as defined in DSM-IV. However, prior to the onset of psychosis, the clinical manifestations of two groups of patients who later develop schizophrenia or not are indistinguishable. The follow-up periods for the schizotypal patients in this

study were relatively short and some of them may have been at risk for developing psychosis later; they could be diagnosed as being in the prodromal phase of schizophrenia but not as SPD according to the concept of DSM-IV. We therefore adopted the ICD-10 criteria for schizotypal disorder in the present study. With regard to the symptom severity, the total BPRS score of our schizotypal subjects (mean=38.4, SD=9.7) was comparable to those (mean=37.5, SD=6.2) of previous MRI studies on mostly neuroleptic-free clinic-based subjects with SPD (Hazlett et al., 1999; Byne et al., 2001). However, our cohort may have included subjects with more serious symptoms than the SPD subjects in previous studies since most of the schizotypal disorder patients in the present study were taking neuroleptic medications.

Our results suggest that the volumes for the short and long insular cortices were reduced in overt schizophrenia but were preserved in schizotypal disorder. This may explain the decreased magnitude in cognitive/social deficits and symptomatology for schizotypal disorder relative to schizophrenia. Interestingly, it has been suggested that the abnormalities associated with the insular cortex are relevant to hallucinations (Crespo-Facorro et al., 2000; Shergill et al., 2000; Shapleske et al., 2002), which are a cardinal feature of schizophrenia but not prominently seen in schizotypal subjects. In a recent review of neurobiological abnormalities found in SPD, Siever and Davis (2004) hypothesized that while temporal volume reductions appear to be common to both SPD and schizophrenia, there may be preservation of frontal lobe volume in SPD compared with schizophrenia. Despite the above-mentioned differences in the sample characteristics between laboratories, Kurachi (2003a,b) suggested a similar hypothesis based on studies concerning cognitive characteristics and brain morphologic changes in schizotypal disorder and schizophrenia patients, i.e., the temporal lobe changes may underlie a vulnerability to schizophrenia and latent dysfunction in these lesions may become clinically apparent due to additional frontal lobe changes in schizophrenia. Based on these hypotheses, it may be reasonable to suppose that the long insular cortex, connecting with the temporal regions, is reduced in schizotypal patients as well as schizophrenia patients, while the short insular cortex, which has close connections with frontal cortex, is preserved in schizotypal patients. Such parallel reductions in associated regions in SPD were found in the volume of the thalamus; Byne et al. (2001) reported that size of the pulvinar, which projects to temporal lobe structures, was reduced in SPD as well as schizophrenia patients, while the size of the dorsomedial nucleus of the thalamus, associated with the prefrontal regions, was decreased only in the schizophrenia patients. Contrary to predictions, however, the present findings suggest that the insular cortex in schizotypal disorder patients shows no topographically specific volume changes. Although not supported directly by the present findings, the validity of these hypotheses seems worthy of further testing. Additional comprehensive assessment of multiple brain regions in the same group would be essential for the understanding of the brain morphologic characteristics of the schizotypal patients.

Some limitations of the present study should be mentioned. First, our results were not in agreement with those of a previous voxel-based MRI study carried out by our group (Kawasaki et al., 2004), in which reduced gray matter of the left insular cortex was found in schizotypal disorder patients. Although the validity of VBM has been tested in comparison with conventional region-of-interest (ROI) measurements (Wright et al., 1999; Suzuki et al., 2002), as discussed by Kasai et al. (2003), the results of the voxel-based methods could remain at odds with manual ROI methods, which are the current gold standard. Although we cannot clearly explain the reason for the differences in the results between the VBM and manual ROI analyses, the morphologic changes of the adjacent structures such as the superior temporal gyrus or the inferior frontal gyrus might have influenced the results for the insular cortex. A second limitation is that most of the patients were receiving neuroleptic medication. A relationship between brain morphologic features and neuroleptic medication has been reported in schizophrenia (Keshavan et al., 1994, 1998; Chakos et al., 1995; Gur et al., 1998), and insular cortex volume in schizophrenia was negatively correlated with duration of neuroleptic medication in the present study. This correlation was not found for the schizotypal patients, and the dosage of neuroleptic medication taken at the time of the scan in this study was not related to insular cortex volume. However, the

effects of cumulative years of medication treatment on the schizophrenia patients cannot be ruled out. A third limitation is that the control subjects in the present study were not selected to be educationally equivalent to the patients with both disorders. However, we optimally matched the parental education among the three groups according to the notion that matching on the basis of the educational level of the parents may reduce confounding factors in selection of control groups when brain measures are studied (Andreasen et al., 1990). In addition to these limitations, the relatively small sample size of female schizotypal disorder patients also limited our ability to generalize the findings of the present study. The morphologic characteristics of this disorder should be extensively examined with a larger female sample in future studies to confirm and extend the present findings.

In conclusion, the volume reduction of the insular cortex may be specific to overt schizophrenia, although there is no evidence for a topographically specific pattern of volume loss between the short and long insular cortices. The findings of the present study suggest that insular involvement may be implicated in the manifestation of overt psychosis.

