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Bilateral volume reduction of the insular cortex in patients with schizophrenia: a volumetric MRI study

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Abstract

The morphologic changes of the insular cortex have been described in schizophrenia, but with inconsistencies between reports. We investigated the insular cortex volume by magnetic resonance imaging in 59 schizophrenia patients (31 males, 28 females) and 62 age- and gender-matched healthy controls (31 males, 31 females). The insular cortex volume was measured on consecutive coronal 1-mm slices. Volumes of the left and right insular cortex were significantly reduced in schizophrenia patients compared with control subjects. There were no effects of gender on the insular cortex volume in the patient group or control subjects. Bilateral insular cortex volumes were correlated negatively with illness duration in the patient group. The findings of this study suggest that there is a possible progressive loss of the gray matter volume of the bilateral insular cortices subsequent to the onset of schizophrenia.

Keywords: Magnetic resonance imaging; Insula; Illness duration; Progressive changes; Gender differences

1. Introduction

The insular cortex is a component of the "limbic integration cortex" and is engaged in emotional and various cognitive functions (Augustine, 1996; Türe et al., 1999). In post-mortem studies, cytoarchitectonic abnormalities have been described in the dorsal insular cortex in schizophrenic brains (Jakob and Beckmann, 1986, 1989). Several functional neuroimaging studies have also suggested insular cortex abnormalities to be involved in the pathophysiology of schizophrenia (Curtis et al., 1998; Shergill et al., 2000; Crespo-Facorro et al., 2001a,b; Desco et al., 2003).

With regard to morphologic studies of the insular cortex in schizophrenia, a volumetric magnetic resonance imaging (MRI) study has reported the left insular cortex volume, but not the right, to be significantly reduced in patients with schizophrenia

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compared with control subjects (Crespo-Facorro et al., 2000). Several voxel-based analyses of MRI have also revealed a gray matter reduction of the insular cortex in patients with schizophrenia (Wright et al., 1999; Hulshoff Pol et al., 2001; Paillère-Martinot et al., 2001; Kubicki et al., 2002; Shapleske et al., 2002), although yielding partly inconsistent results. For example, some studies revealed bilateral reductions in the insular cortex (Wright et al., 1999; Hulshoff Pol et al., 2001; Kubicki et al., 2002; Shapleske et al., 2002) but only left-sided reduction was also reported (Paillère-Martinot et al., 2001). The differences in sample characteristics among reports may be important considerations in interpreting the inconsistencies. Crespo-Facorro et al. (2000) investigated first-episode drug-naïve patients with schizophrenia; by contrast, a majority of the voxel-based analyses that reported bilateral changes of the insular cortex investigated chronically medicated patients (Wright et al., 1999; Hulshoff Pol et al., 2001; Shapleske et al., 2002). Thus, the inconsistencies could be explained by progressive volume loss in the right insular cortex after the onset of illness. Indeed, several brain morphologic studies in schizophrenia have reported progressive volume changes in some brain regions throughout the disease process (DeLisi et al., 1997; Gur et al., 1998; Mathalon et al., 2001; Pantelis et al., 2003). However, it is not clear whether the insular cortex volume reduction also progresses over time in schizophrenic brains.

In schizophrenia, there seem to be gender differences in the degree or patterns of brain morphologic abnormalities (Nopoulos et al., 1997; Lawrie and Abukmeil, 1998; Pearlson and Marsh, 1999; Suzuki et al., 2002). However, most previous MRI studies that reported insular cortex abnormalities in schizophrenia have included only male (Wright et al., 1999; Crespo-Facorro et al., 2000; Paillère-Martinot et al., 2001; Shapleske et al., 2002) or many more male than female (Hulshoff Pol et al., 2001; Kubicki et al., 2002) subjects. Goldstein et al. (2002) evaluated gender-specific effects on brain abnormalities in schizophrenia using MRI; they reported the insular cortex volume to be reduced only in male schizophrenia patients. However, that study might also be limited in part by relatively a smaller number of female patients (27 males and 13 females). Thus, gender effects on the morphology of the insular cortex in schizophrenia have not been clearly established.

In the present study, we used three-dimensional MRI to investigate the volume of the insular cortex in both male and female schizophrenia patients with illness duration up to 15 years and age- and gender-matched healthy control subjects who were balanced by gender. The results of these insular cortex volumes were analyzed for the effects of diagnosis, gender differences, and laterality. From the previous findings, we predicted (1) that insular cortex volume would be reduced bilaterally in chronic schizophrenia patients compared with normal controls and (2) that the insular cortex abnormalities in schizophrenia would possibly be related to illness duration. We also examined whether these volumetric measurements were related to clinical symptoms of schizophrenia.

2. Methods

2.1. Subjects

Fifty-nine right-handed patients with schizophrenia [31 males and 28 females, mean age=25.6±5.0 (S.D.) years (range, 15–36), mean illness duration=3.8±4.1 (S.D.) years (range, 0–15)] were recruited from the inpatient and outpatient clinics of the Department of Neuropsychiatry, Toyama Medical and Pharmaceutical University Hospital. The patient group participating in this study included 40 schizophrenia patients (20 males, 20 females) from our previous studies (Takahashi et al., 2002, 2003) and an additional 19 patients (11 males, 8 females). All patients fulfilled ICD-10 diagnostic criteria for research on schizophrenia (World Health Organization, 1993). All but two of the patients were on neuroleptic medication [mean haloperidol equivalent dose=11.2±9.6 (S.D.) mg/day (range, 0–39.0)], with a mean duration of medication of 2.7±3.3 (S.D.) years (range, 0–13.5). Thirty patients were treated with typical neuroleptics and 27 patients with atypical neuroleptics. All patients were physically healthy at the time of the study, and none had a history of serious head trauma, neurological illness, serious medical or surgical illness, or substance abuse disorder. At the time of MRI study, their mean scores on the Scales for the Assessment of Negative Symptoms (SANS; Andreasen, 1984a) and

the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984b) were 47.2 (S.D.=23.4) and 23.8 (S.D.=20.0), respectively.

The control subjects consisted of 62 right-handed healthy volunteers (31 males and 31 females) recruited from among the hospital staff, medical students and pharmaceutical students. Their mean age was 24.4±5.6 (S.D.) years (range, 14–38). They were given a questionnaire consisting of 15 items concerning their family and past histories, and present illness. They did not have any personal or family history of psychiatric illness in their first-degree relatives, or history of serious head trauma, neurological illness, serious medical or surgical illness, or substance abuse disorder. The Minnesota Multiphasic Personality Inventory (MMPI) was administered to all the control candidates, and they were excluded if any T-score for the validity scales or the clinical scales exceeded 70.

Demographic and clinical characteristics of the patients with schizophrenia and control subjects are shown in Table 1. There were no significant differences between the two groups in age, height, or parental education. However, the control subjects had attained a higher mean level of education than the patients (control subjects, 15.8±2.7 years; patients, 13.4±1.9 years; ANOVA, F=30.94, df=1,119, P<0.001). There were no significant differences between male and female patients in age at onset, duration of illness, dosage or duration of neuroleptic medication, or the total or a subscale scores for the SAPS and SANS.

