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Morphologic alterations of the parcellated superior temporal gyrus in schizophrenia spectrum

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Abstract

Morphologic abnormalities of the superior temporal gyrus (STG) as well as its sub-regions such as Heschl's gyrus (HG) or planum temporale (PT) have been reported in schizophrenia patients, but have not been extensively studied in schizotypal subjects. In the present study, magnetic resonance images were acquired from 65 schizophrenia patients, 39 schizotypal disorder patients, and 72 healthy controls. Volumetric analyses were performed using consecutive 1-mm coronal slices on the temporal pole (TP) and superior temporal sub-regions [planum polare (PP), HG, PT, rostral STG, and caudal STG]. The HG was significantly smaller in schizophrenia patients compared with controls but not in schizotypal patients, while volume reductions of the left PT and bilateral caudal STG were common to both disorders. The TP gray matter was larger in female schizotypal patients compared with female schizophrenia patients. There were no significant group differences in the PP and rostral STG volume. In the subgroup of early phase schizophrenia patients (illness duration < 1.0 year), smaller volumes for the left PP and rostral STG were correlated with hallucinations and delusions. Our findings suggest that morphologic changes in the posterior regions of the STG are common to the schizophrenia spectrum, whereas less involvement of the HG, and possibly the PP and rostral STG might be related to the sparing of schizotypal patients from developing overt psychosis.

Keywords: Schizophrenia; Schizotypal disorder; Magnetic resonance imaging; Superior temporal gyrus; Temporal pole

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1. Introduction

Since the initial report of Barta et al. (1990) showing reduced superior temporal gyrus (STG) volume in schizophrenia, morphologic abnormalities of the STG have been repeatedly described in schizophrenia (reviewed by Shenton et al., 2001), and volume reduction of the STG, especially in the left hemisphere, has been correlated with various positive symptoms such as auditory hallucinations or thought disorder (reviewed by Rajarethinam et al., 2000). Based on recent development in magnetic resonance imaging (MRI)-based topographic parcellation, the focus of attention with regard to the STG abnormalities in schizophrenia has been directed to the changes in its functionally relevant anatomical sub-regions. Although the data are not entirely consistent (e.g., Shapleske et al., 2001), asymmetry anomaly (Barta et al., 1997; Petty et al., 1995) or left-sided volume reduction (Hirayasu et al., 2000; Kwon et al., 1999; Sumich et al., 2002; Yamasue et al., 2004) of the planum temporale (PT) and clinical correlations of these changes to the severity of thought disorder (Barta et al., 1997; Petty et al., 1995; Rossi et al., 1994) have been reported in schizophrenia. With regard to the volumes of the primary auditory cortex (Heschl's gyrus, HG), significant reduction (Hirayasu et al., 2000; Rojas et al., 1997) or inverse association with hallucinations and delusions (Sumich et al., 2005) was noted, while other studies failed to find significant results (Barta et al., 1997; Kwon et al., 1999; Sumich et al., 2002; Yamasue et al., 2004).

In contrast to these two sub-regions, less attention has been paid to morphologic changes in the other superior temporal sub-regions, i.e. the planum polare (PP) and the lateral portion of the STG. The PP is located anterior to the HG on the supratemporal plane and is considered as auditory association cortex, but has rarely been studied. The only volumetric MRI study on this region in schizophrenia revealed neither volume changes nor a correlation with clinical symptoms (Crespo-Facorro et al., 2004a). The lateral portion of the STG, which constitutes the upper bank of the superior temporal sulcus, is concerned with the biological basis for social interaction or mentalizing that is disturbed in schizophrenia (Frith and Frith, 1999). To our knowledge, however, only one volumetric MRI study has attempted a detailed examination of this specific sub-region in schizophrenia (Kim et al., 2003), where a smaller right posterior portion of the lateral STG and a negative correlation between the volume of the left anterior portion and psychotic symptoms were found in male patients. Thus, the structural brain changes of the superior temporal sub-regions and their clinical correlations in schizophrenia remain elusive.

Subjects with schizotypal features diagnosed as schizotypal disorder in ICD-10 (World Health Organization, 1992) or schizotypal personality disorder (SPD) in DSM-IV (American Psychiatric Association, 1994) share genetic, biological, and psychological commonalities with schizophrenia and are thought to be the prototype of schizophrenia spectrum disorders (Siever and Davis, 2004). Based on studies concerning cognitive characteristics and brain morphologic changes in schizotypal subjects (reviewed by Dickey et al., 2002a; Siever and Davis, 2004) and schizophrenia patients, it is hypothesized that while abnormalities in the temporal regions are common to both groups as a neurobiological basis for vulnerability factors as part of the schizophrenia spectrum, the preservation of frontal regions might contribute to the sparing of schizotypal patients from the development of prominent psychosis (Kurachi, 2003a,b; Siever and Davis, 2004). This view received support from a recent volumetric MRI study that examined the medial temporal and prefrontal cortices in schizotypal subjects (Suzuki et al., 2005).

Despite the current emphasis on the importance of the STG in schizophrenia, MRI studies of this region in schizotypal subjects are scarce. Although our previous voxel-based morphometric (VBM) study revealed a gray matter reduction of left STG region in schizotypal disorder patients (Kawasaki et al., 2004), results of volumetric analyses using anatomically defined region of interest (ROI) are controversial. Smaller left STG of the same degree as schizophrenia was reported in male subjects with SPD, but not observed in female subjects (Dickey et al., 1999, 2003). Downhill et al. (2001) noted a bilateral STG reduction in SPD subjects. Dickey et al. (2002b) also examined the HG and PT only in male subjects with SPD and found a significant volume reduction in the left HG compared with healthy controls. To our knowledge, however, no brain morphologic studies have examined changes in the other superior temporal

sub-regions such as the PP and lateral STG in schizotypal subjects.