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Volumetric analysis of sulci/gyri-defined in vivo frontal lobe regions in schizophrenia: Precentral gyrus, cingulate gyrus, and prefrontal region

Shi-Yu Zhou[a,d], Michio Suzuki[a,d,*], Hirofumi Hagino[a], Tsutomu Takahashi[a], Yasuhiro Kawasaki[a,d], Mie Matsui[b,d], Hikaru Seto[c], Masayoshi Kurachi[a,d]

[a]*Department of Neuropsychiatry, Toyama Medical and Pharmaceutical University, 2630 Sugitani, Toyama 930-0194, Japan*
[b]*Department of Psychology, Toyama Medical and Pharmaceutical University, 2630 Sugitani, Toyama 930-0194, Japan*
[c]*Department of Radiology, Toyama Medical and Pharmaceutical University, 2630 Sugitani, Toyama 930-0194, Japan*
[d]*Core Research for Evolutional Science and Technology, Japan Science and Technology Corporation, Tokyo, Japan*

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Abstract

Methodological limitations in most previous magnetic resonance imaging (MRI)-based volumetric studies might have contributed to the inconsistent results regarding the frontal lobe regions of schizophrenia. Thus, applying the largest sample to date among those that have fully taken account of the intrinsic anatomical landmarks, this study aimed at clarifying the volumetric alterations of the frontal lobe and its subregions in schizophrenia. Participants comprised 59 patients with schizophrenia and 58 healthy controls. Measurements were performed on consecutive 1-mm-thick coronal slices reformatted from three-dimensional 1.5-T MR images. The whole frontal lobe was demarcated and then subdivided into the precentral gyrus (PCG), anterior cingulate, and posterior cingulate, and the remainder temporarily as the prefrontal region. Patients with schizophrenia had significant cortical volume reductions in the bilateral whole frontal lobe, prefrontal region, PCG, posterior cingulate, and right anterior cingulate. This study has confirmed that patients with schizophrenia do have cortical volume reductions in the whole frontal lobe and its subregions. Volume reduction in the PCG suggests that the primary motor cortex might contribute to the mechanisms of schizophrenia, considering its important role in the processing of multiple motor-related cognitive functioning suggested by the recent literature.

Keywords: Psychosis; Brain morphometry; Magnetic resonance imaging; Primary motor cortex; Mirror neuron system

1. Introduction

Although frontal lobe dysfunction has been repeatedly shown to be one of the central characteristics of

* Corresponding author. Department of Neuropsychiatry, Toyama Medical and Pharmaceutical University, 2630 Sugitani, Toyama 930-0194, Japan. Tel.: +81 764 34 7321; fax: +81 764 34 5030.
E-mail address: suzukim@ms.toyama-mpu.ac.jp (M. Suzuki).

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schizophrenia, magnetic resonance imaging (MRI)-based volumetric studies attempting to determine in vivo gross structural alterations in this region have failed to provide consistent evidence, with approximately 40% reporting negative results (as reviewed by McCarley et al., 1999; Shenton et al., 2001; Wright et al., 2000 for a meta-analysis). Such inconsistency may partially result from small alterations in the frontal lobe being just at the threshold for MRI detection, but considerable methodological differences in defining boundaries for regions of interest among previous studies might have contributed more. Using arbitrary landmarks (e.g., the coronal level of the genu of the corpus callosum as the posterior boundary of the prefrontal region) (methods reviewed by Convit et al., 2001), superficially, could maintain uniform tracing procedures among subjects and achieve high intra- and inter-rater reliabilities. However, such methods might have failed to take into account the large morphological variance in the frontal lobe structures across subjects and even between the hemispheres. Furthermore, the measured volume of the (pre)frontal lobe could be affected by anatomically abnormal landmark structures. In fact, the corpus callosum has been reported to be abnormal in size or shape (Shenton et al., 2001). Thus, using different arbitrary landmarks could not only have resulted in inconsistency, but also could have made it difficult to document that the measures and the statistical results are valid. Although a number of studies have measured the whole (pre)frontal lobe based on intrinsic anatomical landmarks (Buchanan et al., 1998; Baaré et al., 1999; Crespo-Facorro et al., 2000; Convit et al., 2001; Yamasue et al., 2004), they may not be definitive because only relatively small samples (fewer than 30 patients) were used. We argue that the distributions of anatomical brain measures in schizophrenia populations often have larger variances and considerable overlap with those of the normal population, and the magnitude of the morphological alterations in the brain structures of schizophrenia patients is generally small. So results from small samples could be either unstable or insufficient to examine such small differences. Among these previous approaches, two studies (Crespo-Facorro et al., 2000; Yamasue et al., 2004) employed fairly large samples. However, as the former examined only male patients and the latter had a patient sample composed of 20 males and 7 females, both studies were inappropriate to examine gender effects. There are also two important studies on this topic that must be mentioned here (Gur et al., 2000; Hirayasu et al., 2001), although neither study traced the frontal lobe fully according to the intrinsic anatomical landmarks; one employed a carefully selected sample composed of almost 20 first-episode schizophrenia patients and demonstrated a significant reduction of the total prefrontal gray matter (Hirayasu et al., 2001), and the other had a sample even larger than ours and showed volume reductions in multiple prefrontal regions (Gur et al., 2000). Another main reason for the inconsistent frontal lobe findings in schizophrenia frontal lobe might be taking this anatomically and functionally heterogeneous large tissue as a whole. Although almost all the frontal subregions have at least once been reported to be smaller in schizophrenia (Buchanan et al., 1998; Baaré et al., 1999; Goldstein et al., 1999; Gur et al., 2000; Crespo-Facorro et al., 2000; Convit et al., 2001; Chemerinski et al., 2002; Yamasue et al., 2004), findings are not consistent across studies and rarely replicated, and the use of small samples is still a common limitation of these studies.