All subjects participated in the study after providing written informed consent. This study was approved by the Committee on Medical Ethics of Toyama Medical and Pharmaceutical University. When subjects were less than 18 years old, informed consent was also obtained from their parents.

2.2. Magnetic resonance imaging procedures

Magnetic resonance images were obtained utilizing a 1.5-T Magnetom Vision (Siemens Medical System, 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 1.0×1.0×1.0 mm^3.

The images were transferred to a Unix workstation (Silicon Graphics, Mountain View, CA, USA). The data were coded randomly and analyzed with the

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

Variable	Control subjects		Schizophrenia Patients	
	Male (n=31)	Female (n=31)	Male (n=31)	Female (n=28)
Age (years)	24.5±5.4	24.2±5.9	25.5±4.9	25.8±5.1
Height (cm)[a]	172.5±4.1	159.6±4.3	170.5±5.0	158.1±4.0
Education (years)[b]	16.8±3.1	14.8±1.7	13.5±1.9	13.3±2.0
Parental education (years)	13.0±2.5	12.5±2.4	12.2±1.9	12.0±2.4
Age at onset (years)	–	–	22.0±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
Drug (mg/day, haloperidol equivalent)	–	–	11.9±8.6	10.5±10.7
Total SAPS score	–	–	20.6±19.4 (n=29)	27.1±20.5
Total SANS score	–	–	48.6±22.4 (n=29)	44.2±24.1

Values represent means±S.D.s. SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms.

[a] There were significant differences in height across the four groups (ANOVA, F=85.0, df=3, 117, P<0.001). Post hoc Scheffé's test showed that the male patients and the male controls were taller than the female patients (P<0.001) and the female controls (P<0.001), respectively.

[b] There were significant differences in education across the four groups (ANOVA, F=15.1, df=3, 117, P<0.001). Post hoc Scheffé's test showed the male controls to have a higher level of education than the female controls (P=0.011), the male patients (P<0.001), and the female patients (P<0.001).

software package Dr View 5.2 (Asahi Kasei Joho System, Tokyo, Japan) blind to subjects' gender and diagnosis. Details of the data analyses have been described previously (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 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 magnetic field inhomogeneities, no visible effect on quality of segmentation was detected in any of the cases. Prior to 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 tissue removed. Minimal manual editing of the masks was required.

2.3. Intracranial volume (ICV) measurements

Before creating 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 $1\times1\times5$ mm^3. The intracranial cavity was manually traced in each slice, using the anatomical landmarks according to a study by Eritaia et al. (2000). ICV was calculated by summing the measured volumes of all slices.

2.4. Insular cortex measurements

The left and right insular cortices were separately traced on consecutive coronal 1-mm slices. 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 following the procedure used by Crespo-Facorro et al. (2000). As demonstrated in Figs. 1 and 2, the voxels for the gray matter compartment in the manually delineated area were regarded as the insular cortex.

All measurements were carried out by one rater (TT) without knowledge of subjects' identity, gender, and diagnosis. The ICCs for insular cortex measurements in a subset of five randomly selected subjects were 0.98 for intrarater variability and 0.95 for interrater variability (TT and HH).

2.5. Statistical analysis

Statistical analysis was carried out using the software package SPSS 12.0J (SPSS, Chicago, IL, USA). The absolute intracranial volume (ICV) was analyzed using analysis of variance with height and age as covariates (ANCOVA), and group (patients, control subjects) and gender (male, female) as between-subject factors. 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. The relative volume of the insular cortex was analyzed by repeated measures multivariate analysis of variance (MANCOVA) with age as a covariate, group and gender as between-subject factors, and hemisphere (left, right) as a within-subject variable. Post hoc Scheffé's tests were conducted to follow up the significant main effects or interactions yielded by these analyses.

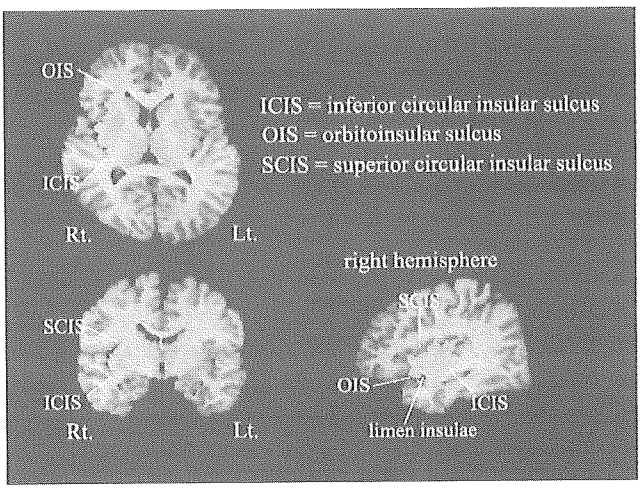

Fig. 1. Regions colored in red indicate the bitmap images of the insular cortex manually traced in this study.

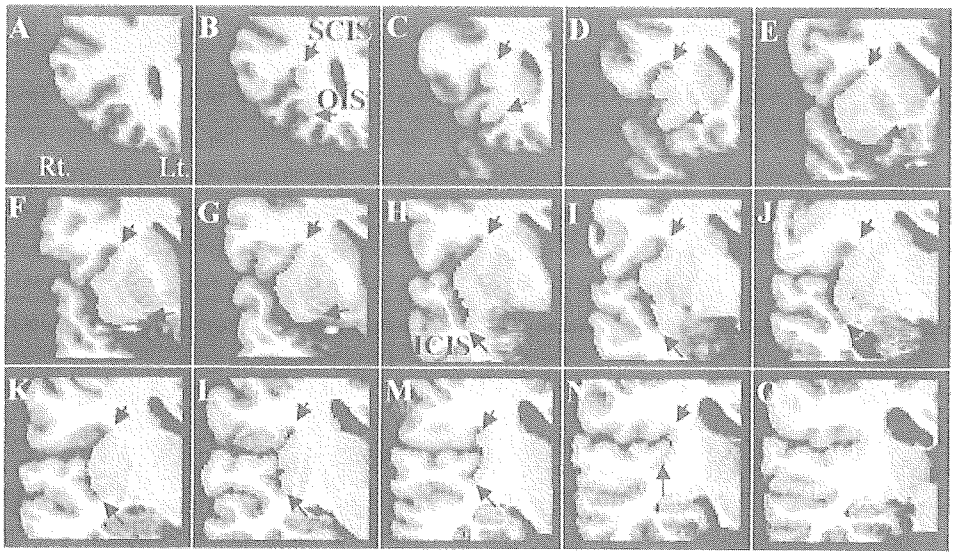

Fig. 2. Delineation of the insular cortex on every two to four coronal slices in a representative subject. Images A through O move progressively in a rostral to caudal direction. The insular cortex was traced from rostral to caudal, beginning with the plane showing the appearance of the cortex (Image A) and ending caudally with that showing the fusion of the superior (SCIS) and inferior circular insular sulci (ICIS) (Image O), following the methods of Crespo-Facorro et al. (2000). On each coronal slice, the insular cortex was bounded superiorly by the SCIS, and inferiorly by the orbitoinsular sulcus (OIS) (Images A–G, rostral to the limen insulae) or the ICIS (Images H–O).

