relationships between a variation in the DISC1 gene and intermediate phenotypes related to schizophrenia such as P300 amplitude (Blackwood and Muir, 2004) or brain morphology and cognitive functioning (Cannon et al., 2005; Hennah et al., 2005) that the DISC1 locus contributes to prefrontal abnormalities in schizophrenia.

Although the DISC1 gene has several single nucleotide polymorphisms (SNPs) in various regions, recent observations suggested that a functional SNP on exon 11 (rs821616, a serine to cysteine substitution at codon 704) might affect brain morphology and function in healthy subjects. Callicott et al. (2005) showed relationships between the Ser allele and hippocampal volume reduction, as well as its altered activity during cognitive tasks. Hashimoto et al. (2006) did not replicate the hippocampus finding but observed a gray matter reduction in the cingulate cortex of individuals carrying the Cys allele. Thomson et al. (2005) suggested that the Cys allele was related to cognitive aging. For schizophrenia, however, the possible effect of this SNP on brain morphology and/or function is largely unknown.

In this study, we used magnetic resonance imaging (MRI) to investigate the genotype effects of the DISC1 Ser704Cys SNP on brain morphology in schizophrenia patients and healthy comparison subjects. Regions of interest (ROIs) for the volumetric measurements were placed widely in the fronto–parietal, temporal, and limbic–paralimbic regions known to be abnormal in schizophrenia. Based on 1) the regional expression pattern of the DISC1 in the human brain (Kirkpatrick et al., 2006), 2) the possible effect of the DISC1 on the prefrontal cortex (Cannon, 2005), and 3) the hypothesized fronto–parietal network disturbance in schizophrenia (Zhou et al., 2007), we predicted that a variation in the Ser704Cys SNP would differentially impact on brain morphology in schizophrenia and healthy comparisons, especially for the prefrontal and parietal regions. We also explored the association between the DISC1 genotype variation and the effect of antipsychotic medication on brain morphology in schizophrenia.

2. Methods

2.1. Subjects

Demographic and clinical data of the subjects in this study are presented in Table 1. This cohort was largely included in our previous MRI studies, which investigated the morphology in the frontal, temporal, parietal, and limbic–paralimbic regions in schizophrenia (Suzuki et al., 2005; Takahashi et al., 2005, 2006a,b; Zhou et al., 2005, 2007). All subjects were right-handed Japanese and physically healthy at the time of the study. None had a lifetime history of serious head trauma, neurological illness, serious medical or surgical illness, or substance abuse. The two diagnostic groups were matched for age, gender, height, and parental education.

Thirty-three schizophrenia patients who met the ICD-10 research criteria for schizophrenia (World Health Organization, 1993) were recruited from the inpatient and outpatient clinics of the Department of Neuropsychiatry, Toyama University Hospital. Diagnoses were made following structured clinical interviews by psychiatrists with the Comprehensive Assessment of Symptoms and History (CASH; Andreasen et al., 1992). Clinical symptoms were rated at the time of scanning using the Scale for the Assessment of Negative Symptoms (SANS) and the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984). All patients were receiving antipsychotic medication at the time of scanning; 15 patients were being treated with typical antipsychotics (8 haloperidol, 3 nemonapride, 2 bromperidol, and 2 sulpiride) and 18 patients were receiving atypical antipsychotics (11 risperidone, 4 olanzapine, 2 quetiapine, and 1 perospirone). Twenty-eight and 25 patients were also receiving anticholinergics and benzodiazepines, respectively.

The control subjects consisted of 29 healthy volunteers recruited from members of the community, hospital staff, and university students. They were given a questionnaire consisting of 15 items concerning their families and past histories, and present illness. They did not have any personal or family history of psychiatric illness among their first-degree relatives. 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. This study was approved by the ethical committees of Toyama University and Nagoya University. Written informed consent was obtained from all subjects.

2.2. Magnetic resonance imaging procedures

Magnetic resonance images were obtained using 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. The 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. Image processing for volumetric analysis has been described in detail elsewhere (Takahashi et al., 2002). Briefly, on a Unix workstation (Silicon Graphics, Inc, Mountain View, CA, USA), the image data were processed using the software package Dr View 5.3 (AJS, Tokyo, Japan). Brain images 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 line. The whole cerebrum was manually separated from the brainstem and cerebellum. The signal-intensity histogram distributions from the T1-weighted images across the whole cerebrum were then used to semi-automatically segment the voxels into gray matter, white matter, and cerebrospinal fluid. The intracranial volume (ICV) was measured to correct for differences in head size as previously described (Zhou et al., 2003); the groups did not significantly differ in their ICV volumes.

Table 1
Clinical and DISC1 Ser704Cys genetic description of healthy comparisons and patients with schizophrenia.

Variable	Healthy comparisons	Schizophrenia patients
	$N=29$	$N=33$
Male/female	17/12	20/13
Age (years)	24.2 ± 6.1	25.6 ± 4.5
Height (cm)	166.0 ± 7.0	165.5 ± 7.8
Education (years)	15.4[a] ± 2.4	13.5 ± 1.7
Parental education (years)	12.2 ± 2.3	12.3 ± 2.2
Age at onset (years)	–	22.2 ± 4.4
Duration of illness (years)	–	3.5 ± 3.6
Duration of medication (years)	–	2.7 ± 2.8
Drug (mg/day, haloperidol equivalent)[b]	–	12.2 ± 8.6
Total SAPS score	–	26.1 ± 24.7
Total SANS score	–	49.7 ± 22.9
Genotypes (*N*; Ser homozygote/Cys carrier)	22/7	24/9
Alleles (*N*; Ser / Cys)	51/7	57/9

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 schizophrenia patients.
[b] The different typical and atypical antipsychotic dosages were converted into haloperidol equivalent according to Toru (2001).

2.3. Volumetric analyses of regions of interest (ROIs)

As presented in Table 2, a broad range of cortical and limbic-paralimbic regions were manually traced on consecutive 1-mm coronal slices with the corresponding sagittal and axial planes simultaneously presented for reference. For the medial temporal lobe structures (amygdala, hippocampus, and parahippocampal gyrus), volumes of gray and white matter were measured together. For the other regions, we measured only the gray matter volumes by using the above-mentioned segmentation procedure. The procedures for delineation of these structures were described in detail previously. Briefly, five parietal subregions (Zhou et al., 2007) were parcellated using the intrinsic anatomical landmarks (sulci/gyri) (Fig. 1A). The whole frontal lobe was separated from the rest of the brain by the central sulcus, and the prefrontal area was demarcated by subtracting the precentral gyrus and the cingulate gyrus. The anterior cingulate gyrus was defined as a part rostral to the coronal level of the center of the anterior commissure (Fig. 1C) (Zhou et al., 2005). Then the prefrontal gyrus was subdivided into seven subregions using the intrinsic landmarks (Fig. 1B), but the superior frontal gyrus was subdivided into the dorsolateral and medial parts by the superior margin of the hemisphere (Suzuki et al., 2005). For the temporal lobe structures (Fig. 1C), the slice containing the temporal stem was chosen as the anterior boundary of the superior, middle, and inferior temporal gyri and parahippocampal gyrus (Takahashi et al., 2006a,b). The posterior boundaries of the superior temporal gyrus and parahippocampal gyrus were defined by the end of the posterior horizontal limb of the sylvian fissure and the last appearance of the fornix, respectively. The anterior tip of the parieto-occipital sulcus was used as the posterior boundary for the fusiform gyrus and middle and inferior temporal gyri. The inferior border of the amygdala in contact with the hippocampus head was determined by reference to the sagittal plane; the alveus was used to differentiate these structures (Suzuki et al., 2005). The insular cortex (Fig. 1D) was traced using the circular insular sulci as the main landmarks, and then divided into long and short cortices by the central insular sulcus (Takahashi et al., 2005).

Four trained raters (HH, LN, SZ, and TT) measured the volumes of each ROI without knowledge of the subjects' identity, gender, or diagnosis. Intra- and inter-rater intraclass correlation coefficients in a subset of five randomly selected brains were over 0.92 for all ROIs.

Table 2
DISC1 genotype differences in relative volume for regions of interest in schizophrenia patients and healthy comparisons[a].

Brain region	Healthy comparisons		Schizophrenia patients		Analysis of covariance ($df = 1, 56$)[b]					
	Ser/Ser	Cys carriers	Ser/Ser	Cys carriers	Effect of genotype		Effect of diagnosis		Diag. × genotype	
	($N=22$)	($N=7$)	($N=24$)	($N=9$)	F	P	F	P	F	P
Parietal lobe										
Postcentral gyrus					0.65	0.423	**4.94**	**0.030**	0.48	0.493
Left	0.924 ± 0.118	0.939 ± 0.127	0.850 ± 0.108	0.890 ± 0.121						
Right	0.845 ± 0.131	0.893 ± 0.105	0.793 ± 0.137	0.753 ± 0.130						
Superior parietal lobule					0.65	0.423	**4.88**	**0.031**	1.80	0.185
Left	0.741 ± 0.137	0.804 ± 0.072	0.693 ± 0.116	0.671 ± 0.145						
Right	0.720 ± 0.108	0.763 ± 0.080	0.690 ± 0.134	0.665 ± 0.122						
Precuneus					2.03	0.159	**15.25**	**<0.001**	1.35	0.250
Left	0.753 ± 0.100	0.815 ± 0.139	0.673 ± 0.117	0.669 ± 0.086						
Right	0.791 ± 0.108	0.852 ± 0.116	0.689 ± 0.124	0.705 ± 0.054						
Supramarginal gyrus					<0.01	0.996	**16.26**	**<0.001**	**6.38**	**0.014**
Left	1.089 ± 0.121	1.217 ± 0.172	1.018 ± 0.121	0.950 ± 0.141						
Right	1.054 ± 0.168	1.102 ± 0.224	0.986 ± 0.179	0.838 ± 0.177						
Angular gyrus					0.15	0.702	**12.31**	**<0.001**	3.46	0.068
Left	1.295 ± 0.187	1.319 ± 0.282	1.201 ± 0.130	1.103 ± 0.168						
Right	1.261 ± 0.166	1.376 ± 0.166	1.169 ± 0.176	1.126 ± 0.168						
Prefrontal gyrus										
Dorsolateral SFG					0.39	0.537	2.75	0.103	0.05	0.817
Left	0.901 ± 0.201	0.905 ± 0.114	0.779 ± 0.158	0.864 ± 0.183						
Right	0.880 ± 0.171	0.871 ± 0.128	0.807 ± 0.182	0.787 ± 0.167						
Medial SFG					**4.26**	**0.044**	**21.68**	**<0.001**	**5.39**	**0.024**
Left	1.115 ± 0.158	1.247 ± 0.134	1.032 ± 0.162	0.994 ± 0.104						
Right	1.029 ± 0.171	1.197 ± 0.147	0.921 ± 0.144	0.916 ± 0.121						
Middle frontal gyrus					1.31	0.258	1.46	0.232	**4.92**	**0.031**
Left	1.766 ± 0.268	1.989 ± 0.352	1.829 ± 0.239	1.688 ± 0.363						
Right	1.709 ± 0.295	1.919 ± 0.336	1.746 ± 0.249	1.700 ± 0.248						
Inferior frontal gyrus					0.04	0.852	**5.43**	**0.023**	0.18	0.671
Left	0.931 ± 0.160	0.914 ± 0.108	0.846 ± 0.132	0.845 ± 0.082						
Right	0.860 ± 0.120	0.911 ± 0.137	0.806 ± 0.128	0.778 ± 0.106						
Ventral medial PFC					0.04	0.837	**5.40**	**0.024**	0.48	0.493
Left	0.392 ± 0.073	0.427 ± 0.088	0.372 ± 0.060	0.369 ± 0.069						
Right	0.404 ± 0.060	0.381 ± 0.046	0.367 ± 0.063	0.337 ± 0.057						
Orbitofrontal cortex					0.42	0.520	1.80	0.185	1.61	0.210
Left	1.022 ± 0.109	1.027 ± 0.126	1.018 ± 0.096	0.963 ± 0.131						
Right	1.040 ± 0.089	1.022 ± 0.091	1.011 ± 0.101	0.962 ± 0.119						
Straight gyrus					0.09	0.768	**12.32**	**<0.001**	**4.90**	**0.031**
Left	0.209 ± 0.029	0.219 ± 0.020	0.196 ± 0.026	0.185 ± 0.020						
Right	0.212 ± 0.031	0.225 ± 0.031	0.204 ± 0.030	0.192 ± 0.028						
Temporal lobe										
Superior temporal gyrus					0.34	0.561	**31.13**	**<0.001**	0.07	0.798
Left	0.857 ± 0.120	0.891 ± 0.091	0.706 ± 0.100	0.739 ± 0.038						
Right	0.758 ± 0.091	0.736 ± 0.132	0.633 ± 0.099	0.611 ± 0.104						
Middle temporal gyrus					0.12	0.733	0.82	0.368	3.10	0.084
Left	0.994 ± 0.137	1.081 ± 0.159	1.045 ± 0.155	0.988 ± 0.154						
Right	1.048 ± 0.115	1.086 ± 0.153	1.039 ± 0.147	0.985 ± 0.139						
Inferior temporal gyrus					<0.01	0.983	**9.83**	**0.003**	**7.92**	**0.007**
Left	0.861 ± 0.088	0.912 ± 0.080	0.865 ± 0.121	0.783 ± 0.108						
Right	0.824 ± 0.090	0.895 ± 0.089	0.794 ± 0.104	0.737 ± 0.123						
Fusiform gyrus					1.77	0.189	**9.27**	**0.004**	0.98	0.326
Left	0.623 ± 0.102	0.523 ± 0.083	0.522 ± 0.103	0.486 ± 0.077						
Right	0.635 ± 0.106	0.595 ± 0.116	0.516 ± 0.113	0.535 ± 0.078						
Parahippocampal gyrus					0.01	0.934	1.07	0.304	0.25	0.621
Left	0.474 ± 0.041	0.473 ± 0.054	0.486 ± 0.046	0.479 ± 0.064						
Right	0.480 ± 0.039	0.474 ± 0.054	0.490 ± 0.039	0.481 ± 0.053						
Amygdala					0.42	0.520	**12.75**	**<0.001**	<0.01	0.973
Left	0.076 ± 0.009	0.076 ± 0.009	0.066 ± 0.010	0.066 ± 0.007						
Right	0.079 ± 0.009	0.077 ± 0.014	0.071 ± 0.009	0.069 ± 0.010						
Hippocampus					0.83	0.366	2.86	0.096	1.26	0.267
Left	0.203 ± 0.022	0.215 ± 0.021	0.196 ± 0.027	0.195 ± 0.025						
Right	0.214 ± 0.021	0.223 ± 0.017	0.209 ± 0.026	0.206 ± 0.031						
Limbic–paralimbic area										
Anterior cingulate gyrus					0.46	0.450	1.01	0.318	0.23	0.630
Left	0.294 ± 0.117	0.279 ± 0.075	0.252 ± 0.089	0.259 ± 0.095						
Right	0.372 ± 0.120	0.306 ± 0.128	0.333 ± 0.105	0.315 ± 0.105						
Long insular cortex					0.07	0.792	0.42	0.518	0.34	0.560
Left	0.192 ± 0.028	0.173 ± 0.040	0.177 ± 0.031	0.174 ± 0.031						
Right	0.177 ± 0.029	0.178 ± 0.040	0.170 ± 0.031	0.176 ± 0.018						
Short insular cortex					1.39	0.244	**14.20**	**<0.001**	**6.26**	**0.015**
Left	0.346 ± 0.032	0.385 ± 0.054	0.334 ± 0.041	0.321 ± 0.035						
Right	0.341 ± 0.042	0.372 ± 0.053	0.321 ± 0.040	0.301 ± 0.043						