The present study has attempted to overcome these various methodological limitations. First, we set up feasible gyri/sulci-based methods for MRI-based parcellation of the frontal lobe, largely following the guidelines of Rademacher et al. (1992) and Crespo-Facorro et al. (1999). With the availability of synchronous–orthogonal views in three dimensions, in conjunction with the context of gyri/sulci on successive coronal slices, decisions of necessary anatomical landmarks could be readily made. Regional white matter was also defined by using the main landmarks. Second, the whole frontal lobe was ultimately subdivided into multiple functionally homogeneous subregions similar to those defined by the Iowa group (Crespo-Facorro et al., 1999). For the first phase of this study, the whole frontal lobe was separated from the rest of the cerebrum and then subdivided into the precentral gyrus (PCG, the primary motor area [M1]), cingulate gyrus (the limbic area), and the remainder temporarily as the prefrontal area (the cognitive area). In contrast to the prefrontal cortex and anterior cingulate gyrus, little attention has been paid to volumetric alteration of the PCG and posterior cingulate in schizophrenia. However, M1 has recently been suggested to play an important role in the processing of motor-related cognitive informa-

tion as a node of the human mirror–neuron system (reviewed by Georgopoulos, 2000), and the posterior cingulate has also been suggested to subserve a variety of cognitive functions (e.g., long-term memory and working memory) (reviewed by Maddock, 1999; Kobayashi, 2001). Third, we performed the measurements in the largest sample to date among those that have fully taken account of the intrinsic anatomical landmarks of the frontal lobe and its subregions in schizophrenia. This sample was composed of roughly equal numbers of male and female patients (about 30 of each) and matched control subjects, thus allowing an observation of gender effects. We expected that patients with schizophrenia would show volume reductions in the whole frontal lobe and some of the subregions (e.g., prefrontal region and cingulate gyrus); as for the PCG, it was difficult to make a special hypothesis because of the background that this region had been rarely mentioned in previous studies. However, given the potential importance of the PCG in cognitive processing, it would be of interest to examine the region morphometrically in schizophrenia.

2. Methods

2.1. Subjects

Table 1 presents the demographic and clinical data of the subjects. All subjects were right-handed. The groups were matched for age, gender, and parental education.

Fifty-nine medicated patients with DSM-IV schizophrenia were recruited from both inpatient and outpatient clinics. Diagnoses were made based on the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1997). Clinical symptoms were rated within 1 month of scanning using the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984a) and the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1984b). Fifty-eight control subjects were healthy volunteers recruited from among the community, hospital staff, and medical students. They were interviewed by psychiatrists using a questionnaire concerning their families, histories, and present illness. Subjects were excluded if they had a history of head trauma, neurological illness, serious medical or surgical illness, or substance abuse disorder. Control subjects with a personal or family history of psychiatric disorder or any T-score of the Minnesota Multiphasic Personality Inventory (MMPI) exceeding 70 were also excluded.

After complete description of the study to the subjects, written informed consent was obtained. This study was approved by the Committee on Medical Ethics of the Toyama Medical and Pharmaceutical University.

2.2. Magnetic resonance image acquisition and processing

Magnetic resonance images (MRI) were obtained using a 1.5-T Magnetom Vision (Siemens Medical

Table 1
Demographic and clinical characteristics of the subjects

Characteristics	Schizophrenia patients		Normal control subjects	
	Male ($n=31$)	Female ($n=28$)	Male ($n=30$)	Female ($n=28$)
Age (years)	25.4 ± 4.9	25.7 ± 5.1	24.9 ± 5.1	24.8 ± 5.9
Education (years)	13.5 ± 1.96*	13.3 ± 2.0*	17.1 ± 2.7	15.0 ± 1.7**
Parental education (years)	12.4 ± 1.8	12.0 ± 2.4	13.0 ± 2.5	12.6 ± 2.5
Age at onset of illness (years)	21.9 ± 4.5	22.0 ± 4.4	–	–
Duration of illness (years)	3.6 ± 4.0	4.1 ± 4.3	–	–
Duration of medication (years)	2.4 ± 2.9	3.1 ± 3.6	–	–
Dose of drug (mg/day; HPD equivalent)	11.9 ± 8.6	10.5 ± 10.7	–	–
Total SAPS score	23.1 ± 21.4	27.1 ± 20.5	–	–
Total SANS score	49.8 ± 22.8	44.2 ± 24.1	–	–

Values represent mean ± S.D.
HPD, haloperidol; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms.
* Significantly different from the same-gender control subjects ($P<0.02$).
** Significantly different from male control subjects ($P<001$).

System, Inc., Erlangen, Germany) with a three-dimensional gradient-echo sequence, FLASH (fast low-angle shots), yielding 160–180 contiguous T1-weighted slices of 1.0 mm thickness in the sagittal plane. Imaging parameters were as follows: repetition time=24 ms, echo time=5 ms, flip angle=40°, field of view=256 mm, and matrix size=256×256 pixels. The voxel size was 1.0×1.0×1.0 mm. The images were transferred to a Unix workstation (Silicon Graphics, Inc., Mountain View, CA, USA) and processed with the software package Dr. View 5.0 (Asahi Kasei Joho System Co., Ltd., Tokyo, Japan). The methods used for image processing have been described in detail elsewhere (Takahashi et al., 2002). Briefly, the scans were realigned in three dimensions to standardize for differences in head tilt during image acquisition and were then reconstructed into entire contiguous coronal images, with a 1-mm thickness, perpendicular to the anterior commissure and posterior commissure (AC–PC) line. The signal-intensity histogram distributions from the T1-weighted images across the whole brain for each subject were used to segment the voxels semiautomatically into gray matter, white matter, and cerebrospinal fluid (CSF), according to the Alpert algorithm (Alpert et al., 1996). Before volumetric analysis, masks were semiautomatically created to demarcate the outer extent of the intracranial contents, with the scalp and neck tissue removed. Minimal manual editing of the masks was required. Magnetic field inhomogeneity in our scanner was monitored with weekly phantom scanning and daily basic control, and remained stable over the MR acquisition time. No visible effect on quality of segmentation was detected in any of the cases.