In order to analyze the volume changes in relation to the clinical symptoms, Spearman's rank correlation was calculated between the relative insular cortex volume and scores for subscales of the SAPS and SANS. Correlation between the relative insular cortex volume and age at onset, duration of illness, medication dosage and duration of neuroleptic medication were also analyzed by using Spearman's rank correlation coefficients. Pearson's correlation, adjusted to age using partial correlation, was also calculated to confirm the association between the relative insular cortex volume and illness duration. Statistical significance was defined as $P<0.05$ by a two-tailed test.

Table 2
Intracranial volume (ICV) and absolute and relative volumes of insular cortex in control subjects and patients with schizophrenia

Brain region	Control Subjects				Schizophrenia Patients			
	Male (N=31)		Female (N=31)		Male (N=31)		Female (N=28)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
ICV (cm^3)[a]	1590[b]	94	1400	94	1568[b]	138	1385	104
Insular Cortex Volume[c]								
Left								
Absolute (mm^3)	8329	705	7421	826	7844	1015	6955	981
Relative	0.525[d,e]	0.404	0.531[d,e]	0.057	0.501[d]	0.058	0.501[d]	0.051
Right								
Absolute (mm^3)	7976	763	7304	817	7531	823	6766	903
Relative	0.503[e]	0.052	0.523[e]	0.059	0.482	0.052	0.488	0.051

Relative insular cortex volume was calculated using the formula: (absolute insular cortex volume/ICV) ×100.
The results of statistical analyses reported here are based on relative insular cortex volumes. The statistical conclusions did not change when we analyzed data using absolute insular cortex volume with age and ICV as covariates.

[a] Significant main effect for gender (F=5.89; df=1,115; P=0.016).
[b] Significantly larger than in females ($P<0.001$).
[c] Significant main effects for group (F=7.12; df=1,116; P=0.009) and hemisphere (F=26.68; df=1,117; $P<0.001$).
[d] Significantly larger than right insular cortex (post hoc test, $P<0.001$).
[e] Significantly larger than in schizophrenia patients (post hoc test, P=0.003).

3. Results

3.1. Intracranial volume (ICV) measurements

The ICV in patients with schizophrenia and control subjects is shown in Table 2. ANCOVA revealed gender to have a significant main effect (F=5.89; df=1,115; P=0.017), although there was no significant main effect for group (F=0.07; df=1,115; P=0.793) or group×gender interaction (F=0.01; df=1,115; P=0.931). Post hoc analysis revealed the ICV to be significantly larger in males than in females (P<0.001).

3.2. Insular cortex measurements

Table 2 summarizes the insular cortex measurements in patients with schizophrenia and control subjects. Repeated measures MANCOVA revealed significant main effects for group (F=7.12; df=1,116; P=0.009) and hemisphere (F=26.68; df=1,117; P<0.001); the patients with schizophrenia had significantly smaller insular cortices than the control subjects bilaterally (post hoc Scheffé's test, P=0.003), and the insular cortex volume was larger on the left than on the right hemisphere in both diagnostic groups (post hoc Scheffé's test, P<0.001). There was no main effect for gender (F=0.84; df=1,116; P=0.362) or interaction among the factors.

3.3. Clinical correlations

The bilateral relative insular cortex volume was correlated negatively with illness duration (left, Spearman's rho=−0.52, P<0.001; right, Spearman's rho=−0.44, P<0.001) (Fig. 3) and duration of neuroleptic medication (left, Spearman's rho=−0.52, P<0.001; right, Spearman's rho=−0.46, P<0.001); however, the insular cortex volume was not correlated with age at the onset or dosage of neuroleptic medication. Pearson correlation analysis controlling for age also revealed a negative correlation between the bilateral relative insular cortex volume and illness duration (left, r=−0.35, P=0.008; right, r=−0.27, P=0.044). If no adjustment was applied, the correlation between the relative insular cortex volume and illness duration was r=0.49 (P<0.001) in the left hemisphere and r=−0.38 (P=0.004) in the right hemisphere.

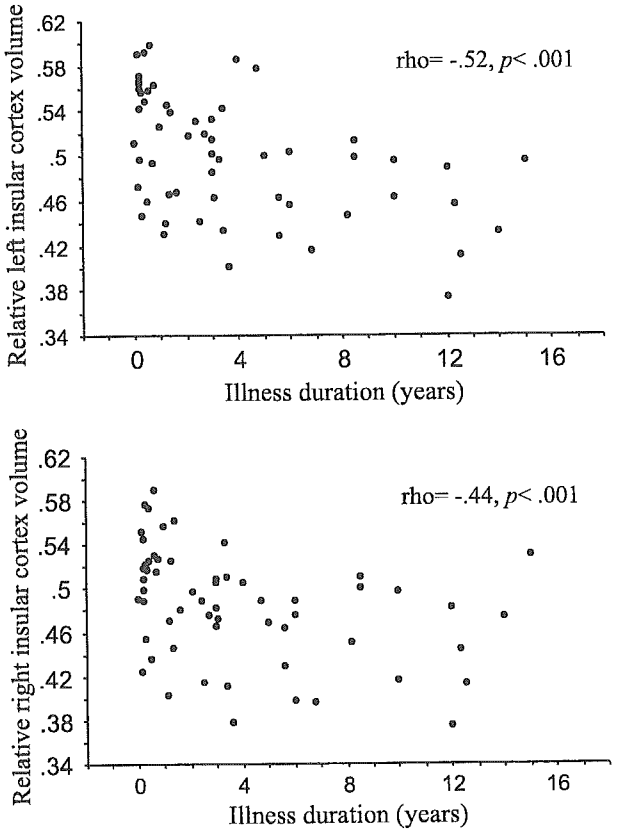

Fig. 3. Correlations between illness duration and relative volumes of the left and right insular cortex. In patients with schizophrenia, there were significant negative correlations between illness duration and relative insular cortex volumes (left, Spearman's rho=−0.52, P<0.001; right, Spearman's rho=−0.44, P<0.001).

There was a negative correlation between the right insular cortex volume and the score for avolition-apathy of the SANS (Spearman's rho=−0.27, P=0.039), but the correlation was not significant after Bonferroni correction for multiple comparisons. There were no significant correlations between the insular cortex volume and the scores for subscales of the SAPS.

4. Discussion

Consistent with some previous voxel-based analyses of MRI (Wright et al., 1999; Hulshoff Pol et al., 2001; Kubicki et al., 2002; Shapleske et al., 2002), we found in a volumetric MRI study that insular cortex volume was significantly reduced bilaterally in patients with schizophrenia. However, our results did not accord with previous volumetric MRI studies that reported left-sided volume reduction of the insular

cortex in first-episode schizophrenia patients (Crespo-Facorro et al., 2000) or in patients with relatively recent illness onset (Kim et al., 2003). These studies support the notion of a predominantly left-sided pathology of schizophrenia (Flaum et al., 1995; Petty, 1999; Narr et al., 2001) and suggest that left insular cortex abnormalities are present at the early stages of the illness. In these studies, however, right insular cortex volume was non-significantly reduced by approximately 4–5% in the patients as compared with findings in the control subjects. As hypothesized, we found negative correlations between the volumes of left and right insular cortex and illness duration in the patient group, supporting the notion of progressive brain structural changes subsequent to the onset of schizophrenia (DeLisi et al., 1997; Gur et al., 1998; Mathalon et al., 2001; Pantelis et al., 2003). From the findings of the present and these previous studies, it may be assumed that there is a progressive loss of gray matter volume of the left and right insular cortices in schizophrenia and that the volume reduction of the right insular cortex becomes evident later than that of the left in the course of the illness.