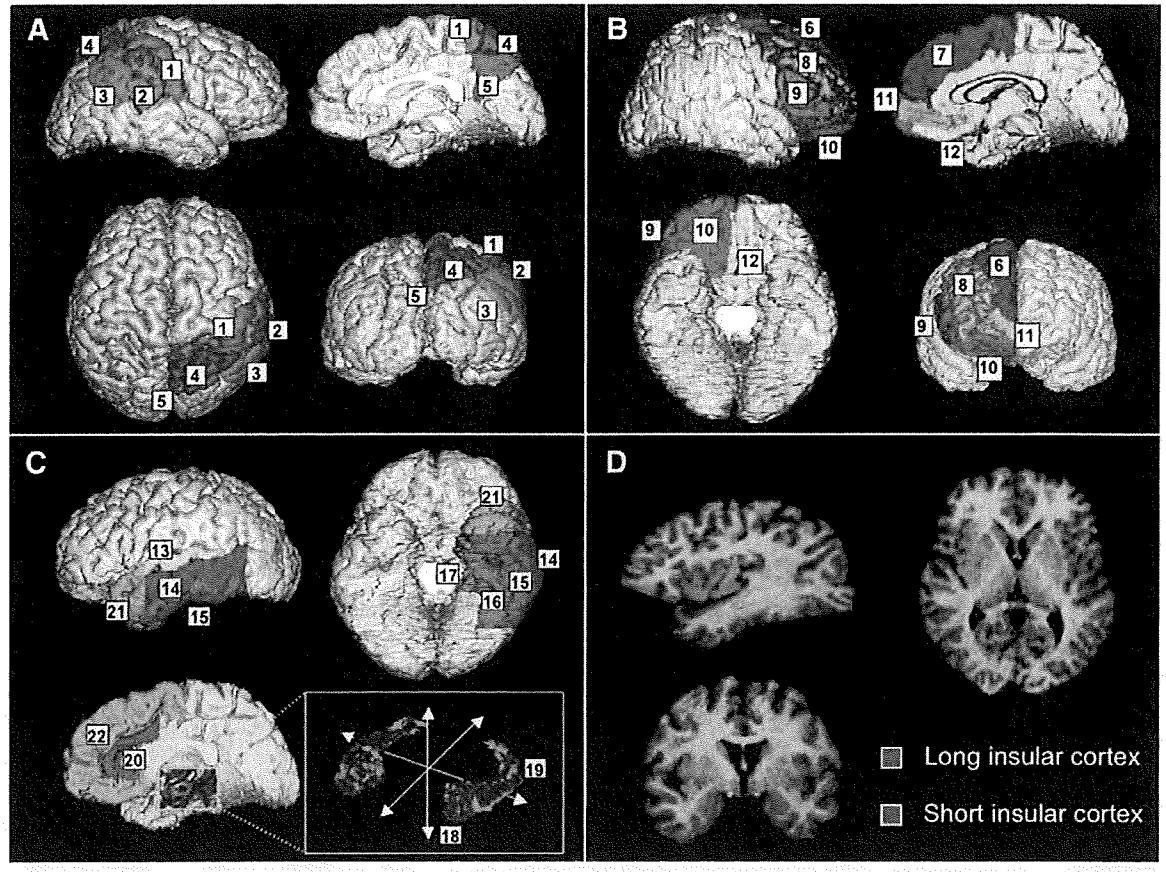

Fig. 1. Regions of interest used in this study [parietal subregions (A), prefrontal subregions (B), temporal and other regions (C), and insular cortex (D)]. 1, postcentral gyrus; 2, supramarginal gyrus; 3, angular gyrus; 4, superior parietal gyrus; 5, precuneus; 6, dorsolateral superior frontal gyrus; 7, medial superior frontal gyrus; 8, middle frontal gyrus; 9, inferior frontal gyrus; 10, orbitofrontal cortex; 11, ventral medial prefrontal cortex; 12, straight gyrus; 13, superior temporal gyrus; 14, middle temporal gyrus; 15, inferior temporal gyrus; 16, fusiform gyrus; 17, parahippocampal gyrus; 18, amygdala; 19, hippocampus; 20, anterior cingulate gyrus; 21, temporal pole; 22, whole prefrontal cortex. The superior frontal gyrus was subdivided into the dorsolateral (6) and medial (7) parts by the superior margin of the hemisphere. The temporal pole was not used in this study but is shown here as a reference for the topography of the temporal lobe structures.

2.4. DNA procedures

Genomic DNA was extracted from EDTA-containing venous blood samples according to standard procedures. The genotyping of the Ser704Cys SNP (rs821616) of the DISC1 gene was carried out using a polymerase chain reaction–restriction fragment length polymorphism assay. Sequences of primer pairs and the restriction enzyme were as follows; Fw: 5′-GGGATGAGGTGAGTCTTCCA- 3′, Rv:5′-TGTCTCAGCTGCAAGTGTCC-3′, Hpy188III.

2.5. Statistical analysis

Genotype frequencies between schizophrenia patients and healthy comparison subjects were compared using the chi-square test to test for Hardy-Weinberg equilibrium (HWE). In order to examine the genotype effects on brain morphology, the relative volumes [(absolute volume/ICV) × 100] for each ROI were analyzed using the repeated measures analysis of covariance (ANCOVA) with age and gender as covariates, with diagnosis (schizophrenia patients versus controls) and genotype [Ser homozygotes versus Cys carriers] as between-subject factors, and hemisphere (left versus right) as a within-subject variable. The volumetric measures for all ROIs in this study were normally distributed (Kolmogorov–Smirnov test). Post hoc Neuman–Keuls tests were carried out to follow up the significant main effects or interactions yielded by ANCOVAs. These analyses were not corrected for multiple comparisons because of the exploratory nature of this study. The association of the antipsychotic medication (dose, duration) to the relative ROI volumes in schizophrenia patients was examined using Spearman's rank correlations. Statistical significance was defined as $P < 0.05$.

3. Results

The observed genotype frequency of SNP was within the distribution as expected according to the HWE. As shown in Table 1, patients with schizophrenia and healthy comparisons did not differ significantly in genotype distributions (chi-square = 0.08, $P = 0.778$). There were no Cys homozygotes in the present sample. There were no significant differences between the Ser homozygotes and Cys carriers in demographic variables (age, gender, height, education, and parental education) for both schizophrenia and control groups. For schizophrenia patients, no differences between the genotype groups were observed on clinical variables (onset age, illness duration, duration and dosage of antipsychotic medication, total SAPS score, and total SANS score).

Table 2 shows a comparison of the relative ROI volumes between the Ser homozygote subjects and Cys carriers. We found significant

Notes to **Table 2**:
Values represent means ± SDs.
PFC, prefrontal cortex; SFG, superior frontal gyrus.
[a] Relative volumes were calculated as follows: 100 × absolute volume/ intracranial volume. Absolute volumes for the medial temporal and frontal regions (Suzuki et al., 2005), parietal (Zhou et al., 2007) and temporal (Takahashi et al., 2006a,b) regions, or limbic areas (Zhou et al., 2005; Takahashi et al., 2005) in a larger sample were published elsewhere.
[b] Genotype-by-side interaction was observed only for the ventral medial PFC ($F = 4.78$, $df = 1, 58$, $P = 0.033$). Diagnosis-by-genotype-by-side interaction was observed only for the postcentral gyrus ($F = 5.28$, $df = 1, 58$, $P = 0.025$). These interactions were not significantly supported by the post-hoc analyses.

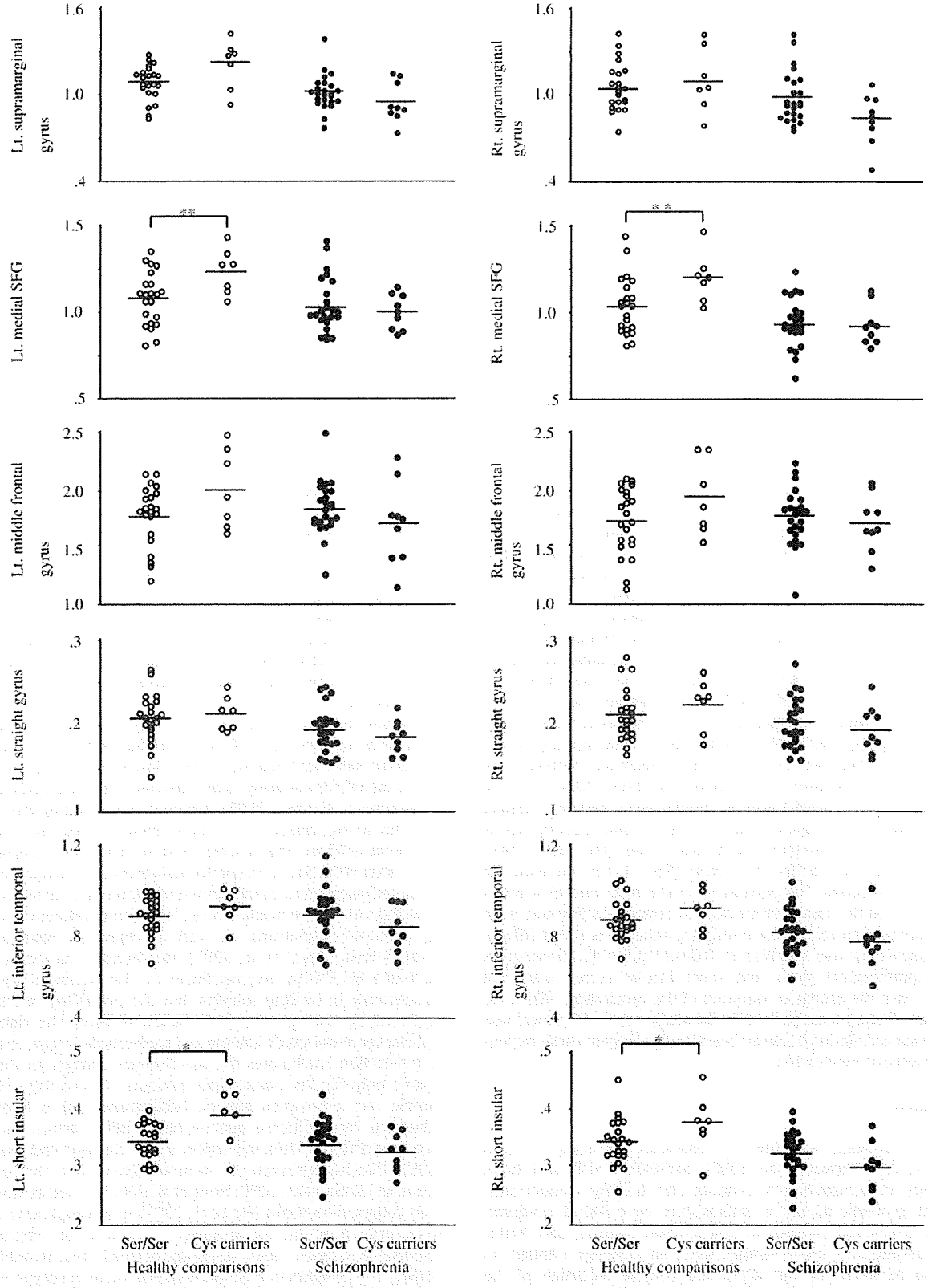

Fig. 2. Scatter plots of relative volumes (100 × absolute volume/intracranial volume) for the brain regions that showed significant diagnosis-by-genotype interactions in healthy comparisons and schizophrenia patients. Horizontal lines indicate means. SFG = superior frontal gyrus. *$P<0.05$, **$P<0.01$.