2.3. Volumetric measurements of regions of interest (ROIs)

For the first phase of the series, the whole frontal lobe was demarcated and then subdivided into three large functional parts: PCG (M1), cingulate gyrus (the limbic area), and prefrontal area (the cognitive area) (Fig. 1). All the volumetric measurements for all the regions of interest (ROIs) were performed in reformatted consecutive 1-mm-thick coronal slices (voxel size=1.0×1.0×1.0 mm). ROIs were defined mainly based on the intrinsic anatomical landmarks, which were largely the same as those applied by the Iowa group (Crespo-Facorro et al., 1999), with minor modifications. Below are the brief descriptions for the delineation methods on coronal slices.

2.3.1. Whole frontal lobe

On the lateral surface of the hemisphere, the posterior boundary was the central sulcus; on the medial wall, the callosal sulcus (CS) constituted the inferior boundary. Delineation began with the most rostral coronal slice that contained brain tissue and included all the tissues until the body of the corpus callosum (CC) appeared. After that, straight lines, which successively linked the marked points when they existed (i.e., the deepest point of the dorsal CS, the superior end of the circular sulcus of the insula, the inferior end of the circular sulcus of the insula, and the deepest point of the ventral CS), were used to remove the brain tissue inside this circle (i.e., basal ganglia, insular gyrus, white matter around them, and CC). More caudally, after the central sulcus appeared, a straight line that linked the deepest point of the central sulcus to that of the CS was used to demarcate the frontal lobe from the rest, until the central sulcus reached the most dorsomedial point; the coronal slice at this point corresponded to the most caudal slice that contained the frontal lobe tissue.

2.3.2. Precentral gyrus

The anterior and posterior boundaries were the precentral sulcus and the central sulcus, respectively. On the medial surface of the hemisphere, when the precentral sulcus did not extend to the cingulate sulcus, the paracentral sulcus was used as the anterior boundary (Crespo-Facorro et al., 1999); the inferior boundary was the cingulate sulcus. The delineation procedure on the coronal slices was as follows: (1) the inner boundary (which separated the PCG from the inner rest of the brain) was the inferior precentral sulcus when it existed; otherwise, a straight line that linked the deepest point of the superior precentral sulcus with that of the central sulcus was used; (2) the inferior boundary for the first several rostral slices was the Sylvian fissure and, after that, it became the inferior precentral sulcus (when it did not extend to the Sylvian fis-

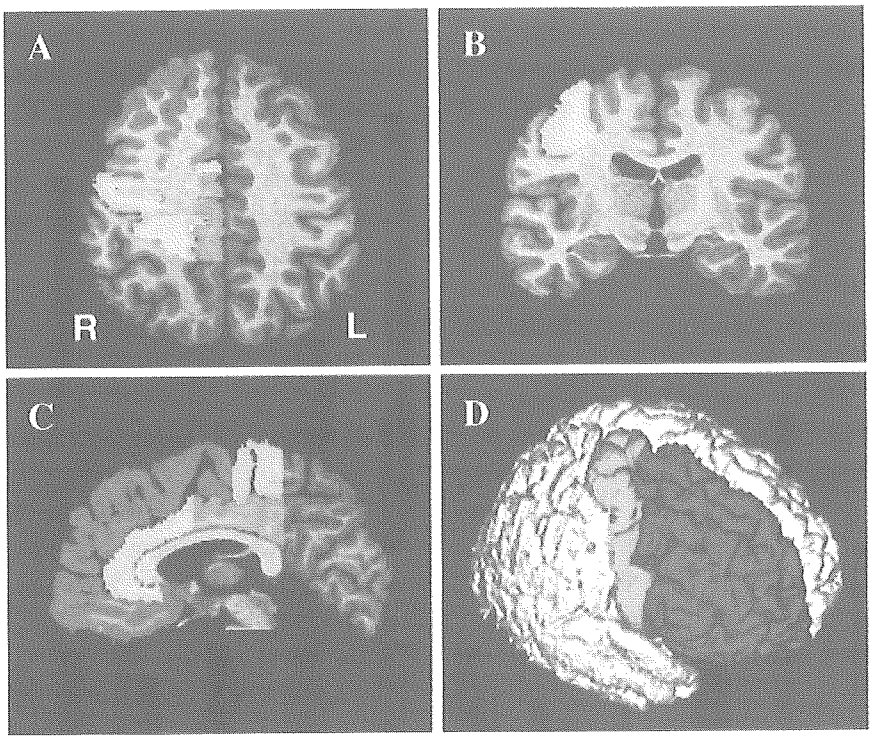

Fig. 1. Views of the frontal lobe regions of interest. (A–C). One set of the synchronous–orthogonal views in three dimensions (A, transaxial; B, coronal; C, sagittal); transaxial and sagittal views were automatically reconstructed when the delineation was performed on consecutive coronal slices. (D) The three-dimensional reconstructed image of the regions of interest. Regions are displayed in distinctive colors: the precentral gyrus in red, prefrontal region in blue, anterior cingulate in pink, and posterior cingulate in green. L, left hemisphere; R, right hemisphere.

sure, the anteriormost subcental sulcus was used; Kates et al., 2002); more caudally, when the central sulcus appeared, it was used as the inferior boundary; and (3) the superior boundary was the precentral sulcus; when two segments of the precentral sulcus appeared on a single coronal slice, the upper one was taken (Crespo-Facorro et al., 1999).