We did not find any effects of gender on insular cortex volume in a group of patients with schizophrenia and control subjects, although we had relatively larger sample sizes of both genders and matched the gender ratios between two groups in order to examine the potential influence of gender on the morphology of insular cortex. In schizophrenia, structural brain abnormalities such as ventricular enlargement or volume reductions of temporal lobe structures have been suggested to be greater in male patients than in female patients (as reviewed by Lawrie and Abukmeil, 1998; Pearlson and Marsh, 1999). In contrast, gray matter reductions in the frontal areas (Nasrallah et al., 1990; Suzuki et al., 2002) have been observed predominantly in female patients. It thus may be assumed that male and female patients with schizophrenia have partially different patterns of structural brain abnormalities. From the results of the present study, gray matter reduction in the insular cortex was common to both genders. In contrast, we have previously examined the volume of the anterior cingulate gyrus using MRI in the partly overlapping subjects as reported here and found the gray matter volume to be significantly reduced only in female patients (Takahashi et al., 2002, 2003). These findings suggest that the gender effects on brain morphology in schizophrenia may vary even among the limbic/paralimbic structures that have a strong interconnection with each other.

In the present study, the right insular cortex volume showed a weak negative correlation with the score for avolition-apathy of the SANS (Spearman's rho=−0.27, P=0.039). This result may be consistent with the observations by McCarley et al. (1989), who found in a computed tomography (CT) study that right sylvian fissure enlargement was correlated with the negative symptoms subscales of the SANS in patients with schizophrenia, since the dilatation of the sylvian fissure suggests a reduction in the volume of the surrounding brain tissues such as the insular cortex. It is known that brain functions such as drive and affect are mediated in part by the insular cortex (Augustine, 1996; Türe et al., 1999). Interestingly, Manes et al. (1999a) found that patients with localized right insular infarction had a significantly higher frequency of subjective anergia, underactivity and tiredness than patients with non-insular lesions or left insular lesions. On the other hand, in previous MRI studies, Crespo-Facorro et al. (2000) reported a negative correlation between bilateral insular cortex volume and psychotic symptom dimensions (delusions and hallucinations) and Shapleske et al. (2002) reported the left insular cortex abnormalities to be related to hallucinations in schizophrenia patients. Kim et al. (2003) also investigated the correlation between insular cortex volume and clinical symptoms of schizophrenia by MRI but did not find any significant results. Many clinical and experimental studies have shown that the insular cortex is part of the multifaceted sensory, motor, vestibular, and language areas (reviewed by Augustine, 1996). In addition, a positron emission tomography (PET) study in normal individuals (Grasby et al., 1994) and a study of patients with left insular cortex infarction (Manes et al., 1999b) suggested the insular cortex to be part of a functional network that mediates verbal memory. Based on prior case reports in patients with strokes and neuroimaging studies, Bamiou et al. (2003) emphasized that the insular cortex is particularly related to auditory processing. As discussed by Crespo-Facorro et al. (2000), abnormalities in sensory and memory functions of the insular cortex may lead to perceptual disturbances that can account for psychotic symptoms in schizo-

phrenia. Therefore, it seems plausible that the insular cortex abnormalities are relevant to both positive and negative symptoms of schizophrenia. The discrepancies among the reports concerning the relationship between insular cortex volume and clinical symptoms in schizophrenia may be caused by different sample characteristics. For example, Crespo-Facorro et al. (2000) recruited drug-naïve first-episode patients whereas we primarily investigated medicated patients in stable clinical condition, who had predominantly negative symptoms. Clinical symptoms of schizophrenia can be reversibly altered with neuroleptic medication, while brain morphologic changes in these patients are considered to be more static. Hence, associations of MRI abnormalities with clinical symptoms should be interpreted with caution, especially in chronically medicated patients. However, our results may be in accordance with the assumption that tissue loss of the right insular cortex becomes evident in later stages of the disease, since older schizophrenia patients have generally more severe negative symptoms than younger patients (Davidson et al., 1995).

A few caveats on the limitations of this study must be considered before any conclusion can be drawn. First, the study design was not longitudinal. Although we suggested a possible progressive loss of gray matter volume of the insular cortex subsequent to the onset of schizophrenia by cross-sectional observation, our hypothesis might not accord with a recent MRI study by Kasai et al. (2003), who reported a bilateral insular volume reduction in first-episode schizophrenia patients. Further studies with a prospective longitudinal design should be performed to clarify the timing and course of the morphologic changes of the insular cortex observed in schizophrenia. A second limitation is that most patients with schizophrenia in the present study were on 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 the bilateral insular cortex volume was correlated negatively with duration of neuroleptic medication in the present study. Although the dosage of neuroleptic medication taken at the time of the scan was not related to insular cortex volume, the effects of cumulative years of medication treatment cannot be ruled out. A third limitation of the present study is that the control subjects were not selected to be educationally equivalent to the patients with schizophrenia. However, we optimally matched the parental levels of education between the patients and control subjects in this study according to the notion that matching on the basis of educational level of parents may reduce confounding factors in the selection of control groups when brain measures are studied (Andreasen et al., 1990). In addition to these limitations, we examined only a single brain structure, i.e. the insular cortex, in the present study. Additional comprehensive assessment of multiple brain regions in the same group of subjects would be essential for the understanding of the brain morphologic characteristics underlying schizophrenia.

In conclusion, we found a bilateral volume reduction of the insular cortex in both male and female patients with schizophrenia. The findings of the present study also suggest that there is a degenerative process concerning the insular cortex morphology in schizophrenic brains.

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ORIGINAL PAPER

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Structural brain differences in patients with schizophrenia and schizotypal disorder demonstrated by voxel-based morphometry

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Abstract Brain abnormalities of schizophrenia probably consist of deviation related to the vulnerability and pathological changes in association with overt psychosis. We conducted a cross-sectional comparison in brain morphology between patients with overt schizophrenia and schizotypal disorder, a schizophrenia-spectrum disorder without florid psychotic episode. Voxel-based morphometry was applied to assess gray matter volume in 25 patients with schizophrenia, 25 patients with schizotypal disorder, and 50 healthy control subjects. In comparison with controls, schizophrenia patients showed gray matter reductions in the bilateral medial frontal, inferior frontal, medial temporal, and septal regions, and the left middle frontal, orbitofrontal, insula, and superior temporal regions, and an increased gray matter in the left basal ganglia. Schizotypal disorder patients showed reductions in the left inferior frontal, insula, superior temporal, and medial temporal regions. There was a significant reduction in the left orbitofrontal region of schizophrenia compared with schizotypal disorder. Gray matter reductions that are common to both patient groups such as those in the left medial temporal and inferior frontal regions may represent vulnerability to schizophrenia, and additional involvement of several frontal regions may be crucial to florid psychosis.