In the present study, three-dimensional MRI was used to parcellate the STG into five sub-regions based on detailed tracing guideline (Kim et al., 2000): PP, HG, PT, rostral STG (anterior portion of lateral STG), and caudal STG (posterior portion of lateral STG). We measured the volumes of the temporal pole and these superior temporal sub-regions in schizophrenia patients, schizotypal disorder patients, and healthy controls to clarify the similarities and differences in the superior temporal morphology between these two disorders. Based on previous VBM findings (Kawasaki et al., 2004) and proposed hypotheses (Kurachi, 2003a,b; Siever and Davis, 2004), we predicted that schizotypal disorder patients would have STG abnormalities similar to those seen in overt schizophrenia. In addition, we examined the correlations between these volumetric measurements and the severity of positive symptoms in schizophrenia to replicate previous observations.

2. Methods

2.1. Subjects

Thirty-nine schizotypal disorder patients (24 males and 15 females) who met the ICD-10 criteria for research (World Health Organization, 1993) were examined. The sample characteristics of the clinic-based schizotypal disorder patients in our laboratory have been previously described (Kawasaki et al., 2004; Suzuki et al., 2004, 2005; Takahashi et al., 2002b, 2004, 2005; Yoneyama et al., 2003). They were recruited from patients who visited the clinics of the Department of Neuropsychiatry, Toyama Medical and Pharmaceutical University Hospital with schizotypal features accompanied by distress or associated problems in their lives and who needed to receive clinical care including medication with low-dose antipsychotics for these problems. Since schizotypal subjects rarely present themselves for clinical care, our clinic-based sample was considered to be more severely ill than schizotypal individuals among the general population. The mental condition of each subject was assessed by experienced psychiatrists to check for the emergence of overt psychotic symptoms, and none of the 39 patients has evolved into overt schizophrenia to date (mean follow-up period after MRI scanning = 2.7 years, S.D. = 2.2). All available clinical information and data obtained from a detailed review of the clinical records and structured interviews for Comprehensive Assessment of Symptoms and History (CASH) including the chapter on premorbid or intermorbid personality (Andreasen et al., 1992) were stored in a database. The subjects were diagnosed by consensus reached by at least two psychiatrists based on these data. Although all of the schizotypal subjects in this study also fulfilled the DSM-IV criteria of the SPD on Axis II, 10 subjects had experienced in the past transient quasi-psychotic episodes fulfilling a diagnosis of brief psychotic disorder on Axis I. At the time of MRI scanning, 34 of the 39 patients were treated with low-dose antipsychotics, of which eleven were treated with typical neuroleptics and twenty-three received atypical neuroleptics. The remaining five patients were neuroleptic-naive. Although the possibility cannot be excluded that in some of our schizotypal subjects the antipsychotic medication prevented the onset of their overt psychotic episodes, they were stable to show typical schizotypal features without developing overt psychosis during more than 2 years of clinical follow-up, and they may primarily constitute a distinct category from schizophrenia.

The schizophrenia group was composed of 65 patients with schizophrenia (35 males and 30 females). Each patient fulfilled the ICD-10 diagnostic criteria for research on schizophrenia (World Health Organization, 1993). All but one of the schizophrenia patients were on neuroleptic medication; 30 were being treated with typical neuroleptics and 34 were receiving atypical neuroleptics. Clinical symptoms of schizotypal disorder and schizophrenia patients were rated at the time of scanning using the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1984a) and the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984b).

Seventy-two control subjects were healthy volunteers (38 males and 34 females) who were recruited from members of the community, hospital staff, and university students. They were given a questionnaire consisting of 15 items concerning their family and past histories, as well as present illness. They did not have any personal or family history of psychiatric illness in their first-degree relatives. All controls were inter-

viewed and administered the Minnesota Multiphasic Personality Inventory (MMPI) by clinical psychologists to obtain a homogenous control group without eccentric profiles on the MMPI, and were excluded if they had an abnormal profile with any *T*-score for the validity scales or the clinical scales exceeding 70.

All subjects were physically healthy at the time of the study, and none had a lifetime history of serious head trauma, neurological illness or substance abuse disorder. The subjects were right-handed except for one female patient with schizotypal disorder of unknown handedness.

Table 1 shows the demographic and clinical data of the subjects. The subject overlap with our previous publication included 69/72 controls, 37/39 schizotypal patients, and 62/65 schizophrenia patients, where we reported bilateral volume reduction in the insular cortex for schizophrenia patients compared with schizotypal disorder patients and control subjects (Takahashi et al., 2005). The three groups were matched for age, height and parental education. Although there were more male than female schizotypal patients, the difference in the gender ratios among the three diagnostic groups was not significant (chi-square analysis, chi-square=0.85, $p=0.653$). The control subjects had attained a higher mean level of education than had the patients with either disorder [ANOVA, $F=25.52(2,173)$, $p<0.001$]. The total SAPS score for the schizophrenia patients was significantly higher than that for the schizotypal patients [ANOVA, $F=7.03(1,101)$, $p=0.009$]. There were significant differences in medication dosage [ANOVA, $F=17.95(1,102)$, $p<0.001$] and duration of neuroleptic medication [ANOVA, $F=4.06(1,102)$, $p=0.046$]. The patients with schizotypal disorder took significantly smaller amounts of neuroleptics than did the patients with schizophrenia.

Written informed consent was obtained from all subjects. This study was approved by the Committee on Medical Ethics of Toyama Medical and Pharmaceutical University.

2.2. Magnetic resonance imaging procedures

Magnetic resonance images were obtained by utilizing a 1.5-T Magnetom Vision (Siemens Medical System, Inc, Erlangen, Germany) with a three-dimensional gradient-echo sequence FLASH (fast low-angle shots) yielding 160–180 contiguous T1-weighted slices of 1.0-mm thickness in the sagittal plane. 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 $1.0\times1.0\times1.0\,mm^3$.