2.3.3. Cingulate gyrus

Delineation of the cingulate gyrus was performed within the range of the frontal lobe. The boundaries were the CS and the cingulate sulcus; a straight line that linked the deepest points of these two sulci was used for demarcation. In cases when the cingulate sulcus was segmented, we followed the rules of the Iowa group (Crespo-Facorro et al., 1999). Differing from them, however, the paracingulate gyrus, when extant, was not included; the principle for judgment of the existence of the paracingulate gyrus was same as in our previous study (Takahashi et al., 2002). In the present study, the cingulate gyrus was further subdivided into the anterior part (AnCiG; Brodmann's area [BA] 24) and the posterior part (PoCiG; BA23 and BA31) at the coronal level of the center of the anterior commissure, according to Talairach and Tournoux (1988), because of the lack of a gross anatomical boundary between them.

2.3.4. Prefrontal area

At present, we temporarily defined the portion of the frontal lobe other than the PCG and cingulate gyrus as the prefrontal area (Fig. 1). On the lateral surface, this area comprises the tissue rostral to the precentral sulcus; on the medial surface, the tissue dorsal to the cingulate sulcus and rostral to the medial extension of the precentral sulcus (or the paracentral sulcus, see Section 2.3.2); on the ventral surface, it covers the whole ventral structure of the frontal lobe (i.e., the straight gyrus and orbitofrontal gyri). In the present study, we did not separate the supplementary motor area (medial BA6) and the premotor area (lateral BA6) from the prefrontal area because of the absence of intrinsic boundaries demarcating these areas; this,

as well as further subdividing the prefrontal area into multiple units, remains a topic for future works.

2.3.5. Regional white matter

Regional white matter was also defined, which corresponded to the white matter involved in each ROI as defined above, and white matter volume was calculated automatically by applying a subprogram of Dr. View, which performed a calculation of 'logic and' between the ROI of a specific subregion and the whole cerebral white matter. Thus, on each coronal slice, the white matter for each ROI corresponded to the portion that was surrounded by the gyral cortex and the straight line that linked the deepest points of the landmark sulci. Before this calculation, the ROI of the whole cerebral white matter was obtained by applying the segmentation procedure as described in Section 2.2.

All measurements were performed by one rater (S.Z.), without knowledge of subjects' identity. The intrarater reliability was established by rating five subjects randomly sampled from the whole subject group; the interrater reliability was also established by independent ratings of five subjects by two skilled raters who were familiar with brain anatomy (S.Z. and H.H.). Before the intraclass correlation coefficients (ICC) were calculated, raters practised on another set of brains. The ICCs were over 0.95 for the whole frontal lobe and whole frontal white matter, 0.94 for the PCG, 0.93 for the AnCiG, and 0.96 for the PoCiG.

2.4. Statistical analysis

Statistical differences in the regional volumetric measures were analyzed for each ROI, using repeated measures multivariate analysis of variance (MANOVA) with intracranial volume (ICV) and age as covariates; group (patients, controls) and gender (male, female) as between-subject factors; and hemisphere (right, left) as a within-subject factor. Post hoc Tukey's honestly significant difference tests were used to follow up the significant main effects or interactions. Correlations between the volumetric measures and the severity of clinical symptoms in the SAPS and SANS were examined within a subgroup of patients (16 males and 22 females) with active psychotic symptoms who had at least one item of the SAPS rated as not less than 3 (moderate). To control for the differences in head size, relative values of regional volume (100 × regional volume/ICV) were used for all correlation analyses. Statistical significance was defined as $P<0.05$ (two-tailed).

3. Results

3.1. Volumes of regions of interest

Tables 2 and 3 present the regional gray matter and white matter volume measures, and the results of volume comparisons between groups, respectively.

3.1.1. Gray matter

MANCOVA revealed significant group effects in the cortices of the whole frontal lobe ($F=9.59$, $df=1,111$, $P=0.002$), prefrontal area ($F=4.70$, $df=1,111$, $P=0.032$), AnCiG ($F=6.79$, $df=1,111$, $P=0.010$), PoCiG ($F=15.46$, $df=1,111$, $P<0.001$), and PCG ($F=8.99$, $df=1,111$, $P=0.003$). Post hoc analysis showed that the significant cortical volume reduction for the AnCiG was unilateral (right side), while that for the other ROIs was bilateral.

Significant main effects of hemisphere were shown in the cortices of all ROIs. Post hoc analysis revealed that, except for the AnCiG and PoCiG (left smaller than right), ROIs in the left hemisphere were larger than in the right. A significant interaction of gender-by-hemisphere was also shown in the cortices of the whole frontal lobe and prefrontal area (post hoc: males larger than females bilaterally).

3.1.2. White matter

Except for the PoCiG ($F=5.77$, $df=1,111$, $P=0.018$; post hoc $P<0.01$ bilaterally), no significant main effect of diagnosis was shown in any other ROI. Significant main effects of gender and hemisphere were detected in the whole frontal lobe, prefrontal region, and PCG (post hoc tests, males larger than females bilaterally, and right larger than left). Main effects of gender in the AnCiG and of hemisphere in the PoCiG were also significant (post hoc tests, males larger than females bilaterally, and left larger than right).