Key words schizophrenia · schizotypal disorder · magnetic resonance imaging · voxel-based morphometry · medial temporal region · medial frontal region

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Introduction

Brain morphometry based on the quantitative volumetric region of interest approach has provided substantial evidence that schizophrenia is associated with abnormalities in the brain structure, and have brought about significant breakthroughs in our understanding of the neurobiology of schizophrenia (see reviews, Lawrie and Abukmeil 1998; Wright et al. 2000; Shenton et al. 2001). The recently developed, voxel-based morphometry (VBM), which allows voxel-wise comparison of the brain structure (Ashburner and Friston 2000), has provided largely consistent results with previous volumetric studies in that the fronto-temporo-limbic regions are principally affected in schizophrenia (Wright et al. 1995; Gaser et al. 1999; Wright et al. 1999; Volz et al. 2000; Paillère-Martinot et al. 2001; Sigmundsson et al. 2001; Wilke et al. 2001; Ananth et al. 2002; Job et al. 2002; Kubicki et al. 2002; Suzuki et al. 2002). The exact meaning of these findings, however, remains uncertain for etiologic origins, pathophysiological mechanisms, and clinicopathological correlations.

Subjects with schizotypal features share a broad range of similarities with patients with schizophrenia in terms of genetics as well as of neurobiology (Siever et al. 2002), which possibly constitute a common basis for the schizophrenia spectrum. Such commonalities may be essential for the pathogenesis of schizophrenia and re-

lated to the predisposing factor or vulnerability to schizophrenia. However additional pathological changes may be required for the development of overt and sustained psychosis. Thus, clarifying the similarities and differences in the neurobiology between schizophrenia patients and schizotypal subjects has significant implications for better understanding of the pathogenesis of schizophrenia.

There is a growing body of literature which examined brain morphology in patients with schizotypal personality disorder (see review, Dickey et al. 2002; Siever et al. 2002) and schizotypal disorder (Takahashi et al. 2002, 2004; Yoneyama et al. 2003). Schizotypal subjects have been reported to show brain structural abnormalities similar to those seen in schizophrenia, although generally to a lesser degree and sparing some brain regions. However the full spatial extent and magnitude of structural changes in schizotypal subjects are not yet established.

In this study, to differentially elucidate the morphological characteristics underlying the vulnerability and pathology of schizophrenia, we conducted a cross-sectional VBM analysis to detect structural differences between established schizophrenia and schizotypal disorder. The criteria for schizotypal disorder of ICD-10 (World Health Organization 1993) are almost identical to those for schizotypal personality disorder of DSM-IV (American Psychiatric Association 1994), but, in addition, include occasional transient quasi-psychotic episode usually occurring without external provocation. A major phenomenological difference between schizophrenia and schizotypal disorder is the presence or absence of overt and sustained psychotic symptoms. Our subjects with schizotypal disorder were recruited from clinical populations and stable to show typical features without developing overt schizophrenia during more than two years clinical follow-up. To constitute a comparable subject group of schizophrenia, early phase schizophrenia patients were recruited. We hypothesized that schizophrenia and schizotypal disorder would share common features in brain morphology as the vulnerability factors and, in contrast, morphological differences between them would be relevant to the mechanism of the development of prominent psychosis.

Subjects and methods

Subjects

As shown in Table 1, two groups of 25 patients (14 males and 11 females), each fulfilling ICD-10 diagnostic criteria for schizophrenia or schizotypal disorder, were recruited from the in-patient and out-patient clinics of the Department of Neuropsychiatry, Toyama Medical and Pharmaceutical University Hospital. All available clinical information and data were obtained from a structured clinical interview using the Comprehensive Assessment of Symptoms and History including the chapter of premorbid or intermorbid personality (CASH, Andreasen et al. 1992). When the DSM-IV criteria were adopted, all of the schizotypal subjects also fulfilled the criteria of the schizotypal personality disorder on Axis II. An additional diagnosis of the brief psychotic disorder was considered in 6 subjects who experienced occasional transient quasi-psychotic episodes. None of the 25 patients with schizotypal disorder has developed overt schizophrenia during more than two years clinical follow-up period after MRI scanning.

Schizophrenia patients recruited for this study were in a relatively early stage of their illness. Their mean age at the onset of the first psychotic episode was 22.4 ± 4.4 (S. D.) years (range 16–30), and the mean duration of illness was 3.1 ± 3.1 years (range 0.3–8.5). All patients were physically healthy at the time of the study, and none had a history of head trauma, serious medical or surgical illness, or substance abuse. All patients except 2 drug naïve subjects with schizotypal disorder were receiving neuroleptic medication. Their mean duration of medication was 1.5 ± 2.1 years (range 0.04–6.0). Of the 23 patients with schizotypal disorder, 9 were being treated with relatively low-dose typical antipsychotics and 14 with atypical antipsychotics. Twenty-two patients with schizophrenia were receiving typical antipsychotic medication, and the other 3 were being treated with atypical antipsychotics. Neuroleptic dosages were converted into haloperidol-equivalents according to the guideline by Toru (2001). There was a significant difference in haloperidol-equivalent dose between the two patient groups.

Symptoms were rated within the one-month of scanning using the Scale for the Assessment of Positive Symptoms (SAPS, Andreasen 1984), Scale for the Assessment of Negative Symptoms (SANS, Andreasen 1983), and the Brief Psychiatric Rating Scale (BPRS, Overall and Gorham 1962). With regard to the negative, positive, and overall symptoms the profiles of their symptom scores indicated that all patients ranged between mildly and moderately ill and relatively predominated to the negative symptoms. Most of the schizophrenia patients were partially remitted as shown in SAPS scores (Table 1). There were no significant differences in the total scores of the SAPS,

Table 1 Demographic and clinical characteristics of subjects

	Schizophrenia		Schizotypal disorder		Control	
Variable	mean (S.D.)	range	mean (S.D.)	range	mean (S.D.)	range
Age (years)	25.8 (4.5)	18–36	25.0 (5.3)	18–37	24.0 (5.7)	18–38
Education (years)	13.8 (2.3)*	12–18	13.1 (1.9)*	9–17	15.2 (2.2)	12–18
Parental education (years)	12.6 (2.5)	9–18	12.5 (2.2)	9–17	12.4 (1.8)	9–16
Medication (mg/day)[a]	8.1 (8.0)	1–20	3.4 (2.3)#	0–8		
SANS summary score (0–25)	10.3 (5.0)	5–17	11.1 (4.8)	0–20		
SAPS summary score (0–20)	5.6 (4.6)	0–14	4.5 (2.6)	0–9		
BPRS total score (18–126)	39.5 (8.4)	24–53	38.8 (10.3)	20–50		

SANS Scale for the Assessment of Negative Symptoms; *SAPS* Scale for the Assessment of Positive Symptoms; *BPRS* Brief Psychiatric Rating Scale

* $p < 0.05$ compared with control (two-tailed t test)

# $p < 0.05$ compared with schizophrenia (two-tailed t test)

[a] haloperidol equivalent dose

SANS, and BPRS between the patients with schizophrenia and schizotypal disorder.