diagnosis-by-genotype interactions for the supramarginal gyrus, medial superior frontal gyrus, middle frontal gyrus, straight gyrus, inferior temporal gyrus, and short insular cortex. Post hoc tests revealed that the Cys carriers had significantly larger volumes of the medial superior frontal gyrus ($P=0.005$) and short insular cortex ($P=0.020$) than the Ser homozygotes in healthy comparisons, but not

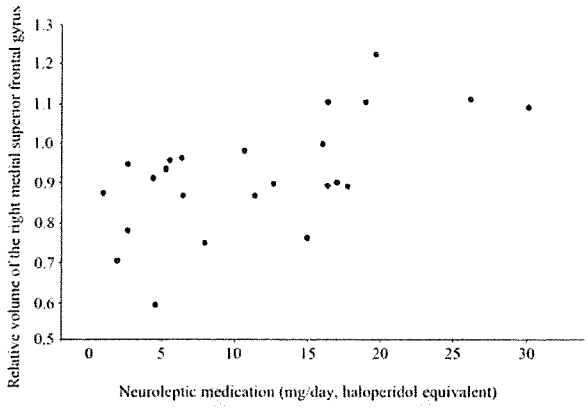

Fig. 3. Correlation between the right medial superior frontal gyrus volume and daily dose of antipsychotic medication in Ser homozygote schizophrenia patients ($N=24$, rho = 0.564, $P=0.004$).

in schizophrenia patients (medial superior frontal gyrus, $P=0.682$; short insular cortex, $P=0.264$). The Cys carriers tended to have a significantly smaller supramarginal gyrus than the Ser homozygotes for schizophrenia patients ($P=0.059$), but not for healthy comparisons ($P=0.118$) (Fig. 2). The interactions of the middle frontal gyrus, straight gyrus, and inferior temporal gyrus were not significantly supported by the post hoc analyses. The effects involving genotype were not significant for the other ROIs investigated.

These ANCOVA analyses suggest that the patients carrying the Cys allele exhibit a lack of volume increase in the frontal and limbic regions, as well as volume reduction in the supramarginal gyrus compared with the Ser homozygote patients. Because all patients were on antipsychotic medication, these findings may raise the possibility that medication ameliorates brain changes in these regions in Ser homozygote patients ($N=24$), but not in those carrying the Cys allele ($N=9$). Thus, we examined the association between the antipsychotic medication and volume of three ROIs (i.e., the supramarginal gyrus, medial superior frontal gyrus, and short insular cortex) in the Ser homozygote patients. The medial superior frontal gyrus volume was correlated with daily dose (left, rho = 0.411, $P=0.046$; right, rho = 0.564, $P=0.004$) (Fig. 3), but not with the duration of medication. The correlation of the right medial superior frontal gyrus and the dosage of medication remained significant even after a Bonferroni correction for multiple comparisons (three ROIs in each hemisphere by two variables; $P<0.0042$ [0.05/12]). The volumes of the supramarginal gyrus and short insular cortex were not correlated with the dosage or duration of the medication. When we included all schizophrenia patients in the analyses ($N=33$), there was no significant correlation between brain morphology in these regions and antipsychotic medication.

4. Discussion

To our knowledge, this is the first volumetric MRI study to report the relationship between the DISC1 Ser704Cys SNP and brain morphology in schizophrenia patients and healthy comparisons. Significant genotype-diagnosis interactions were found predominantly in neocortical (prefrontal and parietal cortices) and limbic regions. Despite the small sample size, our findings implied an association between the Cys allele and volume reduction of the supramarginal gyrus in schizophrenia, but not in healthy comparison subjects. In contrast, the Cys carriers had significantly larger volumes of the medial superior frontal gyrus and short insular cortex than the Ser homozygotes only for healthy comparisons. These different genotype effects of the DISC1 Ser704Cys SNP on brain morphology in schizophrenia patients and healthy comparisons suggest the involvement of this SNP in the morphologic brain changes observed in schizophrenia.

Among the ROIs investigated in this study, the supramarginal gyrus, a part of the posterior parietal cortex, was the only region that showed an association with the DISC1 Ser704Cys genotype in schizophrenia. Increasing evidence supports the pathophysiological role of the parietal regions in schizophrenia as a component of an impaired fronto–parietal network. Functional neuroimaging studies demonstrated that several cognitive impairments evident in schizophrenia such as working memory deficits might be reflective of the fronto–parietal disconnection (Paulus et al., 2002; Kim et al., 2003; Danckert et al., 2004). As discussed elsewhere (Zhou et al., 2007), this disconnection may result in failure to suppress activity in the parietal region, leading to positive symptoms including delusion of control or verbal hallucinations. Fewer significant volume correlations between the parietal and prefrontal cortices in schizophrenia (Zhou et al., 2007) also support the notion of impaired fronto–parietal connectivities. Our findings suggest that the parietal abnormalities in schizophrenia might be at least in part influenced by DISC1 gene variation. Recent data demonstrated the genotype effect of DISC1 on working memory deficits (Burdick et al., 2005; Hennah et al., 2005) or severity of positive symptoms (DeRosse et al., 2007) in schizophrenia. Of note, as described above, these clinical manifestations could be associated with impaired fronto–parietal connectivities. The DISC1 protein seems to be involved in essential processes of neuronal function such as neurite outgrowth, neuronal migration, and synaptogenesis (Hennah et al., 2006; Porteous et al., 2006). Interestingly, Kirkpatrick et al. (2006) examined DISC1 immunoreactivity in the human frontal and parietal cortices and suggested from the presence of DISC1 in multiple types of synapses that DISC1 is involved in cortico–cortical connections. Taken together, it is hypothesized that a variation in the DISC1 gene affects the fronto–parietal connectivities during neural development, which could result in predisposing an individual toward schizophrenia.

Several lines of evidence have suggested the functional and anatomical involvements of the prefrontal cortex in schizophrenia (Goldman-Rakic and Selemon, 1997; Suzuki et al., 2005), and these prefrontal deficits are likely to be reflective of an inherited diathesis to schizophrenia (Cannon, 2005). Although not including the same SNP as in this study, Cannon et al. (2005) demonstrated that a haplotype incorporating three SNP markers within DISC1 was associated with gray matter reduction of the prefrontal cortex in schizophrenia. While the underlying genetic mechanism is unknown, gray matter reduction or dysfunction of the insular cortex has been implicated in manifesting psychotic symptoms, as well as cognitive impairments, in schizophrenia (Nagai et al., 2007). We found a significant effect of the DISC1 Ser704Cys polymorphism on the prefrontal and insular cortices only in healthy subjects, but the possibility exists that, as suggested by the significant correlation between the right medial superior temporal gyrus volume and medication dosage, antipsychotic medication ameliorates the morphologic changes in these brain regions only for Ser homozygote patients. The etiology of schizophrenia has a complex genetic background and is likely to be influenced by additional genetic/non-genetic factors, as well as these interactions (Sawa and Snyder, 2002; Harrison and Weinberger, 2005). Recent observations demonstrated that the treatment responses (Krebs et al., 2000; Hong et al., 2003) as well as longitudinal brain volume alterations (Ho et al., 2007) in schizophrenia are likely to be influenced by the genotype variations of schizophrenia-susceptibility genes such as brain-derived neurotrophic factor (BDNF). The possible interaction between these genotype variations and the ameliorative effect of antipsychotic medication on brain morphologic changes in schizophrenia (Keshavan et al., 1998; Dazzan et al., 2005; Lieberman et al., 2005) seems worthy of examination in future studies in a larger sample.

In previous MRI studies, healthy subjects with the Ser homozygotic genotype for the DISC1 Ser704Cys SNP were reported to have a

significantly smaller hippocampus (Callicott et al., 2005) and larger cingulate gyrus (Hashimoto et al., 2006) as compared with Cys carriers. Although not statistically significant, our results were in line with these findings (Table 2) and further demonstrated the Ser allele to be related to smaller volumes of the medial superior frontal gyrus and short insular cortex. The reason for this opposite direction of volume changes related to the same allele among extensively connected brain regions [e.g., cingulate gyrus and short insular cortex (Augustine, 1996)] is unclear, but compensation to structural and functional brain alterations associated with this allelic variation during neurodevelopment might be relevant. In contrast, we found different genotype effects of the DISC1 Ser704Cys SNP in the same brain regions between schizophrenia patients and healthy controls. The Ser homozygote controls had smaller volumes for most brain regions than Cys carriers, while the Ser homozygote patients had similar or even larger volumes compared with Cys carriers (Fig. 2). Although a specific allelic variant of this SNP conferring risk of schizophrenia remains controversial (Callicott et al., 2005; Qu et al., 2007), the Ser allele appears to be overtransmitted in schizophrenia and also be related to brain functional impairments in healthy subjects (Callicott et al., 2005). Given the complex gene–gene and gene–environmental interactions in the etiology of schizophrenia, it might be possible that the Ser allele increases risk for schizophrenia but the mechanism of this effect is also related to susceptibility to environmental influences including, as discussed above, the ameliorative effect of antipsychotic medication.

There are several confounding factors in the present study. First, the small number of subjects, especially for the Cys carriers, limited our ability to generalize the findings. The weak association between the DISC1 genotypes and brain morphology did not allow for statistical correction for multiple comparisons, representing a clear limitation of the study. We found the genotype effect only on the supramarginal gyrus in schizophrenia, but the current study was potentially underpowered to detect significant genotype effects on other brain regions due to the small sample size as well as the large differences in group size between the Cys carriers and Ser homozygotes. We did not replicate the overtransmission of the Ser allele in schizophrenia (Callicott et al., 2005), but the allelic variation at Ser704Cys should be tested in larger samples. Second, although the DISC1 is a complex gene with protean (Camargo et al., 2007), we examined only a single polymorphism of the DISC1 gene in the present study. A recent MRI study in DISC1 leu607phe SNP also failed to find a specific genotypic effect on brain morphology in schizophrenia (Szeszko et al., 2008). The association between the DISC1 genotype variation and brain morphology in schizophrenia, as well as in healthy subjects, remains obscure and needs further examination.

In conclusion, our preliminary results found different genotype effects of the DISC1 Ser704Cys polymorphism on brain morphology in schizophrenia patients and healthy comparisons. In particular, individuals carrying the Cys allele tended to have smaller gray matter volume of the supramarginal gyrus only in schizophrenia patients. These findings implicate the DISC1 in genetic risk for schizophrenia and further suggest that the mechanism may involve cortical abnormalities including the parietal region. In addition, the positive correlation between the right medial superior frontal gyrus volume and daily dosage of antipsychotic medication in Ser homozygote schizophrenia patients suggests that the DISC1 genotype variation might have some relevance to the ameliorative effect of antipsychotics on brain morphology.

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Diagnostic specificity of the insular cortex abnormalities in first-episode psychotic disorders

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ABSTRACT

Volume reductions of the insular cortex have been described in schizophrenia, but it remains unclear whether other psychotic disorders such as affective psychosis also exhibit insular cortex abnormalities. In this study, we used magnetic resonance imaging to investigate the gray matter volume of the anterior (short) and posterior (long) insular cortices in 162 first-episode patients with various psychotic disorders (46 schizophrenia, 57 schizophreniform disorder, 34 affective psychosis, and 25 other psychoses) and 62 age- and gender-matched healthy comparison subjects. Patients with schizophrenia showed bilateral volume reduction of the anterior and posterior insular cortices compared with controls, but the remaining first-episode psychosis subgroups had normal insular volumes. The volumes of these insular subregions were significantly smaller in schizophrenia patients than in patients with schizophreniform disorder or affective psychoses. There was no association between the insular cortex volume and daily dosage or type of antipsychotic medication in any patient group. These findings suggest that the widespread volume reduction of the insular cortex is specific to established schizophrenia, implicating its role in the neurobiology of clinical characteristics associated with schizophrenia.