Table 2
Gray matter volumes of the frontal lobe regions

Region of interest	Schizophrenia patients		Normal control subjects	
	Male (n=31)	Female (n=28)	Male (n=30)	Female (n=28)
Whole frontal lobe*,**,***,#				
Left	123.08 ± 14.05	110.83 ± 14.12	130.35 ± 12.68	118.92 ± 9.60
Right	118.95 ± 13.67	108.53 ± 13.18	125.41 ± 12.73	116.20 ± 8.63
Precentral gyrus*,**,#				
Left	18.55 ± 2.62	17.75 ± 2.63	20.06 ± 2.36	18.83 ± 1.73
Right	17.58 ± 2.21	16.64 ± 2.59	19.07 ± 2.80	17.89 ± 1.58
Cingulate gyrus (CinG)*,**,#				
Left	8.13 ± 1.76	7.47 ± 1.86	8.92 ± 2.29	8.77 ± 2.36
Right	9.49 ± 2.16	8.80 ± 1.73	10.65 ± 2.17	10.49 ± 1.45
Anterior CinG†,**,‡				
Left	3.98 ± 1.42	3.60 ± 1.49	4.20 ± 1.75	4.33 ± 1.89
Right	5.32 ± 1.74	4.55 ± 1.18	5.74 ± 1.81	5.71 ± 1.36
Posterior CinG *,§,#				
Left	4.15 ± 0.93	3.87 ± 0.85	4.72 ± 0.94	4.44 ± 0.83
Right	4.16 ± 1.28	4.25 ± 0.92	4.91 ± 0.74	4.77 ± 0.70
Prefrontal area†,**,***,#				
Left	96.40 ± 11.73	85.61 ± 11.02	101.37 ± 10.66	91.32 ± 8.52
Right	91.88 ± 11.23	83.09 ± 11.34	95.68 ± 10.81	87.82 ± 8.25

Values represent mean ± S.D. (cm^3); MANCOVA, multivariate analysis of covariance (see Methods).
* MANCOVA revealed a significant main effect of diagnosis (F>8.99, df=1,111, P<0.005).
** MANCOVA revealed a significant main effect of hemisphere (F>39.01, df=1,113, P<0.001).
*** MANCOVA revealed a significant gender-by-hemisphere interaction (F>8.39, df=1,113, P<0.005); post hoc Tukey's test showed significant difference between genders bilaterally (P<0.001).
# Post hoc Tukey's test showed significant reduction in schizophrenia patients (P<0.001 bilaterally).
† MANCOVA revealed a significant main effect of diagnosis (F>4.69, df=1,111, P<0.05).
‡ Post hoc Tukey's test showed significant reduction in schizophrenia patients (P=0.033 on the right side).
§ MANCOVA revealed a significant main effect of hemisphere (F=6.76, df=1,113, P=0.01).

3.2. Relationships between volumetric measures and clinical variables

Cortical volumes of the whole frontal lobe (controls: left, $r=-0.31$, $df=57$, $P=0.017$; right, $r=-0.36$, $df=57$, $P=0.010$; patients: left, $r=-0.39$, $df=58$, $P=0.002$; right, $r=-0.45$, $df=58$, $P<0.001$) and prefrontal region (controls: left, $r=-0.28$, $df=57$, $P=0.035$; right, $r=-0.28$, $df=57$, $P=0.033$; patients: left, $r=-0.37$, $df=58$, $P<0.005$; right, $r=-0.45$, $df=58$, $P<0.001$) had significant negative correlations with age at scanning in both the patient group and the comparison group. In the patient group, cortical volumes of the whole frontal lobe (left, $r=-0.43$, $df=57$, $P=0.001$; right, $r=-0.47$, $df=57$, $P<0.001$) and prefrontal region (left, $r=-0.45$, $df=57$, $P<0.001$; right, $r=-0.49$, $df=57$, $P<0.001$) also had significant negative correlations with duration of illness. However, they did not remain significant when partial correlation controlling for age was applied. No significant correlations were found between any volumetric measures and clinical characteristics (i.e., age at onset, duration of antipsychotic medication, or dose of drugs).

Significant or near significant (trends) correlations between regional cortex volumes and symptom severities included the following: right PCG and the total score on the SAPS ($r=-0.32$, $df=36$, $P=0.049$), left PCG and SAPS subscore of bizarre behavior ($r=-0.32$, $df=36$, $P=0.052$); left PCG ($r=-0.28$, $df=36$, $P=0.085$) as well as the right PoCiG ($r=-0.28$, $df=36$, $P=0.089$) and SANS subscore of apathy; left AnCiG ($r=-0.31$, $df=36$, $P=0.060$) and the subscore of verbal hallucinations (by adding SAPS items 2 and 3).

The white matter volume of the right AnCiG was found to be correlated with the SANS subscore of attention deficits ($r=-0.337$, $df=36$,

Table 3
White matter volumes of the frontal lobe regions

Region of interest	Schizophrenia patients		Normal control subjects	
	Male (n=31)	Female (n=28)	Male (n=30)	Female (n=28)
Whole frontal lobe*,**,***				
Left	71.86 ± 13.35	67.00 ± 8.59	74.79 ± 12.17	67.71 ± 9.79
Right	78.53 ± 15.40	70.25 ± 10.03	79.80 ± 13.77	70.53 ± 11.54
Precentral gyrus*,**,***				
Left	12.00 ± 2.55	11.63 ± 1.66	12.99 ± 2.03	11.64 ± 1.59
Right	13.94 ± 3.48	12.81 ± 1.91	14.59 ± 2.64	12.54 ± 2.17
Cingulate gyrus (CinG)#,*				
Left	2.96 ± 0.80	2.66 ± 0.61	3.19 ± 0.75	2.88 ± 0.56
Right	2.68 ± 0.90	2.40 ± 0.54	3.11 ± 0.72	2.67 ± 0.53
Anterior CinG**				
Left	1.03 ± 0.39	0.85 ± 0.33	1.02 ± 0.34	0.97 ± 0.35
Right	1.04 ± 0.54	0.90 ± 0.31	1.19 ± 0.48	1.03 ± 0.29
Posterior CinG#,*				
Left	1.93 ± 0.54	1.81 ± 0.40	2.18 ± 0.52	1.91 ± 0.35
Right	1.64 ± 0.47	1.50 ± 0.42	1.91 ± 0.39	1.64 ± 0.48
Prefrontal area*,**,***				
Left	56.90 ± 10.59	52.71 ± 6.88	58.60 ± 10.28	53.19 ± 8.24
Right	61.91 ± 11.80	55.04 ± 8.22	62.11 ± 11.24	55.31 ± 9.47