Image processing for volumetric analysis has been described in detail elsewhere (Takahashi et al., 2002a). 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 (Asahi Kasei Joho System Co, Ltd, Tokyo,

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

	Control subjects ($n=72$)	Schizotypal patients ($n=39$)	Schizophrenia patients ($n=65$)
Male/female	38/34	24/15	35/30
Age (years)	23.9 ± 5.3 (range, 18–38)	25.7 ± 5.3 (range, 18–37)	25.8 ± 4.8 (range, 18–36)
Height (cm)	166.1 ± 7.9	165.2 ± 9.0	165.1 ± 7.6
Education (years)	15.7 ± 2.4	13.4[a] ± 1.9	13.4[a] ± 1.9
Parental education (years)	12.7 ± 2.3	12.1 ± 1.7	12.1 ± 2.1
Age at onset (years)	–	–	21.9 ± 4.3
Duration of illness (years)	–	–	4.0 ± 4.1
Duration of medication (years)	–	1.6 ± 3.2	2.9[b] ± 3.4
Drug (mg/day, haloperidol equiv.)[c]	–	4.3 ± 4.6	11.2[d] ± 9.5
Total SAPS score	–	16.6 ± 9.2	26.1[d] ± 21.0
Total SANS score	–	43.3 ± 23.0	47.5 ± 23.3

ANOVA followed by Scheffé's test was used. The value represent means ± SDs. SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms.

[a] $p<0.01$: compared to the controls.

[b] $p<0.05$: compared to the schizotypal patients.

[c] The different typical and atypical neuroleptic dosages were converted into haloperidol equivalents using the guideline by Toru (2001).

[d] $p<0.01$: compared to the schizotypal patients.

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).

2.3. Volumetric analyses of regions of interest (ROIs)

As presented in Fig. 1, the TP and superior temporal sub-regions (PP, HG, PT, rostral STG, and caudal STG) were manually traced on consecutive coronal 1-mm slices based on the tracing guidelines by Kim et al. (2000).

The TP was defined as the temporal cortex rostral to the first slice that contains the temporofrontal junction. The gray and white matter volumes of the TP were obtained using the abovementioned tissue segmentation procedure.

Before tracing each sub-region, the whole STG was delineated on the segmented gray matter images. 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, respectively. On each coronal slice, the whole STG was bounded superiorly by the sylvian fissure and inferiorly by the superior temporal sulcus. The whole STG was then segmented into supratemporal and lateral portions by the lateral limb of the supratemporal plane, and the supratemporal portion was further subdivided into PP, HG, and PT. The HG was

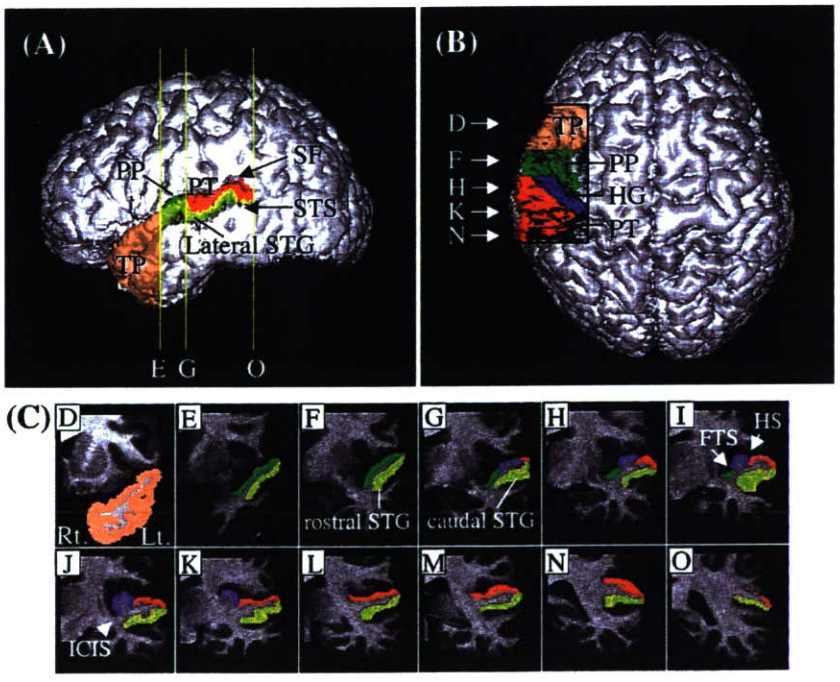

Fig. 1. Regions of interest (ROIs) manually traced in this study. (A) The reference coronal lines are marked on the lateral view of the three-dimensional reconstructed image. The coronal line G corresponds to panel G, a coronal slice containing the anterior end of the HS. The coronal lines E and O represent the most anterior (E) and most posterior (O) slices of the whole STG, respectively. (B) Top–down view of the reconstructed image of the supratemporal plane. The frontal and parietal lobes are partially cut off. (C) The sample coronal slices (panel D–O) show delineations of each ROI, which are labeled with the same colours as panels (A) and (B). The position of each coronal slice is also marked on the panel (B). The lateral STG (yellow) was further subdivided into rostral STG and caudal STG by plane G. Abbreviations: FTS = first transverse sulcus; HG = Heschl's gyrus; HS = Heschl's sulcus; ICIS = inferior circular insular sulcus; PP = planum polare; PT = planum temporale; SF = sylvian fissure; STG = superior temporal gyrus; STS = superior temporal sulcus; TP = temporal pole.