1. Introduction

The insular cortex, which has reciprocal projections to areas of the limbic system such as the amygdala, plays a crucial role in emotional and various cognitive functions as a component of the "limbic integration cortex" (Augustine, 1996). A global [i.e., both anterior (short) and posterior (long) insular cortices (Augustine, 1996; Türe et al., 1999)] (Saze et al., 2007; Takahashi et al., 2005) or anterior-predominant (Makris et al., 2006) gray matter reduction of the insular cortex has been described in schizophrenia including first-episode patients (Crespo-Facorro et al., 2000; Kasai et al., 2003b; Nagai et al., 2007). Functional and structural abnormalities of the insular cortex in schizophrenia have been implicated in association with positive (Crespo-Facorro et al., 2000; Pressler et al., 2005; Shapleske et al., 2002; Shergill et al., 2000) and negative (Crespo-Facorro et al., 2001a; Sigmundsson et al., 2001; Takahashi et al., 2004) symptoms as well as cognitive impairments such as verbal memory deficits (Crespo-Facorro et al., 2001b; Curtis et al., 1998). These observations implicate that the insular cortex abnormalities underlie the specific clinical aspects of schizophrenia, while decreased insular blood flow in patients with major depressive disorder with psychotic features (Skaf et al., 2002) suggests a role for insular abnormalities in psychosis more generally. It thus remains unclear whether the insular cortex abnormalities reported in schizophrenia are diagnostically specific or common to various psychotic disorders such as affective psychosis.

While schizophrenia and bipolar disorder are known to share a number of clinical and epidemiological features potentially on a background of shared genetic predisposition to psychosis (Maier et al., 2006; Murray et al., 2004), neurobiological similarities and differences between schizophrenia and affective disorders with psychotic features (i.e., affective psychosis) have been inconsistent. Magnetic resonance imaging (MRI) studies that directly compared brain morphology in these two major psychotic disorders have identified more structural abnormalities in schizophrenia predominantly in

Abbreviations: ANCOVA, analysis of covariance; ANOVA, analysis of variance; DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders Revised Third Edition; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders Fourth Edition; EPPIC, Early Psychosis Prevention and Intervention Centre; FEP, first-episode psychosis; ICC, intraclass correlation coefficient; ICV, intracranial volume; MRI, magnetic resonance imaging; RPMIP, Royal Park Multidiagnostic Instrument for Psychosis; ROI, region of interest; SCID, Structured Clinical Interview for DSM-III-R; VBM, voxel based morphometry.

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fronto-temporolimbic–paralimbic regions (Hirayasu et al., 2001; Kasai et al., 2003a,b; Koo et al., 2008; McDonald et al., 2005; Velakoulis et al., 2006), brain changes (e.g., ventricular enlargement) common to both disorders (Elkis et al., 1995; Nakamura et al., 2007; Strasser et al., 2005), or less gray matter deficits in schizophrenia compared with affective psychosis (Morgan et al., 2007). The insular cortex findings in psychotic disorders have also been controversial; recent MRI (Kasai et al., 2003b; McDonald et al., 2005) and post-mortem (Pennington et al., 2008) studies demonstrated insular cortex abnormalities in schizophrenia but not in affective psychosis, whereas Morgan et al. (2007) found gray matter reduction only in affective psychosis. Furthermore, no MRI studies have specifically examined the insular cortex gray matter changes in schizophreniform disorder patients, who have a psychotic episode of less than 6 months' duration [DSM-III-R and -IV (American Psychiatric Association, 1987, 1994)].

The present study sought to address the disease specificity of insular cortex abnormalities within various psychotic disorders. We used MRI to measure the gray matter volume of the anterior and posterior insular cortices in patients with first-episode psychoses (i.e., schizophrenia, affective psychosis, schizophreniform disorder, and other psychoses) and healthy controls. On the basis of previous MRI (Kasai et al., 2003b) and post-mortem (Pennington et al., 2008) findings as well as the potential role of the insular cortex in clinical characteristics associated with schizophrenia (Nagai et al., 2007), we predicted that only schizophrenia patients would have widespread insular cortex volume reduction compared with healthy controls. Based on the disconnection hypothesis of schizophrenia (Friston, 1998), we also examined the relationship between volumes of the insular cortex and amygdala, which are extensively connected (Augustine, 1996).

2. Methods

2.1. Subjects

One hundred and sixty-two patients with first-episode psychosis (FEP) participated in this study. Inclusion criteria and demographic characteristics of the same FEP sample, recruited from the Early Psychosis Prevention and Intervention Centre (EPPIC; McGorry et al., 1996) between 1994 and 1999, have been described previously (Velakoulis et al., 2006). Briefly, the FEP patients were: (1) age at onset between 16 and 30 years, (2) current psychosis as reflected by the presence of at least one of; (a) delusions, (b) hallucinations, (c) disorder of thinking or speech other than simple acceleration or retardation, (d) disorganized, bizarre, or markedly inappropriate behavior. DSM-III-R diagnoses (American Psychiatric Association, 1987) were based on chart review and either the Structured Clinical Interview for DSM-III-R (SCID; Spitzer et al., 1990) or the Royal Park Multidiagnostic Instrument for Psychosis (RPMIP; McGorry et al., 1989) administered during the initial treatment episode (median duration of illness = 27 days). Since the current study started at the time when the Structured Clinical Interview for DSM-I-V (First et al., 1997) was not available, the FEP patients were diagnosed based on the DSM-III-R criteria. On the basis of these assessments and clinical follow-up, the 162 FEP patients were divided into 4 subgroups: (1) 46 schizophrenia (31 schizophrenia and 15 schizoaffective disorder), (2) 57 schizophreniform disorder (who had a psychotic episode of <6 months' duration), (3) 34 affective psychosis (22 bipolar and 11 major depressive psychoses), and (4) 25 other psychoses (3 delusional disorder, 6 brief psychosis, 4 substance-induced psychosis, and 12 psychosis not otherwise specified). Because the diagnostic status of schizoaffective disorder remains under debate (Averill et al., 2004), and given evidence that this disorder may be a variant of schizophrenia (Evans et al., 1999), schizoaffective disorder and schizophrenia were categorized together (Velakoulis et al., 2006). All FEP patients were neuroleptic-naïve before admission but 150 had received antipsychotic medication for a short period before the scanning, of which 42 patients were treated with typical antipsychotics and 108 patients received atypical antipsychotics. Accurate values for duration of medication were not available, but mean duration of such a period in our centre is about 30 days (Velakoulis et al., 1999). Seventeen patients (1 schizophrenia, 5 schizophreniform, 9 affective, and 2 other psychoses patients) were also receiving lithium carbonate at the time of scanning.

Sixty-two healthy volunteers were recruited from similar socio-demographic areas as the patients by approaching ancillary hospital staff and through advertisements (Velakoulis et al., 1999, 2006). Control subjects with a personal or family history of psychiatric illness were excluded. All participants in this study were physically healthy, and none had a lifetime history of serious head trauma, neurological illness, serious medical or surgical illness, or DSM-III-R criteria of alcohol or substance abuse or dependence. This study was approved by the regional ethics committee while written informed consent was obtained from all subjects prior to study participation.

2.2. Magnetic resonance imaging procedures

MR scans were acquired with a 1.5-T GE Signa scanner (General Electric Medical Systems, Milwaukee, Wisconsin). A 3D volumetric spoiled gradient recalled echo in the steady state sequence generated 124 contiguous 1.5 mm coronal slices (TR = 14.3 ms, TE = 3.3 ms, Flip = 30°, FOV = 24 × 24 cm, Matrix = 256 × 256, voxel dimension = 0.938 × 0.938 × 1.5 mm). The scanner was calibrated fortnightly with the same phantom to ensure the stability of measurements.

The image data were coded randomly and analyzed with the Dr View software (AJS, Tokyo, Japan). Brain images were realigned in

Table 1
Demographic characteristics of the participants.

	Controls (N = 62)	Sz (N = 46)	Szform (N = 57)	Aff (N = 34)	Other (N = 25)	Group comparisons
Age (years)	21.8 ± 4.4	21.5 ± 3.6	21.0 ± 3.0	22.0 ± 3.1	21.7 ± 4.2	$F(4,219) = 0.58$, $p = 0.68$
Male/female	38/24	34/12	42/15	18/16	14/11	Chi-square = 6.95, $p = 0.14$
Handedness (right/mixed/left)[a]	58/1/3	38/1/7	51/2/4	28/0/5	22/1/1	$p = 0.48$, Fisher's exact test
Height (cm)[a]	175.8 ± 9.2	172.9 ± 9.5	174.1 ± 8.2	169.8 ± 9.8	173.7 ± 9.8	$F(4.218) = 2.32$, $p = 0.06$
Premorbid IQ[a,b]	101.6 ± 10.0	92.4 ± 16.4	94.0 ± 11.7	95.5 ± 13.0	94.6 ± 12.6	$F(4,180) = 3.73$, $p < 0.01$; controls > Sz
Duration of illness (days)[c]	–	82 ± 136 (median = 30)	53 ± 67 (median = 36)	32 ± 24 (median = 24)	38 ± 42 (median = 16)	$F(3,155) = 2.56$, $p = 0.06$
Drug (mg/day, CP equivalent)[d]	–	195.5 ± 167.0	209.0 ± 193.8	158.7 ± 124.4	136.5 ± 104.0	$F(3,152) = 1.48$, $p = 0.22$
Intracranial volume (cm^3)	1449 ± 150	1391 ± 134	1447 ± 118	1433 ± 151	1409 ± 135	$F(4,218) = 1.58$, $p = 0.18$[e]

The values represent means ± SDs. Aff, affective psychosis; CP, chlorpromazine; Other, other psychoses; Sz, schizophrenia; Szform, schizophreniform.
[a] Data misssing for some participants.
[b] Estimated using the National Adult Reading Test (NART).
[c] Data on 3 patients were not available.
[d] Atypical antipsychotic dosages were converted into CP equivalents using the guideline by Woods (2003). 6 patients had incomplete medication data.
[e] ANCOVA with age as a covariate and group as a between-subject factor was used.

three dimensions and reconstructed into contiguous coronal images, with a 0.938-mm thickness, perpendicular to the AC-PC line. The whole cerebrum was manually separated from the brainstem and cerebellum. The signal-intensity histogram distributions from the T1-weighted images across the whole cerebrum were used to semi-automatically segment the voxels into gray matter, white matter, and cerebrospinal fluid. The intracranial volume (ICV) was measured to correct for differences in head size as previously described (Eritaia et al., 2000; Velakoulis et al., 2006); the groups did not differ significantly in their ICVs (Table 1).

Based on the segmented gray matter images, the insular cortex was traced on 0.938-mm consecutive coronal slices as described elsewhere (Takahashi et al., 2009). Briefly, the most rostral coronal slice 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. The insular cortex was then divided into the anterior and posterior insular cortices by the central insular sulcus, which was readily identified using both coronal and sagittal views (Fig. 1). All volumetric data of the insular cortex reported here were measured by one rater (TT), who was blinded to subjects' identities. Intra- (TT)/inter-rater (TT and RT) intraclass correlation coefficients (ICCs) of the insular cortex measurements in 10 randomly selected brains for a total of approximately 580 slices were 0.95/0.99 and 0.96/0.98 for left and right anterior portion, and 0.96/0.92 and 0.99/0.97 for left and right posterior portion, respectively.

The amygdala volumes of the same MR images in this FEP sample have been measured previously (Velakoulis et al., 2006); the amygdala was manually traced on 1.5-mm consecutive coronal slices using ANALYZE software (Mayo Clinic, Rochester, Minn). Intra-/inter-rater reliabilities of the amygdala measurements were 0.87/0.70 (right) and 0.88/0.79 (left).

2.3. Statistical analysis

Clinical and demographic differences between groups were examined with one-way analysis of variance (ANOVA) or chi-square test.

The absolute insular cortex volume was analyzed using repeated measures analysis of covariance (ANCOVA) with age and ICV as covariates, group (schizophrenia, schizophreniform psychosis, affective psychosis, other psychoses, and healthy controls) and gender as between-subject factors, and side (left, right) and subregions (anterior, posterior) as within-subject variables. We then investigated each subregion separately, based on a significant group-by-subregion interaction. Post hoc Scheffé's tests were carried out to follow up any significant main effects or interactions.

Relationships between relative insular volume [(absolute volume/ICV) × 100] and the clinical variables were analyzed using Spearman's rank correlation coefficients because of skewed distribution of these variables (i.e., illness duration, medication dose). The amygdala volume was available for 162 FEP and 61 control subjects (Velakoulis et al., 2006). Pearson's partial correlation coefficients, controlling for ICV, were calculated to examine relationship between the absolute volumes of the insular cortex and amygdala for each hemisphere. The volumes of the insula and amygdala were normally distributed (Kolmogorov–Smirnov test). The group difference between these correlations was tested using Fisher's Z transformation. Statistical significance was defined as $p<0.05$.

3. Results

Comparison of the groups revealed no significant difference in age, gender, handedness and height, but premorbid IQ was higher in controls than in schizophrenia patients (Table 1). Illness duration and medication dosage did not differ significantly between the patient groups.