Values represent mean ± S.D. (cm^3); MANCOVA, multivariate analysis of covariance (see Section 2).

* MANCOVA revealed a significant main effect of hemisphere (F>13.08, df=1,113, P<0.001).

** MANCOVA revealed a significant main effect of gender (F>5.67, df=1,111, P<0.02).

*** MANCOVA revealed a significant gender-by-hemisphere interaction (F>7.32, df=1,113, P<0.01); post hoc Tukey's test showed significant difference between genders bilaterally (P<0.001).

\# MANCOVA revealed a significant main effect of diagnosis (F>5.77, df=1,111, P<0.02).

P=0.038). No other significant correlations were detected between regional white matter volumes and symptom severities. None of the correlations of symptom severity with ROI volume remained significant after Bonferroni correction for multiple comparisons.

4. Discussion

With high-resolution three-dimensional MR images, based on major gyri/sulci landmarks, we defined and measured the whole frontal lobe, prefrontal regions, PCG, and cingulate gyrus. Our study confirmed that patients with schizophrenia do have cortical volume reductions in the bilateral whole frontal lobes, prefrontal regions, and cingulate gyri (right AnCiG and bilateral PoCiG) compared with findings in normal controls. The most notable findings may be the significant volume reduction in the PCG cortex and its relationships with clinical manifestations of schizophrenia.

4.1. Gray and white matter of the whole (pre)frontal lobe

Consistent with our expectation, patients with schizophrenia in the present study showed significant cortical volume reductions in the whole frontal lobes as well as the prefrontal regions. The definitions for the ROIs were based on the main gyri/sulci landmarks; from this aspect, the results of the whole prefrontal region are comparable to two previous studies (Buchanan et al., 1998; Baaré et al., 1999), where patients had nonsignificant gray matter volume reductions in this region by 5–7%, similar to the present results. Use of small samples could be the main reason why similar magnitudes of volume reduction failed to reach statistical significance in both previous studies. Evidence from a study using first-episode schizophrenia patients also supports this finding (Hirayasu et al., 2001).

Although evidence from multiple lines has so far suggested white matter deficits in the frontal lobes of schizophrenia (reviewed by Davis et al., 2003), this

study did not detect any differences in the total frontal or prefrontal white matter volume. These results are consistent with a recently published study, which applied anatomical landmarks and a relatively large sample (Yamasue et al., 2004), as well as with several other important studies that applied carefully designed tracing methods (Baaré et al., 1999; Gur et al., 2000; Hirayasu et al., 2001). To our knowledge, among the few previous studies that have measured the frontal lobe fully based on anatomical landmarks, only one has reported volume reduction in the total prefrontal white matter of schizophrenia (Buchanan et al., 1998). Although the definition and delineation of total frontal white matter in the present study could be among the most comprehensive (Fig. 2), we would like to avoid a conclusion at present. For the next step of the series, we are separating the gyral white matter from the deeper white matter. The former could mainly represent the short association fibers and the latter the projections and long association fibers. Our previous voxel-based and volumetric MRI studies (Suzuki et al., 2002; Zhou et al., 2003) in the anterior internal capsule have provided strong evidence that schizophrenia patients have bilaterally reduced reciprocal corticothalamic connections, so we expect that such white matter deficits would be reflected in the prefrontal deeper white matter.

4.2. Anterior cingulate gyrus

Our group has been concentrating on the volume measurement of the AnCiG for years (Takahashi et al., 2002, 2003), while the present study is not a simple replica of our previous work and there are some improvements in methods, making it more complete. First, the ROI was extended to the whole AnCiG including the portion around the genu of the CC, which corresponded to a completed BA24. Second, instead of using relative values (to the whole cerebral volume) for MANCOVA with age as a covariate, the present study used absolute volumetric values with both age and ICV as covariates, thus avoiding the confounding of a coexisting smaller whole cerebrum. Third, the present study has a larger sample (patients: 59 vs. 40; controls: 58 vs. 40; 38 patients and 40 normal controls overlapped, respectively) and is thus more effective for examining group differences. However, the main results of these two studies are in congruence with each other: (1) the patient group had smaller gray matter volume (previous study