Table 2
Intracranial volume (ICV) and absolute volumes for each region of interest in the control subjects, patients with schizotypal disorder, and patients with schizophrenia

Brain region	Controls		Schizotypal patients		Schizophrenia patients		Analysis of covariance[a]					
	(Male 38, Female 34)		(Male 24, Female 15)		(Male 35, Female 30)		Group		Side		Group × Side	
	Mean	S.D.	Mean	S.D.	Mean	S.D.	$F(2,167)$	p	$F(1,170)$	p	$F(2,170)$	p
ICV (cm^3)	1487	144	1516	150	1487	147	1.06	0.348	–	–	–	–
Temporal pole GM (mm^3)							4.19	0.017	53.64	<.001	0.03	0.972
Left	12598	2077	13188	2043 (+4.7%)	12201	2081 (−3.2%)						
Right	11709	2032	12221	1785 (+4.4%)	11359	1832 (−3.0%)						
Temporal pole WM (mm^3)							1.09	0.340	159.24	<.001	0.67	0.514
Left	1672	683	1679	656 (+0.4%)	1656	52 8(−1.0%)						
Right	2353	886	2209	572(−6.1%)	2322	797 (−1.3%)						
Whole STG (mm^3)							36.48	<.001	85.29	<.001	6.43	0.002
Left	12641	1670	10029	1580 (−20.7%)	10505	1868 (−16.9%)						
Right	10917	1465	9418	1324 (−13.7%)	9354	1499 (−14.3%)						
Planum polare (mm^3)							2.07	0.129	12.19	<.001	2.20	0.114
Left	1443	462	1349	351 (−6.5%)	1363	384 (−5.5%)						
Right	1672	461	1513	426 (−9.5%)	1399	502 (−16.3%)						
Heschl's gyrus (mm^3)							3.62	0.029	84.24	<.001	1.00	0.369
Left	2083	540	1889	529 (−9.3%)	1835	569 (−11.9%)						
Right	1587	458	1529	394 (−3.7%)	1430	449 (−9.9%)						
Planum temporale (mm^3)							10.33	<.001	89.59	<.001	3.79	0.025
Left	3047	705	2407	600 (−21.0%)	2435	609 (−20.1%)						
Right	2285	655	1987	584 (−13.0%)	1984	567 (−13.2%)						
Rostral STG (mm^3)							0.77	0.466	2.61	0.108	0.83	0.438
Left	1240	767	1175	591 (−5.2%)	1255	755 (+1.2%)						
Right	1213	636	1057	495 (−12.9%)	1039	675 (−14.3%)						
Caudal STG (mm^3)							31.80	<.001	6.50	0.012	6.99	0.001
Left	4827	1087	3209	850 (−33.5%)	3615	1088 (−25.1%)						
Right	4158	1026	3330	700 (−19.9%)	3499	861 (−15.8%)						

Abbreviations: GM, gray matter; STG, superior temporal gyrus; WM, white matter.
The numbers in parentheses indicate percent differences from the controls.
For the results of the post hoc tests, see text.
[a] The main effect of gender was not significant for any region. Gender-by-group interaction was observed only for the temporal pole gray matter.

traced from posterior to anterior, beginning with the plane showing the appearance of the Heschl's sulcus (HS), which forms a lateral border of the gyrus, and ending anteriorly with the plane including the most anterior point of HS or the sulcus intermedius (SI) if it existed [plane G (Fig. 1)]. The deepest point of the sylvian fissure, inferior circular insular sulcus or the first transverse sulcus formed the medial boundary of the HG. When two convolutions originated separately from the retroinsular regions, only the most anterior gyrus was regarded as HG. When they originated medially from a common stem, however, both were defined as HG (Kasai et al., 2003a); the lateral border of the HG was changed to the SI after the HS disappeared into the surface or lateral limb of the supratemporal plane while Kim et al. (2000) changed

the lateral border to the SI immediately after it appeared. After tracing the HG that 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 (Fig. 1). In the anterior–posterior direction, plane G bounded the PP and PT. The lateral portion of the whole STG was also divided into rostral and caudal portions (rostral and caudal STG) by plane G.

All volumetric data reported here were measured by one rater (TT) who was blinded to the subjects' identity, gender, and diagnosis. The volumes of the temporal pole and superior temporal sub-regions in a subset of five randomly selected brains were measured independently by two raters (TT and RT), and each volume was then remeasured after at least 4 weeks by the first rater; both intra- and inter-rater intraclass correlation coefficients for each ROI measurement were over 0.88.

2.4. Statistical analysis

Statistical analyses were performed using repeated measures multivariate analysis of variance with age, ICV, and dosage of neuroleptic medication as covariates (MANCOVA) for each ROI, with group (schizophrenia patients, schizotypal disorder patients, and controls) and gender (male and female) as between-subject factors, and side (left and right) as a within-subject variable. The relative volumes for each ROI [(absolute volume/ICV) × 100] were also analyzed using the same model but with only age and dosage of neuroleptic medication as covariates. The statistical analyses for group comparisons reported here are based on the absolute volumes, but the results were considered significant only when the results with both absolute and relative volumes reached significance. For the comparison of ICV, age, height, and daily medication dosage were treated as covariates; the groups did not significantly differ in their ICV volumes (Table 2). In the case of significant volume changes in a particular sub-region, the absolute volume was also analyzed by using MANCOVA with age, daily medication dosage, and whole STG volume as covariates for each hemisphere with group and gender as between-subject variables to further expose sub-regional effects. The asymmetry index of volume for each region was calculated by the following formula: 2 × (left − right/left + right); it was then analyzed by two-factor (group, gender) analysis of covariance (ANCOVA) with age as a covariate. The post hoc Scheffé's test was employed to follow up the significant main effects or interactions yielded by these analyses.

For the schizophrenia group, Spearman's rho was calculated to explore correlations between the relative volumes of TP gray matter, PP, HG, PT, rostral STG, and caudal STG in the left/right hemisphere and scores for the subscales of SAPS (hallucinations, delusions, bizarre behavior, positive formal thought disorder). To prevent possible Type I error due to multiple comparisons, we limited the analyses to the severity of positive symptoms based on previous findings. Correlational analyses were not performed for schizotypal disorder patients because of the very low scores for these subscales.

To examine the effects of neuroleptic medication, correlations between the relative volumes for each region and daily medication dosage and duration of neuroleptic medication were analyzed by using Spearman's rank correlation coefficients. For the patients with schizophrenia, the correlations between the relative volumes for each region and duration of illness and age of onset were also analyzed. For 62 schizophrenia patients and 69 control subjects overlapped with our previous study on the insula (Takahashi et al., 2005), Spearman's correlations for relative values were analyzed to test whether the volume changes in the insular cortex are correlated with the changes in the superior temporal sub-regions reported in this study. For these analyses, statistical significance was defined as $p < 0.05$.