Repeated measures ANCOVA of the insular cortex volume revealed significant main effects for group [$F(4,212)=9.13$, $p<0.001$], side [$F(1,214)=21.85$, $p<0.001$], and subregion [$F(1,214)=2319.36$, $p<0.001$] and significant group-by-subregion [$F(4,214)=3.23$, $p=0.013$] and side-by-subregion [$F(1,214)=6.88$, $p=0.009$] interactions. Post hoc tests showed that the total insular cortex volume was significantly smaller in schizophrenia patients compared with controls ($p<0.001$, left = −13%, right = −13%), but there was no difference between the remaining FEP subgroups and controls (affective psychosis, $p=0.999$, left = −1.6%, right = −1.9%; schizophreniform disorder, $p=1.000$, left = −0.5%, right = +0.8%; other psychoses, $p=0.560$, left = −4.5%, right = −4.3%). Lower order analyses showed that the schizophrenia patients had a significantly smaller anterior insula than all other groups and a significantly smaller posterior insula than controls, affective psychosis patients, and schizophreniform disorder patients (Table 2, Fig. 2). The anterior insular cortex was larger in the left than in the right hemisphere for all diagnostic groups.

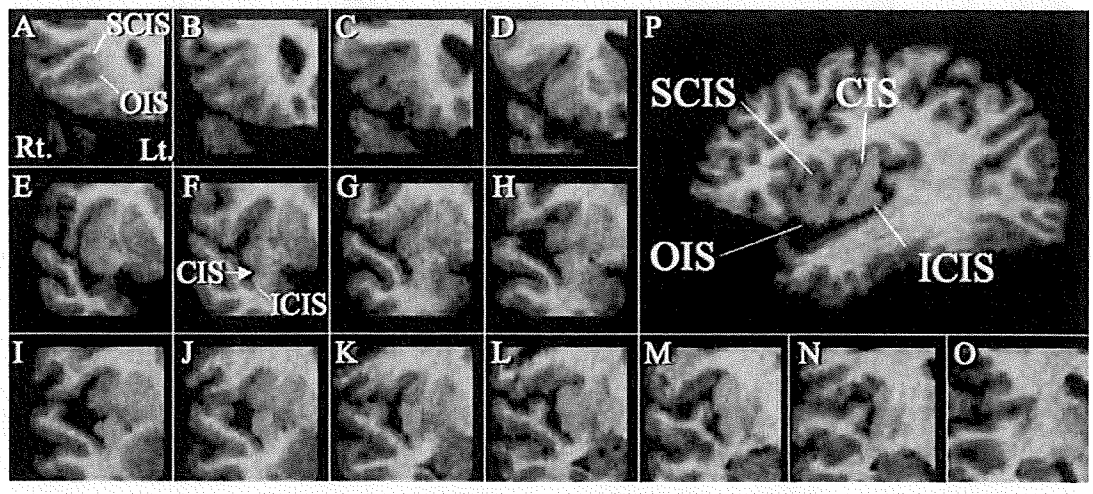

Fig. 1. Region of interest manually traced in this study. The sample coronal slices (panels A–O) show delineations of the right anterior (blue) and posterior (red) insular cortices, and panel P shows a sagittal view of the right insular cortex. Abbreviations: CIS = central insular sulcus; ICIS = inferior circular insular sulcus; OIS = orbitoinsular sulcus; SCIS = superior circular insular sulcus.

Table 2
Absolute gray matter volumes of the whole brain and insular cortex (mm^3) and number of 0.938-mm coronal slices used to measure the insular volume.

Brain region	Controls		Sz		Szform		Aff		Other		Analysis of covariance[a]					
	(N=62)		(N=46)		(N=57)		(N=34)		(N=25)		Group		Side		Group×side	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	P	F	p	F	p
Whole gray matter	756,092	78,385	715,788	73,477	758,580	58,244	735,991	70,346	729,585	66,706	1.85	0.120	-		-	
Number of slices											6.00	<0.001	54.44	<0.001	0.46	0.764
Left[b]	60.4	4.3	56.5[c]	3.7	59.6	4.0	59.8	4.3	57.5	3.5						
Right	59.0	4.9	54.8[c]	3.6	57.8	3.7	58.1	4.0	56.8	5.2						
Anterior insular cortex											8.64	<0.001	20.55	<0.001	1.37	0.247
Left[b]	5433	861	4661[d]	657	5390	677	5357	843	5359	860						
Right	5285	713	4515[d]	788	5295	615	5166	754	4991	789						
Posterior insular cortex											3.75	0.006	0.12	0.730	0.87	0.485
Left	3172	632	2808[e]	587	3172	493	3114	643	2863	500						
Right	3079	480	2776[e]	566	3132	488	3036	604	3010	569						

Aff, affective psychosis; Other, other psychoses; Sz, schizophrenia; Szform, schizophreniform.

[a] Anterior and posterior insular cortices were separately analyzed with age and intracranial volume as covariates, group and gender as between-subject factors, and side as a within-subject variable. Number of slices was analyzed using the same model, $Df = 4, 212$ for the effect of group, 1, 214 for the effect of side, and 4, 214 for group-by-side interaction. The effect involving gender was not significant for both anterior and posterior insular cortices as well as slice number, but whole gray matter was larger in males than in females [ANCOVA, $F(1,212) = 4.74$, $p = 0.031$; post hoc test, $p < 0.001$].

The statistical conclusions did not change when we analyzed data using relative insular cortex volume (100 × absolute volume/intracranial volume) with age as a covariate.

[b] $p < 0.001$: larger than on right side.

[c] $p < 0.001$: smaller than controls, Szform, and Aff.

[d] $p < 0.001$: smaller than controls, Szform, and Aff; $p = 0.001$: smaller than Other.

[e] $p < 0.001$: smaller than controls and Szform; $p = 0.004$: smaller than Aff.

Number of coronal slices used to measure the insular cortex volume was significantly fewer in schizophrenia patients than in controls, affective psychosis patients, and schizophreniform disorder patients (Table 2), suggesting that the insular cortex volume changes in schizophrenia demonstrated in this study were at least partly related to shortening of the anterior–posterior length.

Exclusion of schizoaffective disorder patients ($N = 15$), who were categorized together with established schizophrenia patients ($N = 31$), did not change the ANCOVA results of the anterior insula [effect of group, $F(4,197) = 6.19$, $p < 0.001$], while the group difference of the posterior insula became a trend-level [$F(4,197) = 2.28$, $p = 0.062$]. However, insular cortex volume did not differ significantly between patients with schizoaffective disorder and schizophrenia [$F(1,42) = 0.05$, $p = 0.833$]. In contrast, schizoaffective patients had significantly smaller insular cortex compared with affective psychosis patients [ANCOVA, $F(2,44) = 3.98$, $p = 0.026$; post hoc test, $p < 0.001$]. No significant difference was found between the two affective psychosis subgroups [i.e., bipolar disorder ($N = 22$) and major

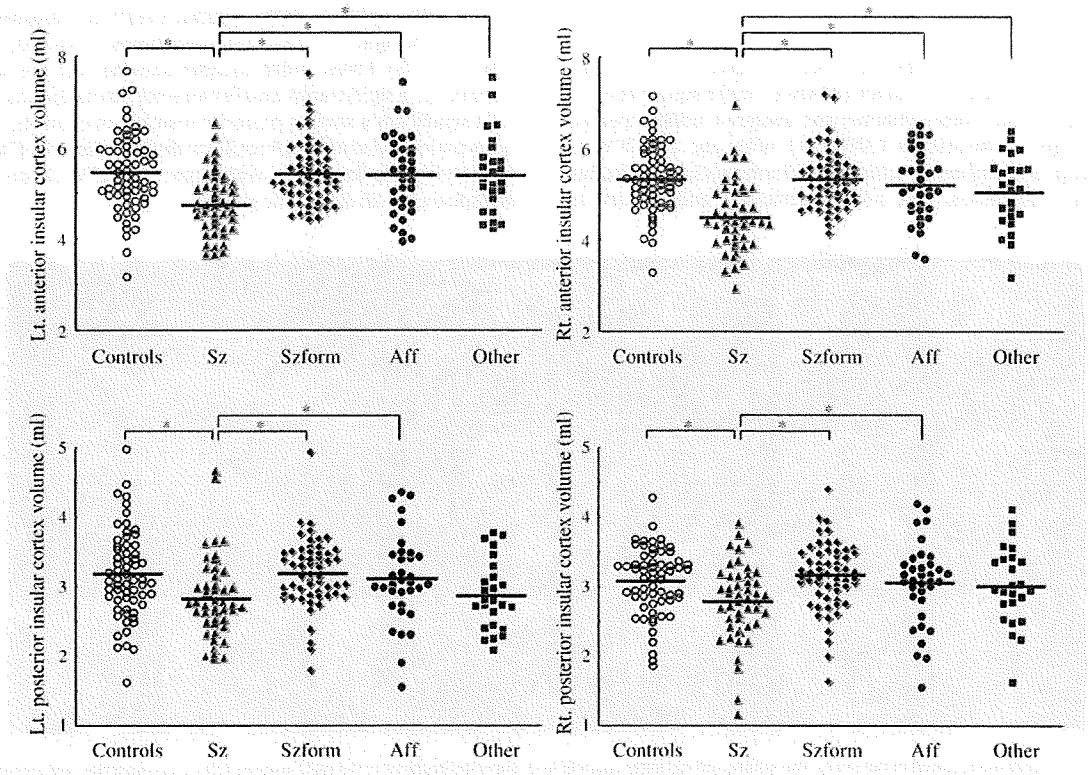

Fig. 2. Scatter plots of absolute volumes of anterior and posterior insular cortices in healthy controls, first-episode patients with schizophrenia (Sz), schizophreniform psychosis (Szform), affective psychosis (Aff), and other psychoses (Other). Horizontal bars indicate means of each group. *$p < 0.01$.

depression ($N = 12$)] [$F(1,30) = 1.63$, $p = 0.212$]. Insular cortex volume did not differ between patients taking typical ($N = 42$) and atypical ($N = 108$) antipsychotic medications [$F(1,146) = 0.55$, $p = 0.460$].

There was a negative correlation between the right posterior insular cortex volume and illness duration (rho = −0.344, $p = 0.022$) only in first-episode schizophrenia patients, but the insular cortex volume was not correlated with dosage of antipsychotic medication in any patient group. For healthy controls, the anterior insular volume was correlated with amygdala volume in both hemispheres (left, $r = 0.286$, $p = 0.027$; right, $r = 0.374$, $p = 0.003$). This correlation remained significant on right hemisphere even after Bonferroni correction [two comparisons on each hemisphere, $p < 0.0125$ (0.05/4)]. We then tested whether there were any alterations in this normal relationship between these regions on right hemisphere in the FEP subgroups. Right anterior insular cortex volume in affective psychosis patients was correlated with right amygdala volume ($r = 0.417$, $p = 0.016$). No significant correlation was found between the volumes of the right anterior insular cortex and amygdala for schizophreniform ($r = 0.217$, $p = 0.108$) or other psychoses ($r = 0.033$, $p = 0.877$) groups. In contrast, for schizophrenia patients, there was a negative correlation between these volumes ($r = -0.323$, $p = 0.031$); this correlation was significantly different from that in the controls ($p < 0.001$). This disruption of normal correlation remained significant even after excluding 15 schizoaffective disorder patients ($r = -0.252$, $p = 0.179$; versus controls, $p = 0.005$).

4. Discussion

The current MRI study investigated gray matter volumes of the insular subdivisions in first-episode patients with various psychotic disorders (schizophrenia, schizophreniform disorder, affective psychosis, and other psychoses). As predicted, the schizophrenia patients showed widespread gray matter reduction in the insular cortex compared with healthy comparison subjects, whereas the schizophreniform and affective psychosis patients had normal insular volumes. The 'other psychoses' group, which included small numbers of patients with less common diagnoses (e.g., delusional disorder, brief psychosis), also did not exhibit significant insular volume changes compared with controls. Our findings thus suggest that morphologic changes of the insular cortex are specific to schizophrenia among various disorders with psychotic features.

Consistent with previous MRI studies of first-episode schizophrenia (Crespo-Facorro et al., 2000; Kasai et al., 2003b), we found marked gray matter reductions of the insular cortex bilaterally in first-episode schizophrenia patients, indicating that these changes are unlikely due to the effects of chronic medication or choronicity of the illness. Regarding the subdivisional specificity, the more peri-allocortical anterior insula, which has extensive connections with the peri-allocortical sector of the temporal pole, orbitofrontal cortex, and amygdala, is more involved in emotional and language-related functions (e.g., speech production), whereas the more peri-isocortical (granular) posterior insula has dense reciprocal connections with somatosensory association cortex and includes somatosensory and auditory processing areas (Augustine, 1996; Bamiou et al., 2003; Nagai et al., 2001; Naidich et al., 2004; Türe et al., 1999). The present findings are in line with previous region of interest (ROI)-based studies of insular subdivisions in schizophrenia indicating a global (Kasai et al., 2003b; Saze et al., 2007; Takahashi et al., 2005) or anterior-predominant (Makris et al., 2006) reduction, as we found larger reduction in the anterior [effect size (Cohen's d) = 1.0] rather than in the posterior [effect size (Cohen's d) = 0.6] subdivision compared with controls (Table 2). The insular cortex has reciprocal connections with the amygdala (Augustine, 1996), but the normal positive correlation between the volumes of these structures was reversed in schizophrenia patients. Interestingly, a recent postmortem finding of neuronal somal size reduction within the insular cortex specific to schizophrenia suggested an alteration in connectivity between the insular cortex and related brain regions at the cellular level (Pennington et al., 2008). These observations support the disconnection hypothesis of schizophrenia (Friston, 1998) and further suggest that disconnectivity within functional networks involving the insular cortex may underlie the pathophysiology of schizophrenia.