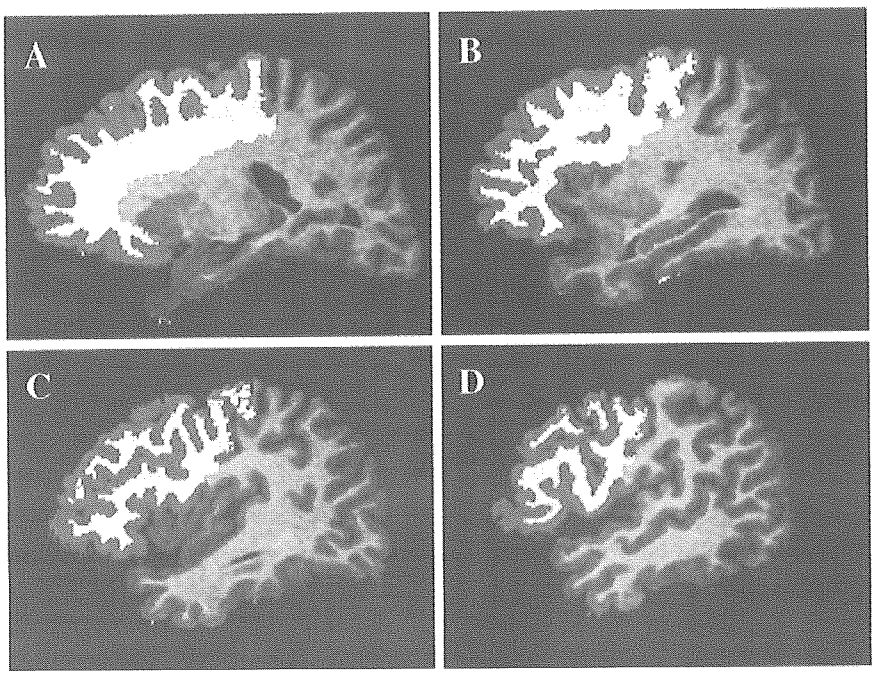

Fig. 2. Views of the frontal lobe tissues at different sagittal levels. (A–D). Views of the tissues (gray matter in blue and white matter in yellow) of the right frontal lobe at different sagittal levels. Sagittal views were automatically reconstructed synchronously when the delineation was performed on consecutive coronal slices. Distinct tissues were calculated automatically by applying the segmentation procedure described in Methods.

showed a trend, $P=0.061$); (2) significant gray matter reduction was detected only in the right AnCiG (which was limited to the female patients in the previous study); and (3) main effect of hemisphere in the whole sample expressed as right-larger-than-left (this asymmetry was observed to be diminished in female patients in the previous study).

4.3. Posterior cingulate gyrus

In contrast to the AnCiG, the PoCiG has not been extensively studied. The results of this study were consistent with the observation of reduced gray matter density in the PoCiG made by two voxel-based morphometric studies (Sowell et al., 2000; Hulshoff Pol et al., 2001), which was further demonstrated to predate the onset of frank schizophrenic symptoms and appear in association with their first expression (Pantelis et al., 2003). The present definition of the PoCiG within the frontal lobe corresponded largely to BA23 and BA31 (Talairach and Tournoux, 1988), which has diffusing reciprocal neural connections with multiple cortical and subcortical structures, including the AnCiG, prefrontal area, precuneus, superior temporal gyrus, parahippocampal cortex, and the anterior and lateral thalamic nuclei (reviewed by Maddock, 1999; Kobayashi, 2001). Such neural connections suggest that the PoCiG might subserve a variety of cognitive functions, especially those related to long-term memory as well as working memory (Andreasen et al., 1995). Observations from human lesion studies and PET studies support this concept (Maddock, 1999; Kobayashi, 2001). Patients with schizophrenia showed an increased resting perfusion or rate in the PoCiG compared with normal controls (Andreasen et al., 1997; Haznedar et al., 1997), and this was negatively correlated with Schneiderian first-rank symptoms (Franck et al., 2002); on the other hand, they also showed reduced activation in the same region during memory-related tasks (Kiehl and Liddle, 2001; Hofer et al., 2003). One possible explanation for this paradox is that overcompensation during the resting state resulted in a failure to respond to excessive demands. In other words, the functioning potential of the PoCiG in schizophrenia is diminished. The significant PoCiG tissue reduction in both gray matter and white matter, as demonstrated by this study, might be a substrate of such functional deficits.

More recently, Maddock (1999) and Maddock et al. (2003) proposed that the PoCiG's role in episodic memory functions may be specifically involved in the interactions between emotion and memory (i.e., in the modulation of memory by emotionally arousing stimuli). At present, there is a lack of direct evidence that deficits in the PoCiG are related to emotional abnormalities of schizophrenia; indirect evidence, however, shows that ketamine-induced emotional blunting in healthy men results in very different responses in the PoCiG (BA23), expressed as a success in activation to neutral stimuli but a failure in activation to fearful stimuli (Abel et al., 2003). Further understanding of the PoCiG in the pathophysiology of schizophrenia could be expected in the emotion–memory interface.

4.4. Precentral gyrus

The PCG cortex comprises the whole M1 (BA4) and a very small part of it is located by the most caudal edge of the premotor cortex (BA6) (Talairach and Tournoux, 1988), so it is rational to say that the PCG cortical volume reduction was mainly derived from M1. This finding is consistent with the observation of neuronal density reduction in M1 of postmortem schizophrenic brains (Benes et al., 1986). Reduced M1 volume could have partially resulted in impaired motor functioning as well as abnormal physiological and primitive reflexes in schizophrenia (Ismail et al., 1998); in fact, the presence of abnormal reflexes could have more directly suggested the existence of abnormalities in the upper motor neurons, which is quite in accord with the present finding. However, it would be difficult to fully understand the implications of the robust reduction of M1 volume observed in schizophrenia if M1 were merely an executive organ of voluntary movements. First, generally, patients with schizophrenia have grossly normal motor function; the soft signs of motor impairment are regarded as indicators of nonspecific brain damage (Andreasen et al., 1998). Second, no patient with overt movement disorders such as tardive dyskinesia was included in this study. Increased metabolic rate in M1 in patients with tardive dyskinesia has been reported and interpreted as the results of patients' maneuvers in trying to incorporate or suppress the involuntary movements,