3. Results

3.1. Volumes of ROIs

Table 2 shows the absolute volumes for each ROI in the three groups.

MANCOVA of the whole STG revealed significant main effects for the group and side and a significant group-by-side interaction. The whole STG was significantly reduced in the schizophrenia ($p < 0.001$) and schizotypal ($p < 0.001$) patients compared with the control subjects bilaterally, but there was no difference between both disorders ($p = 0.659$). Leftward asymmetry was found for the controls ($p < 0.001$) and schizophrenia patients ($p < 0.001$) but not for the schizotypal patients ($p = 0.352$).

For the planum polare (PP), MANCOVA revealed a significant main effect for the side, where the PP in the right hemisphere was larger than that in the left for all diagnostic groups ($p=0.001$).

For the Heschl's gyrus (HG), MANCOVA revealed significant main effects for the group and side; schizophrenia patients had a significantly smaller HG than control subjects ($p=0.007$), and the HG was significantly asymmetrical (left>right) in all groups ($p=0.001$). The HG volume of the schizotypal patients did not significantly differ from those of schizophrenia patients ($p=0.524$) or controls ($p=0.292$). When covarying for whole STG volume, the main effect for the group was not significant for both left [$F=1.72(2,167)$; $p=0.181$] and right [$F=2.37(2,167)$; $p=0.097$] hemispheres.

For the planum temporale (PT), MANCOVA revealed significant main effects for group and side and a significant group-by-side interaction. While the left PT volume was significantly smaller in the schizophrenia patients ($p<0.001$) and schizotypal patients ($p<0.001$) compared with the control subjects, there was no difference between both disorders ($p=0.992$). The PT was larger in the left than in the right hemisphere for all diagnostic groups ($p<0.001$). MANCOVA of the left PT covarying for left whole STG volume showed a significant group-by-gender interaction [$F=3.90(2,167)$; $p=0.022$]; the left PT was smaller in the schizophrenia patients (male, $p<0.001$; female, $p=0.002$) and male schizotypal patients ($p<0.001$) compared with the controls.

For the rostral STG, MANCOVA showed no main effects or interactions among the factors. MANCOVA of the caudal STG revealed significant main effects for group and side and a significant group-by-side interaction. Post hoc analyses showed the caudal STG to be significantly reduced in schizophrenia ($p<0.001$) and schizotypal ($p<0.001$) patients as compared with the control subjects bilaterally. No significant differences in the caudal STG volume emerged between the schizophrenia and schizotypal patients ($p=0.181$). The caudal STG volume showed asymmetry with the left side being larger than the right for the control subjects ($p<0.001$), whereas this asymmetry was not significant for the schizophrenia ($p=0.983$) or schizotypal ($p=0.997$) patients. When covarying for the whole STG volume, a significant effect for group in MANCOVA was revealed in the left [$F=3.34(2,167)$; $p=0.038$], but not in the right caudal STG [$F=1.28(2,167)$; $p=0.279$]. Post hoc analyses showed that the left caudal STG was significantly reduced in both schizophrenia ($p<0.001$) and schizotypal disorder ($p<0.001$) patients. This indicates the prominent sub-regional effects of the left caudal STG among the superior temporal sub-regions.

MANCOVA of the temporal pole (TP) gray matter revealed significant main effects for group and side and a significant group-by-gender interaction [$F=3.11(2,167)$; $p=0.047$]. Post hoc tests showed the TP gray matter of female schizotypal patients to be larger than that of female schizophrenia patients ($p=0.022$), but there were no differences between the control subjects and schizophrenia ($p=0.335$) or schizotypal ($p=0.164$) patients. The TP gray matter was larger in the left than in the right hemisphere for all groups ($p<0.001$). For the TP white matter, MANCOVA showed no main effect for group but the main effect for side was significant; the TP white matter volume was larger in the right than in the left hemisphere ($p<0.001$).

3.2. Laterality effects

Asymmetry indices of the regions are presented in Table 3. ANCOVAs for the asymmetry index of the whole STG and caudal STG revealed significant main effect for diagnosis; the schizotypal disorder patients had significantly reduced leftward asymmetry of the whole STG volume than the controls (post hoc test, $p=0.017$), and both schizophrenia (post hoc test, $p=0.033$) and schizotypal disorder (post

Table 3
Asymmetry indices of regions of interest in the control subjects, patients with schizotypal disorder, and patients with schizophrenia

Brain region	Controls (Male 38, Female 34)		Schizotypal patients (Male 24, Female 15)		Schizophrenia patients (Male 35, Female 30)		Analysis of covariance Diagnosis effect	
	Mean	S.D.	Mean	S.D.	Mean	S.D.	$F(2,169)$	p
Whole STG	0.146	0.139	0.060[a]	0.145	0.112	0.158	3.30	0.039
Planum polare	−0.152	0.382	−0.106	0.332	0.004	0.384	2.53	0.083
Heschl's gyrus	0.272	0.352	0.199	0.314	0.236	0.279	0.73	0.483
Planum temporale	0.295	0.290	0.199	0.319	0.207	0.324	1.24	0.291
Rostral STG	−0.039	0.852	0.052	0.790	0.240	0.907	1.53	0.220
Caudal STG	0.153	0.271	−0.051[b]	0.328	0.011[c]	0.368	4.07	0.019

STG, superior temporal gyrus.
The asymmetry index of volume for each region was calculated by the following formula: 2 × (left − right/left + right).
[a,c] $p<0.05$: compared to the controls.
[b] $p<0.01$: compared to the controls.

hoc test, $p=0.008$) patients were significantly less lateralized for the caudal STG volume than the control subjects. There was no significant main effect for gender or group-by-gender interaction in these ANCOVAs.