In contrast to significant insular volume changes in schizophrenia, our negative insular findings in affective psychoses are in line with previous ROI-based (Kasai et al., 2003b) and voxel based morphometric (VBM) (McDonald et al., 2005) MRI studies that demonstrated insular gray matter reduction in schizophrenia but not in affective psychosis patients. In addition to the overlap in clinical presentations (e.g., mania with psychosis versus schizoaffective disorders), several lines of evidence suggest that bipolar disorder with psychotic features is quite similar to schizophrenia in genetic and neurobiological respects (Maier et al., 2006; Murray et al., 2004). However, previous neuroimaging studies in established schizophrenia have demonstrated that structural and functional abnormalities of the insular cortex could underlie the greater level of negative symptoms (Crespo-Facorro et al., 2001a; Sigmundsson et al., 2001; Takahashi et al., 2004) and more pronounced cognitive impairments (Crespo-Facorro et al., 2001b; Curtis et al., 1998) in schizophrenia compared to bipolar disorder. The present and these previous MRI findings thus imply that the insular cortex abnormalities are associated with different underlying pathological mechanisms between schizophrenia and affective psychosis. On the other hand, two VBM studies in affective disorders have provided conflicting results; Morgan et al. (2007) reported regional gray matter deficits including the left insular region in affective psychosis but not in schizophrenia, while Lochhead et al. (2004) showed increased left insular volume in bipolar disorder patients compared with controls. These differences across studies may be partly explained by medication effects (Morgan et al., 2007; Pressler et al., 2005), illness heterogeneity [e.g., psychotic and non-psychotic subtypes (Strasser et al., 2005)], and methodological issues [VBM versus ROI approach (Giuliani et al., 2005)].

Assuming that the schizophreniform group only differs from schizophrenia on duration of symptoms, the lack of insular findings in this group raises the possibility that the insular abnormalities are related to persistent psychosis or chronic course. The insular cortex has been associated with sensory and memory functions (Augustine, 1996), and damage may lead to perceptual disturbances that can account for several psychotic symptoms (Crespo-Facorro et al., 2000). Together with our previous data of normal insular volume in schizotypal disorder (Takahashi et al., 2005), however, the current data suggest that the gray matter reductions of the insular cortex are specific to schizophrenia even among schizophrenia spectrum disorders that have attenuated or transient psychosis.

The present study provides evidence of diagnostically-specific insular cortex abnormalities in schizophrenia at first presentation, while a few longitudinal studies have demonstrated that first-episode patients with bipolar disorder have, at least partly, similar gray matter changes (e.g., cingulate gyrus) over time as those observed in schizophrenia (Farrow et al., 2005; Koo et al., 2008). Our own data identified that the insular cortex abnormalities associated with psychotic disorders (predominantly schizophrenia spectrum) predate the onset of overt psychosis (Pantelis et al., 2003) but further progress over time during the prodromal phase (unpublished data) as well as the early phase after the illness onset (Takahashi et al., 2009), although it was not possible to examine diagnostic subgroups of psychosis in these studies. Previous functional neuroimaging studies have demonstrated abnormal metabolism and function of the insula in various neuropsychiatric disorders such as affective disorders (reviewed by Nagai et al., 2007). These findings raise the possibility that other neuropsychiatric disorders also exhibit some forms of deficits in the insular cortex, which may be difficult to assess with structural MRI especially early in the course of illness. Thus, the morphologic differences and similarities of the insular cortex

abnormalities among various psychoses in the course of the illnesses should be further tested in a longitudinal design.

Several limitations of the current study should be taken into account. First, although the insular cortex abnormalities in schizophrenia have been implicated in both positive and negative symptoms as described above, detailed clinical data of the patients such as the symptomatology and clinical course were not available, representing a clear limitation of the study. Second, most patients in this study were receiving antipsychotic for a brief period. A relationship between gray matter reduction and typical antipsychotics has been reported in schizophrenia, while atypical antipsychotics may ameliorate structural changes (Scherk and Falkai, 2006). Given the similar medication status among our patient groups, however, the effects of medication alone could not explain a specific gray matter reduction in schizophrenia. In addition, we found no relationship between insular cortex volume and type or dosage of antipsychotics in any patient group, suggesting that a short period of medication (approximately 4 weeks) might not significantly affect brain morphology. More affective psychosis patients (9 of 34 patients, 26.5%) were taking lithium, which may increase gray matter volume (Moore et al., 2000), compared with other FEP groups (8 of 128 patients, 6.3%), but exclusion of the patients receiving lithium did not change the findings. Finally, we included schizoaffective disorder patients in the schizophrenia group despite the debate on it as a separate diagnostic entity (Averill et al., 2004). In this study, however, the insular cortex volume did not differ between schizoaffective psychosis and established schizophrenia patients. In contrast, the schizoaffective patients had significantly smaller insular cortex compared with affective psychosis patients, suggesting that schizoaffective disorder may represent a variant of schizophrenia rather than of affective disorder or an intermediate condition between these disorders (Evans et al., 1999).

5. Conclusion

We have demonstrated that bilateral gray matter reductions of the anterior and posterior insular cortices are specific to first-episode schizophrenia patients among first-episode patients with various psychotic disorders. These changes are unlikely due to the effects of medication. Our findings thus implicate global abnormalities of the insular cortex as having a role in the neurobiology of schizophrenia specifically.

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ORIGINAL ARTICLE

Progressive Gray Matter Reduction of the Superior Temporal Gyrus During Transition to Psychosis

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Context: Longitudinal magnetic resonance imaging studies have shown progressive gray matter reduction in the superior temporal gyrus during the earliest phases of schizophrenia. It is unknown whether these progressive processes predate the onset of psychosis.

Objective: To examine gray matter reduction of the superior temporal gyrus over time in individuals at risk for psychosis and in patients with first-episode psychosis.

Design: Cross-sectional and longitudinal comparisons.

Setting: Personal Assessment and Crisis Evaluation Clinic and Early Psychosis Preventions and Intervention Centre.

Participants: Thirty-five ultrahigh-risk individuals (of whom 12 later developed psychosis [UHRP] and 23 did not [UHRNP]), 23 patients with first-episode psychosis (FEP), and 22 control subjects recruited from the community.

Main Outcome Measures: Volumes of superior temporal subregions (planum polare, Heschl gyrus, planum temporale, and rostral and caudal regions) were measured at baseline and follow-up (mean, 1.8 years) and were compared across groups.

Results: In cross-sectional comparisons, only the FEP group had significantly smaller planum temporale and caudal superior temporal gyrus than other groups at baseline, whereas male UHRP subjects also had a smaller planum temporale than controls at follow-up. In longitudinal comparison, UHRP and FEP patients showed significant gray matter reduction (approximately 2%-6% per year) in the planum polare, planum temporale, and caudal region compared with controls and/or UHRNP subjects. The FEP patients also exhibited progressive gray matter loss in the left Heschl gyrus (3.0% per year) and rostral region (3.8% per year), which were correlated with the severity of delusions at follow-up.

Conclusions: A progressive process in the superior temporal gyrus precedes the first expression of florid psychosis. These findings have important implications for underlying neurobiologic features of emerging psychotic disorders and emphasize the importance of early intervention during or before the first episode of psychosis.

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SEVERAL LINES OF EVIDENCE SUPport the notion that schizophrenia arises as a consequence of both an "early neurodevelopmental" disturbance[1] and a pathological process in "late neurodevelopment" occurring during the initial stage of illness.[2-5] Previous magnetic resonance (MR) imaging studies have demonstrated progressive brain changes in the years following illness onset,[4,6-11] whereas more recent longitudinal studies of high-risk populations around the period of transition to psychosis have provided a clue to the underlying neurobiologic features of emerging psychotic disorders.[12-15]

In our previous voxel-based morphometric (VBM) study in ultrahigh-risk (UHR) individuals, those who had developed psychosis within 12 months (30%-40% of UHR subjects)[16,17] showed progressive gray matter reductions in temporal, orbitofrontal, and cingulate regions[13] over the transition phase, although there was no significant group × follow-up interaction in that study, comparing those who developed psychosis with those who did not. In a VBM study from the Edinburgh High-Risk Study,[18] genetically high-risk individuals with transient or isolated psychosis or who later developed schizophrenia showed progressive changes mainly in the left temporal lobe regions.[12] Despite the lack of a comparison cohort of patients with first-episode psychosis (FEP) and potential methodologic problems of brain registration,[19] these VBM findings provide evidence that brain abnormalities associated with psychotic disorders predate the on-

set of frank symptoms and are not due to medication. Our recent study based on cortical pattern matching,[20] which allows more sensitive analysis of the lateral cortical surface than does VBM, demonstrated increased brain surface contraction in prefrontal regions during illness transition.[14] This approach cannot examine the medial brain surface or detailed cortical regions in deep sulci such as Heschl gyrus (HG).

Morphologic abnormalities of the superior temporal gyrus (STG)[21-23] and its functionally relevant subregions such as the primary auditory cortex (HG)[24-26] and planum temporale (PT),[24,26-29] a neocortical language region,[30] have been repeatedly described in schizophrenia. Volume reduction of these regions, especially in the left hemisphere, have been found to correlate with auditory hallucinations or thought disorder.[26,31-34] In contrast, the auditory association cortex located anterior to the HG (planum polare [PP]) or the lateral portion of the STG, which is related to auditory speech perception[35] or mentalizing tasks,[36] have rarely been studied as specific regions of interest (ROIs) in psychotic disorders. Longitudinal MR imaging studies in first-episode schizophrenia have reported marked progressive reductions in left posterior portions of the STG gray matter during the initial years after the first hospitalization.[8,9] These changes were highly correlated with progressive impairments of the normal neurophysiologic response of the region, specifically mismatch negativity.[37] However, progressive gray matter changes of other STG subregions are not well documented. Borgwardt et al[38] demonstrated that clinical high-risk subjects, recruited via criteria similar to ours, had a smaller left STG than did control subjects in a cross-sectional VBM study, whereas one volumetric MR imaging study in genetically high-risk individuals reported bilateral STG reduction.[39] An inverse correlation between the volume of the left STG, especially the PT, and the duration of the initial untreated period of psychosis in schizophrenia[40,41] suggests a regional progressive pathological process in the STG during the earliest stages of psychosis. To our knowledge, no ROI-based MR imaging studies have undertaken a detailed longitudinal examination of the STG subregions in a high-risk cohort.

The present study aimed to clarify the timing and course of the gray matter changes of the STG as well as its subregions in psychotic disorders by detailed ROI analyses of longitudinal MR imaging data in healthy controls, individuals at UHR of developing psychosis, and patients with FEP. On the basis of our own[13] and other[8,9] work, we predicted that UHR subjects who later developed psychosis (UHRP) would show progressive gray matter loss in the STG during the transition into psychosis to a degree similar to that observed in FEP, and that UHR subjects who did not develop psychosis (UHRNP) would not show marked STG volume changes over time.

METHODS

PARTICIPANTS

Thirty-five UHR subjects were recruited from admissions to the Personal Assessment and Crisis Evaluation Clinic.[17,42] The UHR identification criteria (**Table 1**) and the rationale for these criteria have been previously described.[16,17] The UHR subjects were assessed with the Brief Psychiatric Rating Scale,[43] the Scale for the Assessment of Negative Symptoms,[44] and the Comprehensive Assessment of At Risk Mental States.[45] All UHR subjects were approximately age 14 to 30 years, had not experienced a previous psychotic episode, had never received antipsychotic medication, and were not intellectually disabled (IQ >70). After baseline MR imaging, UHR subjects were monitored regularly on the basis of operationalized criteria for psychosis onset[17] and were then divided into subgroups according to 12-month outcome; 12 UHR subjects (34%) developed psychosis (UHRP) and 23 (66%) did not (UHRNP). The disorders in the 12 UHRP subjects were schizophrenia (n=4), schizoaffective disorder (n=1), brief psychotic episode (n=1), psychosis not

Table 1. Ultrahigh-Risk Intake and Exit Criteria[a]

	Criteria
Intake criteria	
Group 1: attenuated psychotic symptoms	Presence of ≥1 of following symptoms: idea of reference, magical thinking, perceptual disturbance, paranoid ideation, and odd thinking and speech (score of 2-3 on unusual thought content subscale, 1-2 on hallucinations subscale, 2-3 on suspiciousness subscale, or 1-3 on conceptual disorganization subscale of BPRS)
	Held with reasonable degree of conviction, as defined by score of 2 on CASH rating scale for delusions
	Frequency of symptoms is several times a wk
	Change in mental state present for ≥1 wk but not longer than 5 y
Group 2: BLIPS	Transient psychotic symptoms: presence of ≥1 of following symptoms: idea of reference, magical thinking, perceptual disturbance, paranoid ideation, and odd thinking and speech (score of ≥4 on unusual thought content subscale, ≥3 on hallucinations subscale, ≥4 on suspiciousness subscale [or it is held with strong conviction, as defined by score of ≥3 on CASH rating subscale for delusions], or ≥4 on conceptual disorganization subscale of BPRS)
	Duration of episode of <1 wk
	Symptoms resolve spontaneously
	BLIPS must have occurred within past year
Group 3: trait and state risk factors	First-degree relative with psychotic disorder or schizotypal personality disorder or individual has schizotypal personality disorder
	Significant decrease in mental state or functioning maintained for ≥1 mo (reduction in GAF scale of 30 points from premorbid level)
	Decrease in functioning occurred within past year
Exit criteria: acute psychosis	Presence of ≥1 of following symptoms: hallucinations (defined by score of ≥3 on hallucinations subscale of BPRS), delusions (defined by score of ≥4 on unusual thought content subscale of BPRS or ≥4 on suspiciousness subscale of BPRS), or it is held with strong conviction, as defined by score of ≥3 on CASH rating scale for delusions or formal thought disorder (defined by score of ≥4 on conceptual disorganization subscale of BPRS)
	Frequency of symptoms is at least several times a week to daily
	Duration of mental state change is >1 wk

Abbreviations: BLIPS, brief limited intermittent psychotic symptoms; BPRS, Brief Psychiatric Rating Scale; CASH, Comprehensive Assessment of Symptoms and History; GAF, Global Assessment of Function.
[a] People were included if they met criteria for 1 or more of the 3 groups.