The age and gender-matched control subjects consisted of 50 healthy volunteers (28 males and 22 females) recruited from the hospital staff, medical or pharmaceutical students, and volunteers from the community. Subjects were excluded if they had a history of psychiatric illness, head trauma, neurological illness, serious medical or surgical illness, or substance abuse. The healthy control group was also screened for history of psychiatric disorders in their first-degee relatives. All control subjects were given the Minnesota Multiphasic Personality Inventory, and subjects were excluded if they showed deviated personality profiles, i. e., clinical scale elevated to a T-score of 70 or higher. All patients and the control subjects were right-handed and more than 18 years old. Although the control group had significantly higher educational achievement than the groups of schizophrenia and schizotypal disorder, there was no significant difference in the educational levels of their parents. There was no between-group difference in height or weight.

After the purpose and procedures of the present study were fully explained, written informed consent was obtained individually from each of the subjects. This study was approved by the Committee on Medical Ethics of Toyama Medical and Pharmaceutical University.

MRI data acquisition and image analysis

The subjects underwent brain MRI scans with a Siemens 1.5 T Magnetom Vision system (Siemens Inc, Erlangen, Germany). A three-dimensional gradient-echo sequence (fast low-angle shot, FLASH) yielding 160–180 contiguous slices of 1.0-mm thickness in the sagittal plane was used for volume analysis. This sequence provided high-resolution T1-weighted images with good contrast between gray and white matter. Imaging parameters were: TE = 5 ms; TR = 24 ms; flip angle = 40°; field of view = 256 mm; matrix size = 256 x 192; voxel size = 1.0 x 1.0 x 1.0 mm.

Image analysis was performed on a Sun SPARC 20 workstation (Sun Microsystems Inc, Palo Alto, CA, USA) using ANALYZE version 7.5.5 (BRU, Mayo Foundation, Rochester, MN, USA) and on a personal computer with Windows 98 (Microsoft Corporation, USA) using statistical parametric mapping (SPM) 99 software (Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK) running under MATLAB 5.3 (Mathworks Inc., Sherborn, MA, USA). Images were first re-sliced in the axial plane with ANALYZE. Image process and analysis by SPM99 were performed according to the methodological description of Ashburner and Friston (2000). The first step was spatial normalization (Ashburner et al. 1997; Ashburner and Friston 1999) which involves transforming all the subjects' MRI images to the same stereotactic space of Talairach and Tournoux (1988). The spatially normalized images were written out with 1.0 x 1.0 x 1.0 mm voxels. Next, the normalized images were partitioned into gray matter, white matter, cerebrospinal fluid, and other compartments by a modified mixture model cluster analysis technique (Ashburner and Friston 1997) with a correction for image intensity non-uniformity. The segmented images were then automatically processed to remove any remaining nonbrain matter. The spatially normalized segments of gray matter were smoothed with a 12-mm full-width at half maximum (FWHM) isotropic Gaussian kernel. Each voxel in the smoothed image contained the average concentration of gray matter from the surrounding voxels (i. e., gray matter concentration). The smoothing procedure has the advantage of rendering the data more normally distributed and of increasing the validity of parametric voxel-by-voxel statistical analysis.

Statistical analysis

Statistical evaluation comparing three diagnostic groups was performed by an analysis of covariance (AnCova) model for global normalization with overall grand mean scaling (Friston et al. 1990). This statistical option normalizes the segmented brain images to the same total amount of gray matter, while preserving regional differences in gray matter concentration. Gender and age were also treated as nuisance covariates.

Since statistics based on cluster spatial extent are not valid for VBM (Ashburner and Friston 2000), voxel-wise parametric statistical tests were performed using the general linear model (Friston et al. 1995), and the significance of differences ascertained using the theory of Gaussian random fields (Worsley et al. 1996). Three pair-wise SPM {T} analyses were performed comparing each of the patient groups to controls, and to each other, testing for regions of more or less gray matter between two diagnostic groups. Considering the exploratory nature of the present study, we defined statistical significance at $p < 0.05$ corrected for the entire volume.

Results

The results of SPM analysis are displayed in three orthogonal planes using a "glass brain" allowing a visual comparison of the regional distribution of statistical findings. Pair-wise SPM {T} statistics for more or less gray matter concentrations among three groups are shown in Fig. 1. Voxel-wise coordinates of significant regions and their corrected p-values are shown in Table 2.

The results demonstrated that compared to controls schizophrenia patients had a significantly reduced gray matter concentration in the bilateral medial frontal cortex including the anterior cingulate cortex, inferior frontal gyrus, and medial temporal region as well as the septal region. The gray matter in the left middle frontal gyrus, orbitofrontal cortex, insula, and superior temporal gyrus including the planum temporale and the right inferior frontal gyrus was also decreased in the schizophrenia subjects. Moreover, there was a significant increase in gray matter concentration of the left basal ganglia. In comparison with the controls, patients with schizotypal disorder showed much less gray matter voxels with significantly reduced concentration than schizophrenia patients in more selected brain regions confined to the left hemisphere: these regions included the inferior frontal gyrus, insula, anterior part of the superior temporal gyrus and medial temporal region.

The reduction in gray matter concentration of several frontal regions especially in the medial frontal, middle fontal, and orbitofrontal regions in schizophrenia, but not in schizotypal disorder, was noteworthy. A direct comparison between the schizophrenia and schizotypal disorder groups resulted in a significant difference in the left orbitofrontal gray matter concentration. Comparisons of brain gray matter between patients receiving typical neuroleptics and atypical neuroleptics did not reveal any significant difference in each patient group.

Discussion

In the present study, the ICD-10 criteria for schizotypal disorder were adopted for recruiting schizotypal subjects. Yung and McGorry (1996) postulated that a subthreshold form of psychotic symptoms and transient isolated psychotic experience are candidates for phenomenological indicators of liability to schizophrenic psychosis. Although 6 out of the 25 present schizotypal