3.3. Correlational analysis

There was a negative correlation between the relative volume of the left rostral STG and the score for delusions of the SAPS (rho=−0.390, $p=0.001$) in the schizophrenia group. When the analysis was made for the subgroup of early phase schizophrenia patients (illness duration <1.0 year, 12 males and 8 females), negative correlations were found between the relative volume of the left PP and the scores for hallucinations (rho=−0.577, $p=0.008$) and delusions (rho=−0.596, $p=0.006$) and between the relative volume of the left rostral STG and the scores for hallucinations (rho=−0.541, $p=0.014$) and delusions (rho=−0.680, $p<0.001$). The correlation between the left rostral STG volume and the severity of delusions in the early phase group remained significant even after Bonferroni correction for multiple comparisons [six ROIs in the left/right hemisphere by four symptom ratings; $p<0.001$ (0.05/48)].

For schizophrenia patients, the relative volumes for each ROI were not correlated with the illness duration, age at onset, medication dosage or duration of neuroleptic medication. For the schizotypal disorder patients, the relative volumes for the TP gray matter (left, rho=−0.374, $p=0.019$; right, rho=−0.430, $p=0.006$), right HG (rho=−0.387, $p=0.015$) and right caudal STG (rho=−0.318, $p=0.049$) were negatively correlated with the dosage of neuroleptic medication, and the relative volume for the left HG was negatively correlated with the duration of medication (rho=−0.385, $p=0.015$).

In control subjects, the insular cortex was positively correlated with all of the superior temporal sub-regions that significantly reduced in schizophrenia patients (bilateral HG, left PT, and bilateral caudal STG) for both hemispheres (rho= 0.264 to 0.499, $p=0.028$ to <0.001), but there were no such correlations in schizophrenia. This might suggest the altered connections between cortical regions in schizophrenic brains.

4. Discussion

To our knowledge, this is the first volumetric MRI study to report similarities and differences in the morphology of the reliably parceled superior temporal sub-regions including the lateral portion of STG between schizophrenia and schizotypal disorder. Compared with the controls, volumes of the bilateral caudal STG and left PT were comparably reduced in both disorders, whereas volume reduction in the HG was found only in the schizophrenia patients.

In this study, volumes of the superior temporal sub-regions were mostly reduced in the schizophrenia patients compared to the controls with the exception of the PP and rostral STG, but these regions also showed approximately 15% volume reductions in the right hemisphere. Our results of left-lateralized PT volume reduction, bilateral volume reduction of the HG, and no significant volume change of the PP were generally in line with previous MRI findings for schizophrenia (Crespo-Facorro et al., 2004a; Hirayasu et al., 2000; Kwon et al., 1999; Sumich et al., 2002; Yamasue et al., 2004). On the other hand, the present finding showing bilateral volume reduction of the caudal STG in schizophrenia did not accord with previous study suggesting right-sided volume reduction of caudal STG in schizophrenia (Kim et al., 2003). The reason for this discrepancy is unclear because we basically used the same parcellation strategies for subdividing the STG (Kim et al., 2000). However, it may be worth noting that we found marked volume changes in the left caudal STG for schizophrenia even after controlling for whole STG volume. Although its functional significance has not yet been established, the caudal STG is a region activated during auditory speech perception (Price, 2004) and also during "mentalizing" tasks (Gallagher and Frith, 2003). Deficit in mentalizing (interpretation of the mental states of others) abilities may account for the varying range of symptoms in schizophrenia (Brüne, 2005; Frith and Frith, 1999). It would be worthwhile to further study the functional and structural abnormalities of the caudal STG in relation to language- or sociality-related functions in schizophrenia patients.

The principal focus of this study is on the similarities and differences in the superior temporal morphology between schizophrenia and schizotypal patients. Consistent with previous VBM study (Kawasaki et al., 2004), we found in this volumetric MRI study that the STG volume is significantly reduced as a whole in both schizophrenia and schizotypal disorder patients, especially in the left hemisphere. In previous volumetric MRI studies, Dickey et al. (1999, 2003) reported a smaller left STG to the same degree as schizophrenia in male but not female SPD subjects who were recruited from community. We found no gender effects on whole STG in contrast to these reports, but our findings may be partly limited by the relatively small sample size of

female schizotypal patients. Thus, the issue of gender on STG morphology in schizotypal subjects needs to be further studied. Another MRI study on clinic-based SPD subjects found that the gray matter reduction of the STG in both hemispheres was greater than that in schizophrenia patients (Downhill et al., 2001). Taken together, these previous and present studies support the notion that the abnormalities in temporal regions are a common neurobiological basis for schizophrenia spectrum (Kurachi, 2003a,b; Siever and Davis, 2004). For the superior temporal sub-regions, we found that the HG was relatively preserved in the schizotypal patients, while volume reductions of the left PT and caudal STG were common to both disorders. These findings did not accord with a previous report by Dickey et al. (2002b), who examined the volumes of the HG and PT in male SPD subjects and found a significant volume reduction only in the left HG compared with healthy controls. These inconsistencies may be due in part to the different sample characteristics of the schizotypal subjects among reports as discussed elsewhere (Takahashi et al., 2005); our cohort may have included subjects who were more severely ill than SPD individuals among the general population. Although further replication is required, our findings suggest that morphologic changes of the HG may partly represent the liability to develop positive psychotic symptoms in schizophrenia spectrum patients. This view is consistent with a previous functional imaging study that found direct evidence of the involvement of HG in auditory hallucination (Dierks et al., 1999).

In this study, we found significant group-by-side interaction particularly for the caudal STG volume; the left-greater-than-right laterality seen in the normal controls was remarkably reduced in schizophrenia patients and even reversed in schizotypal patients. As first clearly recognized by Crow (1990), anomalous cerebral asymmetry is one of the most characteristic features of the brain in schizophrenia (reviewed by DeLisi et al., 1997) and probably represents the genetic/developmental abnormalities in the disease (Crow et al., 1989; Crow, 1990; Sharma et al., 1999). Our findings support the altered laterality hypothesis of Crow (1990) and suggest that both schizophrenia and schizotypal disorder patients share at least in part the same cerebral asymmetry abnormalities, possibly reflecting a pathophysiologic process common to both disorders.