Table 2. Demographic and Clinical Data of Healthy Control Subjects, UHR Individuals, and Patients With FEP[a]

		UHR Subjects			
	Control Subjects (n=22)	Nonpsychotic (n=23)	Psychotic (n=12)	Patients With FEP (n=23)	Group Comparisons
Sex, No. M/F	12/10	12/11	7/5	16/7	χ^2=1.68, *P*=.64
Handedness, No. right/mixed/left[b]	22/0/0	18/1/4	10/0/2	18/0/5	χ^2=7.70, *P*=.26
Height, cm[c]	175.3 (12.0)	169.0 (10.1)	173.2 (9.2)	171.3 (7.8)	$F_{3,69}$=1.43, *P*=.24[d]
Premorbid IQ[e]	102.7 (9.6)	93.3 (13.7)	94.3 (13.6)	92.8 (15.0)	$F_{3,61}$=2.30, *P*=.09[d]
Age at baseline imaging, y	22.0 (4.7) [16.2 to 32.8]	20.2 (4.0) [14.3 to 27.5]	19.5 (5.1) [13.9 to 29.1]	21.6 (3.5) [16.8 to 28.3]	$F_{3,76}$=1.28, *P*=.29[d]
Age at second imaging, y	24.1 (4.9) [18.1 to 35.7]	21.6 (4.0) [15.4 to 28.5]	20.7 (5.2) [15.4 to 30.9]	23.6 (4.0) [17.7 to 32.3]	$F_{3,76}$=2.29, *P*=.08[d]
Days between images	780 (312) [313 to 1428]	511 (289) [329 to 1361]	443 (186) [237 to 826]	739 (279) [294 to 1527]	$F_{3,76}$=6.39, *P*<.001[d]
Age at onset, y	NA	NA	20.1 (5.0) [15.3 to 29.5]	21.4 (3.6) [15.6 to 28.3]	$F_{1,33}$=0.78, *P*=.38[d]
Days between baseline image and onset	NA	NA	211 (141) [84 to 538]	NA	NA
Days between onset and baseline image	NA	NA	NA	64 (102) [−2 to 429]	NA
Days between onset and second image	NA	NA	232 (144) [15 to 534]	803 (266) [345 to 1676]	$F_{1,33}$=47.46, *P*<.001[d]
BPRS score at intake	NA	18.0 (7.7)	20.1 (8.7)	NA	$F_{1,33}$=0.53, *P*=.47[d]
SANS score at intake	NA	18.7 (10.7)	29.3 (16.1)	NA	$F_{1,33}$=5.43, *P*=.03[d]
PANSS positive at follow-up[f]	NA	NA	NA	20.6 (7.8)	NA
PANSS negative at follow-up[f]	NA	NA	NA	18.7 (7.9)	NA
PANSS general at follow-up[f]	NA	NA	NA	40.7 (10.3)	NA
Intracranial volume, cm^3	1401.7 (149.9)	1415.3 (154.3)	1485.6 (135.8)	1402.0 (137.4)	$F_{3,75}$=1.12, *P*=.35[d]

Abbreviations: BPRS, Brief Psychiatric Rating Scale; FEP, first-episode psychosis; NA, not applicable; PANSS, Positive and Negative Syndrome Scale; SANS, Scale for the Assessment of Negative Symptoms; UHR, ultrahigh-risk.

[a] Data are presented as mean (SD) [range].

[b] Effect of handedness on the laterality of the superior temporal gyrus in patients with FEP was tested by means of a laterality index (eTable 1, http://www.archgenpsychiatry.com).

[c] Data were not available for 7 subjects.

[d] By analysis of variance.

[e] National Adult Reading Test data were available for 65 subjects (18 controls, 18 UHR nonpsychotic subjects, 11 UHR psychotic subjects, and 18 with FEP).

[f] Data were available for 21 patients with FEP.

otherwise specified (n=1), bipolar disorder with psychotic features (n=2), and major depression with mood incongruent psychotic disorder (n=3). After baseline imaging, 9 subjects (7 without and 2 with psychosis) received risperidone (mean dosage, 1.3 mg/d) and cognitive behavior therapy, and 5 (3 without and 2 with psychosis) received supportive therapy as part of a double-blind randomized study examining a 6-month therapeutic intervention study.[42] Most UHRP subjects received atypical antipsychotics after onset, but complete information on medications was not available. Three subjects (2 without and 1 with psychosis) were receiving antidepressants at baseline for depressive symptoms.

Twenty-three FEP inpatients were recruited from the Early Psychosis Preventions and Intervention Centre.[46] Inclusion criteria for FEP patients were (1) age at onset between 16 and 30 years and (2) current psychosis as reflected by the presence of at least 1 symptom (delusions, hallucinations, disorder of thinking and/or speech other than simple acceleration or retardation, and disorganized, bizarre, or markedly inappropriate behavior).[47] The *DSM-IV* diagnoses were based on medical record review, Structured Clinical Interview for *DSM-IV*,[48] and the Royal Park Multidiagnostic Instrument for Psychosis[49] administered during the initial treatment episode (median illness duration, 29.0 days). All patients were neuroleptic-naive before admission, but 17 had received neuroleptics for a short period before the first imaging; 8 were treated with atypical antipsychotics and 9 were receiving typical antipsychotics (mean [SD] dosage, 161.8 [102.2] mg/d, chlorpromazine equivalent). Accurate values for the duration of medication use were not available, but the mean duration of such a period in our center is about 30 days.[47] Patients were also receiving benzodiazepines (n=10), antidepressants (n=2), and/or lithium carbonate (n=3). The medication status was unknown for 4 patients at the first imaging. The final diagnoses of these patients during the follow-up were as follows: schizophrenia (n=16; 3 paranoid, 3 disorganized, 3 undifferentiated, and 7 residual subtypes), schizoaffective disorder (n=3), schizophreniform disorder (n=1), delusional disorder (n=1), psychotic disorder not otherwise specified (n=1), and a psychosis with affective features (diagnosis by Structured Clinical Interview for *DSM-IV* unavailable, n=1). Clinical symptoms were assessed at follow-up imaging by means of the Positive and Negative Syndrome Scale (PANSS)[50] (**Table 2**). At the second imaging, 15 of 23 patients were taking antipsychotic medication; 8 were using atypical antipsychotics and 7 were using typical antipsychotics (mean [SD] dosage, 193.5 [198.9] mg/d, chlorpromazine equivalent). They were also receiving benzodiazepines (n=4), antidepressants (n=2), lithium carbonate (n=2), or combination lithium carbonate and valproate sodium (n=1). Twenty-two healthy volunteers were recruited from sociodemographic areas similar to those of the patients by approaching ancillary hospital staff and through advertisements.[47]

Clinical information including handedness, illness onset, premorbid IQ (where available) as assessed by the National Adult Reading Test,[51] and medication data was obtained from patient interview and medical record review. All participants were screened for comorbid medical and psychiatric conditions by clinical assessment and physical and neurologic examination. Exclusion criteria were a history of significant head injury, neurologic diseases, impaired thyroid function, corticosteroid use, or *DSM-IV* criteria for alcohol or substance abuse or dependence.[52] Comparison subjects with a personal or family history of psychiatric illness were excluded. This study was approved by local research and ethics committees. Written informed consent was obtained from all subjects.

There is overlap between the subjects in this study and those in our previous longitudinal MR imaging studies. Of the 35 UHR subjects, 20 subjects also participated in our VBM study.[13] All

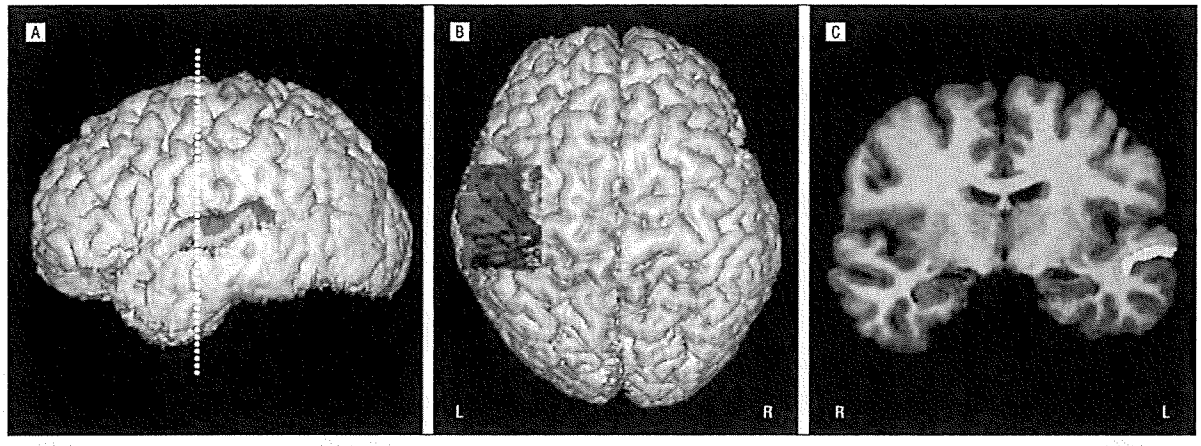

Figure 1. Three-dimensional reconstructed images presenting lateral (A) and top-down (B) views and a sample coronal image (C) of superior temporal subregions of the left hemisphere. The frontal and parietal lobes in B are partially cut away to disclose the regions examined. The lateral superior temporal gyrus (STG) was further subdivided into rostral STG and caudal STG by a plane containing the anterior end of the Heschl gyrus (dotted line in A). Each of the STG subregions is differentially colored: planum polare, green; Heschl gyrus, blue; planum temporale, red; and lateral STG, yellow.

35 UHR subjects, 16 of 23 FEP patients, and 14 of 22 controls were included in our recent studies using cortical pattern matching.[10,14] Eighteen FEP patients and 20 controls were the same as those in our study of the hippocampus.[11]

MR IMAGE ACQUISITION AND PROCESSING

Subjects underwent imaging twice on a 1.5-T imager (GE Signa; General Electric Medical Systems, Milwaukee, Wisconsin). A 3-dimensional volumetric spoiled gradient–recalled echo in the steady state sequence generated 124 contiguous 1.5-mm coronal sections. Imaging parameters were as follows: echo time, 3.3 milliseconds; repetition time, 14.3 milliseconds; flip angle, 30°; matrix size, 256 × 256; field of view, 24 × 24-cm matrix; and voxel dimensions, 0.9375 × 0.9375 × 1.5 mm. Head movement was minimized by using foam padding and Velcro straps across the forehead and chin. The imager was calibrated fortnightly with the same proprietary phantom to ensure the stability and accuracy of measurements.

On a Unix workstation (Silicon Graphics Inc, Mountain View, California), the image data were coded randomly and analyzed with the software package Dr View (AJS, Tokyo, Japan). Brain images were realigned in 3 dimensions to standardize for differences in head tilt and reconstructed into entire contiguous coronal images, with a 0.9375-mm thickness, perpendicular to the intercommissural line. The whole cerebrum was manually separated from the brainstem and cerebellum. According to the Alpert algorithm,[53] the signal-intensity histogram distributions from the T1-weighted images across the whole cerebrum were then used to semiautomatically segment the voxels into gray matter, white matter, and cerebrospinal fluid.[54] The intracranial volume (ICV) was measured on a sagittal reformat of the original 3-dimensional data set using the dura mater, undersurface of the frontal lobe, dorsum sellae, clivus, and C1 vertebra as major landmarks to correct for differences in head size[55,56]; the 4 groups did not differ significantly in their ICVs (Table 2).

VOLUMES OF STG SUBREGIONS

The gray matter of the STG subregions (PP, HG, PT, rostral STG, and caudal STG) was manually traced on 0.9375-mm consecutive coronal sections (**Figure 1**).