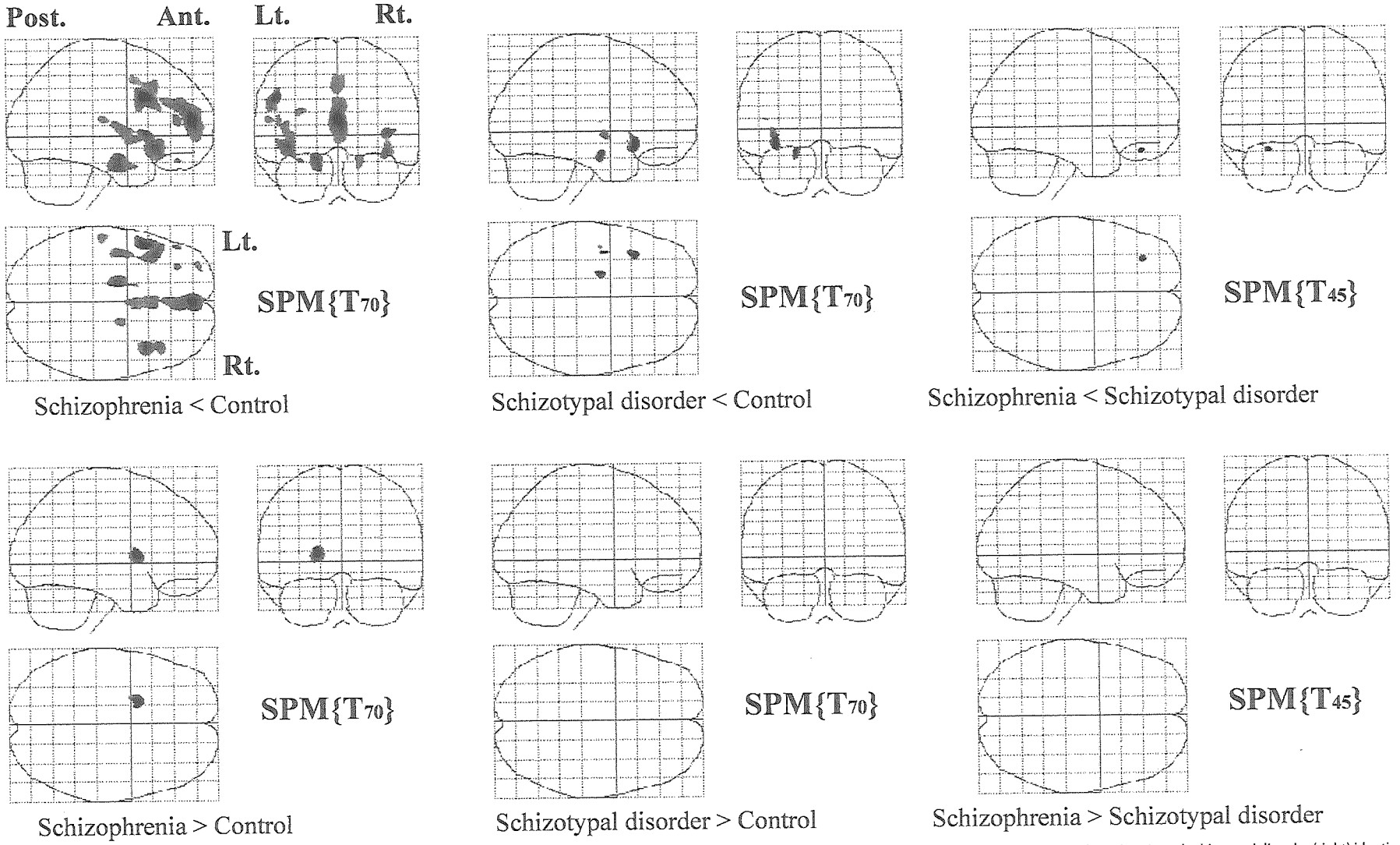

Fig. 1 Decreased and increased regional gray matter concentrations between healthy controls and schizophrenia (left), healthy controls and schizotypal disorder (middle), and schizophrenia and schizotypal disorder (right) identified by SPM (T) maps. All maps are thresholded at $p < 0.05$, corrected for the entire volume

Table 2 Diagnosis related regional findings of gray matter concentration using SPM99 T statistics

Anatomical region	[area*]	Schizophrenia vs. Control					Schizotypal disorder vs. Control					Schizophrenia vs. Schizotypal disorder				
		T	p-value (corrected)	coordinates			T	p-value (corrected)	coordinates			T	p-value (corrected)	coordinates		
				x	y	z			x	y	z			x	y	z
Medial frontal cortex	[9] Lt.	6.52	< 0.001	−1	54	19 ↓										
	[9] Rt.	6.21	0.001	4	44	24 ↓										
	[10] Lt.	6.39	< 0.001	−2	57	8 ↓										
	[10] Rt.	6.58	< 0.001	1	54	6 ↓										
	[32] Lt.	5.48	0.011	−1	36	26 ↓										
	[32] Rt.	5.79	0.004	2	22	41 ↓										
Middle frontal gyrus	[9] Lt.	8.11	< 0.001	−50	15	32 ↓										
	[10] Lt.	5.57	0.008	−31	59	20 ↓										
	[46] Lt.	5.89	0.003	−48	42	13 ↓										
Inferior frontal gyrus	[47] Lt.	6.65	< 0.001	−41	24	−10 ↓	5.82	0.003	−36	21	−11 ↓					
	[47] Rt.	6.43	< 0.001	39	27	−14 ↓										
Orbitofrontal cortex	[11] Lt.	5.72	0.005	−30	42	−21 ↓						6.22	0.003	−29	41	−20 ↓
Insular cortex	Lt.	5.57	0.008	−41	−3	5 ↓	5.37	0.017	−40	−4	−4 ↓					
Superior temporal gyrus	[22] Lt.	5.32	0.020	−46	−10	8 ↓	5.01	0.041	−44	−8	8 ↓					
	[42] Lt.	5.49	0.011	−57	−20	14 ↓										
Medial temporal region	[28] Lt.	6.58	< 0.001	−18	−7	−19 ↓	5.65	0.006	−21	−8	−21 ↓					
	[28] Rt.	5.76	0.004	17	−6	−22 ↓										
Septal region		5.58	0.008	1	5	−3 ↓										
Basal ganglia	Lt.	6.61	< 0.001	−19	3	10 ↑										

* corresponding to the area of Brodmann
Rt. right hemisphere; *Lt.* left hemisphere
↓ significantly decreased gray matter concentration
↑ significantly increased gray matter concentration

subjects had transient quasi-psychotic episodes in addition to fulfilling the criteria for schizotypal personality disorder of DSM-IV, none of these subjects developed overt schizophrenia during relatively long-term clinical follow-up. Thus, the schizotypal subjects in this study may primarily constitute a distinct category from schizophrenia, but the possibility cannot be excluded that in some of them the antipsychotic medication prevented the onset of their overt psychotic episodes. Furthermore, prior to the onset of overt and sustained psychosis, it is not possible at present to reliably predict whether or not the patient will later develop schizophrenia. Medication status and clinical symptoms suggest that the present schizotypal subjects were clinically more impaired than those in the previous studies of schizotypal personality disorder (Dickey et al. 2002; Downhill et al. 2001).

This VBM study demonstrated reduced gray matter concentrations in the medial, lateral and orbital frontal regions, the superior and medial temporal regions, and the insula in the schizophrenia patients. These results support and replicate previous findings reported in volumetric region-of-interest studies (see reviews, Lawrie and Abukmeil 1998; Wright et al. 2000; Shenton et al. 2001) as well as in VBM studies of schizophrenia. With the use of SPM 96, Wright et al. (1995, 1999) reported regional gray matter reduction in the dorsolateral prefrontal cortex, the superior and medial temporal regions and the insula, and Paillère-Martinot et al. (2001) reported significant gray matter reduction in the medial frontal region, the medial temporal region and the insula. In our previous study using SPM 96 (Suzuki et al. 2002) a regional gray matter decrease was observed in the lateral and medial frontal regions, the superior temporal gyrus, and the hippocampus. Wilke et al. (2001) used SPM 99 and reported gray matter reduction in the inferior and medial frontal, superior temporal and insular regions in schizophrenia. In SPM 99 studies of the first episode subjects, Job et al. (2002) reported decreased gray matter in the anterior cingulate, medial frontal lobe, middle temporal gyrus, and limbic lobe, and Kubicki et al. (2002) showed decreased gray matter within the superior temporal gyrus. Ananth et al. (2002) used optimized-VBM and reported gray matter loss in several regions including the ventral and medial prefrontal cortices. Moreover, a deformation-based morphometric study by Volz et al. (2000) revealed volume reductions in the medial and lateral frontal, and the superior temporal regions.