We also investigated the morphology of the TP, a component of the olfactocentric paralimbic circuit along with the orbitofrontal cortex and the insula (Mesulam, 2000). Consistent with a previous MRI study (Crespo-Facorro et al., 2004b) but not with a study by Kasai et al. (2003b) who reported left TP reduction in schizophrenia patients, we found no volume changes in the TP between the schizophrenia patients and the controls. On the other hand, we found the TP gray matter to be significantly larger in the female schizotypal patients compared with the female schizophrenia patients. Interestingly, evidence suggests that the insula, the other main component of the paralimbic structures, is also even larger in schizotypal patients than in control subjects (Takahashi et al., 2005). Dysfunction of these paralimbic structures may lead to the disturbances in various cognitive and emotional functions that can partly account for the symptomatology in schizophrenia (Crespo-Facorro et al., 2004b; Kasai et al., 2003b). It thus may be assumed that increased volumes of some paralimbic structures in schizotypal subjects reflect a compensatory mechanism, which has also been suggested in the prefrontal cortex of schizotypal subjects (Siever and Davis, 2004; Suzuki et al., 2005).

In this study, the severity of hallucinations or delusions within the early phase schizophrenia patients was negatively correlated with the volumetric measures of the left PP and the left rostral STG. These findings are consistent with the findings that the volume reduction of anterior STG, especially in the left hemisphere, is associated with the severity of hallucinations in schizophrenia (Barta et al., 1990; Flaum et al., 1995; Kim et al., 2003; Levitan et al., 1999; Rajarethinam et al., 2000). However, our results do not support previous MRI studies that implicate the posterior STG, which includes the PT or caudal STG, in thought disorder (Barta et al., 1997; Menon et al., 1995; Petty et al., 1995; Rajarethinam et al., 2000; Rossi et al., 1994; Shenton et al., 1992). It is possible that this discrepancy arises from the differences in the sample characteristics between the reports; our early phase schizophrenia group was probably not suitable for exploring the morphologic changes related to thought disorder because of their very low score for the positive formal thought disorder of the SAPS [mean score = 0.8 ± 1.8 (S.D.) (range, 0–7)]. Functional neuroimaging studies suggested that delusions or hallucinations are related to abnormalities in brain areas such as the left inferior frontal cortex, ventral

striatum, temporal gyrus, and parahippocampal regions (Liddle et al., 1992, 2000; McGuire et al., 1995; Shergill et al., 2000, 2004; Silbersweig et al., 1995; Suzuki et al., 1993), but the structural brain changes underlying these symptoms remain elusive, and they may not be related to a single site of the brain (Suzuki et al., 2005). However, our results suggest that structural brain changes in the left PP and left rostral STG may represent part of a disturbed neural network that generates or modulates hallucinations or delusions. Although not directly supported by the present morphologic findings in schizotypal patients, the less severe involvement of these regions may be related to the decreased magnitude in symptomatology for schizotypal disorder relative to schizophrenia.

Some limitations of the present study should be mentioned. First, a significant difference in medication dosage between the schizophrenia and schizotypal patients might have affected the volumetric results. We therefore used the daily medication dosage as a covariate for all MANCOVA analyses to control for the differences in medication status between both disorders. A second limitation is related to the anatomical definition of the rostral STG. Although each ROI was traced based on the intrinsic anatomical landmarks, there was little rostral STG volume when the anterior end of the Heschl's sulcus or the sulcus intermedius if present was positioned very close to the temporofrontal junction. However, the frequencies of such cases were similar in all diagnosis groups at 5–10%, and the exclusion of these cases did not change the statistical conclusions.

In conclusion, changes in the STG, especially the left posterior regions, might represent a common neurobiological basis for schizophrenia spectrum. However, the volume of the HG is relatively preserved in schizotypal disorder and the less severe involvement of this region and possibly of the PP and rostral STG might be related to the sparing of schizotypal patients from the development of overt psychosis.

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Temporal lobe gray matter in schizophrenia spectrum: A volumetric MRI study of the fusiform gyrus, parahippocampal gyrus, and middle and inferior temporal gyri

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Abstract

Although several brain morphologic studies have suggested abnormalities in the temporal regions to be a common indicator of vulnerability for the schizophrenia spectrum, less attention has been paid to temporal lobe structures other than the superior temporal gyrus or the medial temporal region. In this study, we investigated the volume of gray matter in the fusiform gyrus, the parahippocampal gyrus, the middle temporal gyrus, and the inferior temporal gyrus using magnetic resonance imaging in 39 schizotypal disorder patients, 65 schizophrenia patients, and 72 age and gender matched healthy control subjects. The anterior fusiform gyrus was significantly smaller in the schizophrenia patients than the control subjects but not in the schizotypal disorder patients, while the volume reduction of the posterior fusiform gyrus was common to both disorders. Volumes for the middle and inferior temporal gyri or the parahippocampal gyrus did not differ between groups. These findings suggest that abnormalities in the posterior region of the fusiform gyrus are, as have been suggested for the superior temporal gyrus or the amygdala/hippocampus, prominent among the temporal lobe structures as a common morphologic substrate for the schizophrenia spectrum, whereas more widespread alterations involving the anterior region might be associated with the development of full-blown schizophrenia.