The parcellation strategy and terminology have been previously described.[26] Briefly, on the basis of the established tracing guidelines,[57] the first coronal plane showing the temporofrontal junction and the coronal plane containing the posterior end of the posterior horizontal limb of the sylvian fissure were chosen as anterior and posterior boundaries of the whole STG, respectively. On each coronal section, the whole STG was bounded superiorly by the sylvian fissure and inferiorly by the superior temporal sulcus. The whole STG was then segmented into the supratemporal plane and inferior portion (lateral STG)[26,37] by the lateral limb of the supratemporal plane. The HG was traced posterior to anterior, beginning with the first section containing the Heschl sulcus and ending anteriorly with the section containing the most anterior point of the Heschl sulcus or the sulcus intermedius if it existed. On each coronal section, the HG was bounded medially by the sylvian fissure, inferior circular insular sulcus, or first transverse sulcus and laterally by the Heschl sulcus. When 2 convolutions were oriented separately from the retroinsular regions, the most anterior gyrus was regarded as the HG. When they were oriented medially from the common stem, however, both were defined as the HG. After tracing of the HG, which takes a diagonal course on the supratemporal plane, the regions lying anteromedial and posterolateral to the HG within the remaining gray matter of the supratemporal plane were regarded as the PP and PT, respectively. The inferior portion of the STG (lateral STG) was divided into rostral and caudal STG portions by the plane including the anterior tip of the HG.

All volumetric data reported herein were measured by 1 rater (T.T.), who was blinded to the subjects' identities and time of imaging. Intrarater (for T.T.)/interrater (between T.T. and Y.K.) intraclass correlation coefficients in 8 randomly selected brains in this sample were as follows: 0.96/0.88 (PP), 0.97/0.98 (HG), 0.96/0.95 (PT), 0.99/0.96 (rostral STG), and 0.98/0.93 (caudal STG).

STATISTICAL ANALYSIS

Clinical and demographic differences between groups were examined with 1-way analysis of variance or the χ^2 test.

For cross-sectional comparison at baseline and second imaging, the absolute STG volume was assessed by means of a repeated-measures analysis of variance with ICV as a covariate (analysis of covariance [ANCOVA]), with group (controls, UHRNP, UHRP, and FEP) and sex as between-subject factors, and subregion (PP, HG, PT, rostral STG, and caudal STG) and side (left and right) as within-subject variables. We then investigated each subre-

Table 3. Absolute Gray Matter Volume of the Whole Brain and Superior Temporal Gyrus Subregions at Baseline and Second Image and Annual Percentage of Change[a]

Brain Region	Mean (SD)			
		UHR Subjects		
	Control Subjects	Nonpsychotic	Psychotic	Patients With FEP
Whole brain				
Baseline	724 263 (84 307)	710 743 (95 937)	759 148 (78 830)	710 584 (63 151)
2nd image	701 540 (88 796)	706 167 (89 854)	738 340 (82 330)	685 085 (68 399)
% Change	−1.7 (2.4)	−0.5 (4.2)	−2.1 (5.0)	−1.5 (2.3)
Whole STG				
Left				
Baseline	13 461 (2587)	13 564 (3008)	13 475 (1902)	12 645 (2134)
2nd image	13 601 (2676)	13 606 (3134)	12 772 (1736)	11 714[b,c] (1900)
% Change	0.4 (1.8)	0.1 (4.8)	−5.0[b,c] (4.4)	−3.6[b,c] (2.9)
Right				
Baseline	11 801 (2390)	11 538 (2022)	12 221 (1930)	10 807 (1627)
2nd image	11 880 (2355)	11 473 (1970)	11 656 (1778)	10 404[b,c] (1391)
% Change	0.4 (2.1)	−0.5 (4.9)	−3.9[b] (5.7)	−1.5 (4.1)
Planum polare				
Left				
Baseline	1725 (580)	1874 (616)	2089 (302)	2130 (537)
2nd image	1754 (572)	1869 (632)	1958 (269)	2010 (529)
% Change	1.0 (4.3)	0.1 (7.9)	−5.6[b] (6.1)	−2.6[b] (4.5)
Right				
Baseline	1666 (509)	1664 (705)	1686 (389)	1817 (508)
2nd image	1658 (451)	1675 (738)	1559 (349)	1741 (508)
% Change	0.6 (4.1)	0.2 (5.9)	−6.3[c] (7.4)	−1.5 (4.6)
Heschl gyrus				
Left				
Baseline	2226 (585)	2135 (666)	2252 (908)	1804 (869)
2nd image	2242 (589)	2118 (691)	2150 (864)	1688 (787)
% Change	−0.1 (3.6)	−1.2 (5.4)	−4.3 (6.0)	−3.0[b] (3.6)
Right				
Baseline	1619 (483)	1655 (478)	1796 (587)	1470 (433)
2nd image	1632 (478)	1631 (490)	1728 (609)	1423 (365)
% Change	0.5 (3.9)	−1.3 (7.5)	−3.5 (8.3)	−0.7 (9.3)
Planum temporale				
Left				
Baseline	3519 (865)	3439 (989)	3096 (711)	3059[b,c,d] (627)
2nd image	3554 (836)	3474 (995)	2934[b,d] (678)	2845[b,c,d] (575)
% Change	0.9 (4.3)	0.9 (5.0)	−5.2[b,c] (5.2)	−3.3[b,c] (2.5)
Right				
Baseline	2846 (921)	2820 (750)	2974 (630)	2435[b,c,d] (614)
2nd image	2924 (918)	2819 (717)	2851[b,d] (616)	2331[b,c,d] (623)
% Change	2.1 (4.2)	0.3 (5.9)	−3.9[b] (4.9)	−2.2[b] (4.4)

(continued)

gion separately on the basis of a significant group × subregion interaction for both time points (**Table 3**).

For the longitudinal comparison, the STG changes over time (absolute volume at second imaging − absolute volume at baseline) were analyzed by means of a repeated-measures ANCOVA with ICV and interimage interval (year) as covariates, with group and sex as between-subject factors, and with subregion and side as within-subject variables. On the basis of interactions with subregion and side but no effects involving sex in this analysis (Table 3), 5 subregions for each hemisphere were then separately analyzed covarying for baseline volume of each subregion and interimage interval with only group as a between-subject factor. The post hoc Tukey honestly significant difference test was used.

For the FEP patients whose PANSS scores at follow-up were available (n = 21), Spearman ρ was calculated to explore correlations between the percentage of volume change per year of the left and right STG subregions and 4 selected positive syndrome subscores of PANSS (delusions, conceptual disorganization, hallucinatory behavior, and suspiciousness/persecution). To minimize type I error due to multiple comparisons, we limited the analyses to the severity of these positive symptoms based on previous observations.[26,31-33,39] Correlations between daily dosage of antipsychotics and relative volumes (100 × absolute volume/ICV) and annual gray matter loss (percentage of change) for each subregion as well as the PANSS subscores were also evaluated. Statistical significance was defined as $P < .05$ (2-tailed).

RESULTS

DEMOGRAPHIC VARIABLES

Groups were matched for age, sex, handedness, height, or premorbid IQ, but there was a difference in time be-

Table 3. Absolute Gray Matter Volume of the Whole Brain and Superior Temporal Gyrus Subregions at Baseline and Second Image and Annual Percentage of Change[a] (continued)

	Mean (SD)			
		UHR Subjects		
Brain Region	Control Subjects	Nonpsychotic	Psychotic	Patients With FEP
Lateral STG				
Left				
Baseline	5951 (1257)	6071 (1426)	5986 (828)	5599 (1020)
2nd image	6021 (1386)	6083 (1507)	5669 (713)	5119[b,c] (877)
% Change	0.2 (2.9)	−0.1 (5.5)	−5.0 (4.2)	−4.2[b,c] (3.8)
Right				
Baseline	5632 (1320)	5364 (959)	5736 (996)	5047 (840)
2nd image	5646 (1323)	5308 (892)	5497 (844)	4871[b,c] (688)
% Change	0.0 (3.2)	−0.8 (4.9)	−3.2 (6.0)	−1.4 (4.3)
Rostral STG				
Left				
Baseline	1335 (776)	1654 (945)	1721 (418)	1868 (808)
2nd image	1339 (775)	1675 (967)	1631 (365)	1675 (581)
% Change	0.0 (5.2)	0.8 (10.5)	−4.3 (7.1)	−3.8[b,c] (6.2)
Right				
Baseline	1356 (685)	1290 (744)	1343 (625)	1490 (600)
2nd image	1344 (641)	1277 (751)	1282 (571)	1451 (596)
% Change	0.0 (3.7)	−1.6 (7.2)	−2.6 (7.5)	−1.5 (3.8)
Caudal STG				
Left				
Baseline	4616 (1055)	4416 (1095)	4264 (1073)	3730[b,c,e] (885)
2nd image	4682 (1161)	4408 (1079)	4038 (902)	3444[b,c,e] (829)
% Change	0.3 (3.2)	−0.1 (5.1)	−4.8[b] (5.3)	−3.9[b,c] (3.2)
Right				
Baseline	4276 (1264)	4074 (830)	4394 (1068)	3557[b,c,e] (802)
2nd image	4302 (1263)	4031 (763)	4215 (1051)	3420[b,c,e] (640)
% Change	0.1 (3.7)	−0.6 (5.4)	−3.6 (6.2)	−1.2 (6.1)

Abbreviations: FEP, first-episode psychosis; STG, superior temporal gyrus; UHR, ultrahigh-risk.

[a] Values indicate absolute volumes (in cubic millimeters) except percentage of change per year values, which were calculated as follows: (100 × [absolute volume at second imaging − absolute volume at baseline]/absolute volume at baseline)/interimaging interval (in years). Negative values indicate decreases in volume. The statistical analyses for longitudinal gray matter changes reported herein were based on absolute volume changes covarying for interimaging interval and baseline volume. Analysis of covariance (ANCOVA) of the whole STG at baseline showed significant main effects for side ($F_{1,72}$=77.51, P<.001) and subregion ($F_{4,288}$=265.42, P<.001) and group × subregion ($F_{12,288}$=2.93, P<.001) and sex × subregion ($F_{4,288}$=2.47, P=.045) interactions. An ANCOVA of the STG at follow-up showed significant main effects for group ($F_{3,71}$=4.36, P=.007), side ($F_{1,72}$=81.18, P<.001), and subregion ($F_{4,288}$=271.08, P<.001) and group × subregion ($F_{12,288}$=3.76, P<.001), sex × subregion ($F_{4,288}$=2.59, P=.04), and side × subregion ($F_{4,288}$=2.59, P=.04) interactions. For the lower-order ANCOVAs and post hoc tests of each subregion, see the "Results" section. An ANCOVA of the absolute STG volume change over time demonstrated significant main effects for group ($F_{3,70}$=6.83, P<.001) and subregion ($F_{4,286}$=2.84, P=.03) and group × side ($F_{3,72}$=3.40, P=.02) and group × subregion ($F_{12,288}$=2.02, P=.02) interactions. For the lower-order ANCOVAs and post hoc tests of each subregion, see text.

[b] Significantly different from controls.

[c] Significantly different from UHR nonpsychotic subjects.

[d] Significant only for males.

[e] Significantly different from UHR psychotic subjects.

tween imaging sessions (Table 2), with the interimaging interval being shorter in UHR subjects than in controls (UHRNP, P=.01; UHRP, P=.007) or FEP patients (UHRNP, P=.04; UHRP, P=.02). Mean interimaging interval of the whole sample was 1.8 years.

CROSS-SECTIONAL VOLUME COMPARISON

The results of the STG measures are summarized in Table 3. At baseline, ANCOVA of the caudal STG showed a significant group difference ($F_{3,71}$=4.12, P=.009); the FEP patients had a smaller caudal STG than did the other groups (vs controls, P=.004; UHRNP, P=.03; and UHRP, P=.046). An ANCOVA of the PT showed a significant group × sex interaction ($F_{3,71}$=3.05, P=.03), where male FEP patients had a smaller PT than did male controls (P=.02) and male UHRNP subjects (P=.03). All STG subregions except the caudal STG had a significant left-greater-than-right asymmetry for all groups (PP: $F_{1,72}$=14.85, P<.001; HG: $F_{1,72}$=40.68, P<.001; PT: $F_{1,72}$=37.42, P<.001; and rostral STG: $F_{1,72}$=9.46, P=.003).

At the second imaging, ANCOVAs for the PT ($F_{3,71}$=4.23, P=.008) and caudal STG ($F_{3,71}$=7.18, P<.001) showed a significant main effect for group. An ANCOVA of the PT showed a group × sex interaction ($F_{3,71}$=3.37, P=.02). Post hoc tests indicated that FEP patients had a significantly smaller caudal STG than did the controls (P<.001), UHRNP subjects (P=.003), and UHRP subjects (P=.04). For male subjects only, the PT of the FEP patients was smaller than that of the controls (P<.001) or UHRNP subjects (P=.002), and UHRP subjects had a smaller PT than did controls (P=.04). The volumes of the PP ($F_{1,72}$=16.94, P<.001), HG ($F_{1,72}$=35.45, P<.001), PT ($F_{1,72}$=34.52, P<.001), and rostral STG ($F_{1,72}$=9.28,