We found evidence of a significant volume reduction in both schizophrenia and schizotypal groups in the left inferior frontal gyrus, the left insula, the left superior temporal gyrus, and the left medial temporal lobe structures. Reduced volume of the superior temporal gyrus and the medial temporal structures in schizophrenia has been consistently emphasized in previous reviews (Lawrie and Abukmeil 1998; Shenton et al. 2001; Wright et al. 2000). Involvements of the temporal lobe structures in schizotypal subjects have been controversial. Decreased superior temporal volume and preserved volume of the hippocampus and amygdala were reported in male subjects with schizotypal personality disorder recruited from the community (Dickey et al. 1999). However volume reduction in the superior temporal gyrus was not observed in female subjects (Dickey et al. 2003). A study on clinic-based schizotypal personality disorder patients showed a smaller temporal lobe but preserved superior temporal gyrus, and the authors deduced a volume reduction in the medial temporal lobe (Downhill et al. 2001). The present study has provided evidence for the superior and medial temporal abnormalities in a relatively large sample of clinic-based schizotypal subjects.

In a study by Lawrie et al. (1999), a significant volume reduction in the amygdala-hippocampal complex was observed both in the schizophrenia patients in their first-episode and the subjects at high familial risk for schizophrenia, and the magnitude of the volume reduction was greater in the schizophrenia patients than in the high-risk subjects. A study by Van Erp et al. (2002) showed that the psychotic probands had smaller hippocampal volumes than did their siblings, who in turn had smaller hippocampal volumes than did the healthy subjects. Seidman et al. (2002) reported that schizophrenic relatives had smaller left hippocampus compared with controls and that hippocampal volumes did not differ between schizophrenia patients and their relatives. A cross-sectional comparison by Pantelis et al. (2003) reported that ultra high-risk individuals who later developed psychosis showed a gray matter reduction in the medial temporal, superior temporal, and inferior frontal regions compared with those who did not develop psychosis. They further reported in a longitudinal comparison that individuals who developed psychosis showed progressive gray matter reduction in the medial temporal regions. Taking together the present and previous findings, the extent of pathology in the medial temporal regions, and presumably in the superior temporal gyrus, may account for the degree of vulnerability to schizophrenia, but further progress of the medial temporal pathology may contribute to the transition to psychosis. Present results also suggest that volume deficits in the lateral part of the inferior frontal gyrus and the insula are associated with the vulnerability.

The most noteworthy finding was that only in the schizophrenia patients, unlike the schizotypal subjects, the decreased gray matter concentration of the medial frontal cortex and the left middle frontal gyrus was evident with convincing statistical power. Moreover, the comparison between these two groups highlighted the left orbitofrontal cortex. These results are in accord with the notion that both schizotypal subjects and schizophrenia patients appear to show abnormalities in the temporal lobe volume, but schizotypal subjects do not appear to show the volumetric decreases in the frontal cortex or frontal-lobe related structures that schizophrenia patients showed (Siever et al. 2002; Suzuki et al.

2004), although prefrontal gray matter decrease was reported in a mixed sample of individuals with schizotypal/paranoid personality disorder (Raine et al. 2002). Moreover, a longitudinal comparison of individuals before and after psychosis development stressed the cingulate cortex as well as the orbitofrontal cortex (Pantelis et al. 2003). These results suggest that frontal cortical changes especially in the medial frontal regions including the anterior cingulate cortex are critical for the development of florid psychotic symptoms (Kurachi 2003).

A few recent studies reporting contradictory findings to our conclusion must be referred to. In a twin study by Cannon et al. (2002), the genetic vulnerability to schizophrenia was associated with deficits primarily in the polar and dorsolateral prefrontal cortex, whereas the psychotic phenotype was associated with deficits primarily in the dorsolateral prefrontal cortex, superior temporal gyrus, and superior parietal lobule. Job et al. (2003) demonstrated that subjects at genetic high risk of schizophrenia had reduced gray matter in the bilateral anterior cingulate compared to controls. Although these findings are inconsistent with other previous studies reporting temporal lobe abnormalities as main results in subjects at genetic risk (Lawrie et al. 1999; Seidman et al. 2002; Van Erp et al. 2002), they raise the possibility that the genetic risk for schizophrenia is distinct from the schizotypal trait in its morphological basis for vulnerability. Further data will be needed to resolve this issue.

A recent review (Shenton et al. 2001) pointed to the increased volume of the basal ganglia in schizophrenia and stated that prior neuroleptic exposure is an important factor in this finding. In the present study, all the patients with schizophrenia had received antipsychotic medication, while two subjects with schizotypal disorder were drug-naive and others had received significantly smaller amounts of neuroleptics than schizophrenia patients. The increased gray matter concentration in the basal ganglia of patients with schizophrenia but not schizotypal disorder may be explained by the differences in antipsychotic medication. Moreover, Shihabuddin et al. (2001) reported that the basal ganglia volume was smaller in patients with schizotypal personality disorder than in controls. A failure to find significant changes in the basal ganglia of schizotypal subjects may also be explained by the medication.

Several limitations of this study need to be taken into account. Because of the FWHM resolution of 12 mm in the image smoothing, it appears to be more appropriate to consider peak coordinates located in the midline as bilateral findings. Moreover, a subtle change in the small brain structure with increased variance between subjects may lead to false-negative statistical results, because a voxel of such a region may not represent exactly the same small structure for each subject in the group. Systematic shape differences such as the enlarged ventricle of the patients may also lead to allocation during the spatial normalization (Bookstein 2001; Ashburner and Friston 2001). The possibility exists that the septal region, and perhaps the insula and the anterior part of the superior temporal gyrus, extracted by SPM represent the enlarged ventricle or fissure per se. Although observed gray matter reductions surrounding these CSF spaces are intriguing, care must be taken not to over-interpret the extracted coordinates. Further refinement of spatial normalization such as the optimized-VBM (Good et al. 2001; Ananth et al. 2002) will help to clarify this issue.

The VBM clearly elucidated structural abnormalities in schizophrenia and schizotypal disorder. The present findings require replication in a study with a larger number of subjects with consideration of gender differences. Optimally, a longitudinal study design that includes measurements before and after the onset of schizophrenia would be used. The common features of left sided gray matter changes in the medial temporal region, the superior temporal gyrus, the inferior frontal gyrus, and the insula may represent vulnerability to schizophrenia. In addition, involvement of several frontal regions, namely the bilateral medial frontal cortex, the left middle frontal gyrus, the left orbitofrontal cortex and the right inferior frontal gyrus, may be of crucial significance to the development of florid psychotic symptoms in schizophrenia.

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