Keywords: Magnetic resonance imaging; Schizophrenia; Schizotypal disorder; Fusiform gyrus; Middle temporal gyrus; Inferior temporal gyrus

1. Introduction

Subjects with schizotypal features diagnosed as schizotypal disorder in ICD-10 (World Health Organization, 1992) or schizotypal personality disorder (SPD) in DSM-IV (American Psychiatric Association, 1994) share genetic, biological, and psychological commonalities with schizophrenia and are suggested to constitute a

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prototypic disorder for the schizophrenia spectrum (Siever et al., 1993; Siever and Davis, 2004). Previous studies concerning brain morphologic changes and cognitive characteristics in schizotypal subjects (reviewed by Dickey et al., 2002; Siever and Davis, 2004) and schizophrenia provided a theoretical model that the abnormalities in temporal regions are common to both groups as a neurobiological basis for vulnerability factors as part of the schizophrenia spectrum (Kurachi, 2003a,b; Siever and Davis, 2004). More specifically, recent volumetric (Suzuki et al., 2005b; Takahashi et al., 2006) and voxel-based morphometric (VBM) (Kawasaki et al., 2004) magnetic resonance imaging (MRI) studies by our group have demonstrated the regional gray matter reductions for the superior temporal gyrus (STG) and the medial temporal lobe structures such as the amygdala and the hippocampus in schizotypal disorder patients to the same degree as those seen in schizophrenia patients. However, whether schizotypal subjects exhibit abnormalities in other temporal regions has yet to be elucidated.

The fusiform gyrus, or the occipitotemporal gyrus, is a spindle-shaped structure located on the ventral occipitotemporal surface and is selectively engaged in face recognition (George et al., 1999; Grill-Spector et al., 2004; Haxby et al., 2000, 2002; Kanwisher et al., 1997) which has been reported to be disturbed in schizophrenia (Martin et al., 2005; Sachs et al., 2004). Although there have been relatively few morphologic studies of this region in schizophrenia, postmortem (McDonald et al., 2000) and MRI (Lee et al., 2002; Onitsuka et al., 2003) studies have reported volume reduction and its correlation with poor facial recognition. For schizotypal subjects, who exhibit face recognition deficits similar to schizophrenia patients (Conklin et al., 2002; Mikhailova et al., 1996; Poreh et al., 1994), only a single volumetric MRI study has examined the fusiform gyrus, and it found no significant volume changes in male SPD subjects (Dickey et al., 2003b). However, they have not taken into account the presumable differences in the connectivities and functions of the anterior versus posterior portions of the fusiform gyrus (George et al., 1999; Haxby et al., 2002; Kanwisher et al., 1997). Thus, more data on the volumetric changes of the fusiform gyrus in both schizophrenia and schizotypal patients are needed to evaluate the potential role of the fusiform gyrus in the neurobiology of the schizophrenia spectrum.

The middle and inferior temporal gyri, which contribute to visual recognition and are also related to speech perception (Hickok and Poeppel, 2004), have received less attention in the search for the neural substrate of schizophrenia. The only volumetric MRI study on these regions in schizophrenia revealed gray matter reductions in the left middle temporal gyrus and bilateral inferior temporal gyrus (Onitsuka et al., 2004), but most VBM studies found no significant gray matter changes (reviewed by Honea et al., 2005). For patients with SPD, Downhill et al. (2001) found a more marked reduction in temporal gray matter in the non-STG region, which includes the middle and inferior temporal gyri, than in the STG. To our knowledge, however, no volumetric MRI studies have specifically delineated the middle and inferior temporal gyri in schizotypal subjects.

The present study aimed to extend volumetric analyses of the temporal lobe in schizophrenia spectrum disorders to structures other than the STG and the medial temporal region. We used MRI to measure the volume of gray matter in the anterior and poster portions of the fusiform gyrus, the parahippocampal gyrus, the middle temporal gyrus, and the inferior temporal gyrus in schizophrenia patients, schizotypal disorder patients, and healthy controls. Based on previous VBM (Kawasaki et al., 2004) and volumetric (Dickey et al., 2003b) MRI studies, we predicted that volumetric changes in the temporal lobe in schizotypal disorder patients would be localized to the STG and the amygdala/hippocampus but would not be marked for the other temporal structures. We also examined whether these volumetric measures were related to clinical symptoms in schizophrenia and schizotypal disorder patients.

2. Methods

2.1. Subjects

Thirty-nine schizotypal disorder patients (24 males and 15 females), 65 schizophrenia patients (35 males and 30 females), and 72 control subjects (38 males and 34 females) were included in this study. The subjects were right-handed except for one female patient with schizotypal disorder of unknown handedness. Table 1 shows the demographic and clinical data of the subjects. MRI findings of the superior temporal sub-regions in the same group of subjects have been reported previously (Takahashi et al., 2006).

The schizotypal disorder patients who met the ICD-10 criteria for research (World Health Organization, 1993) were recruited from among patients who visited the clinics of the Department of Neuropsychiatry, Toyama Medical and Pharmaceutical University Hospital with schizotypal features accompanied by distress

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

Variable	Control subjects		Schizotypal patients		Schizophrenia patients	
	Male (N=38)	Female (N=34)	Male (N=24)	Female (N=15)	Male (N=35)	Female (N=30)
Age (years)	24.1±4.9	23.8±5.8	25.7±5.8	25.6±4.5	25.6±4.7	26.0±5.1
Height (cm)	172.2[a]±4.9	159.2±4.5	170.8[a]±5.9	156.3±4.7	170.7[a]±4.9	158.5±4.0
Education (years)	16.6[b]±2.7	14.8±1.6	13.4±1.9	13.2±2.0	13.5±1.9	13.3±1.9
Parental education (years)	12.9±2.3	12.5±2.3	12.1±1.5	12.1±2.1	12.2±1.9	11.9±2.4
Age at onset (years)	–	–	–	–	21.9±4.5	21.9±4.2
Duration of illness (years)	–	–	–	–	3.7±3.9	4.4±4.3
Duration of medication (years)	–	–	2.1±3.8	0.8±1.4	2.6[c]±3.1	3.3[c]±3.7
Drug (mg/day, haloperidol equiv.)[d]	–	–	5.1±5.5	3.1±2.2	11.5[c]±8.8	10.8[c]±10.4
Total SAPS score	–	–	15.8±8.7	17.9±10.2	24.9[c]±22.2	27.7[c]±19.8
Total SANS score	–	–	40.4±23.4	48.4±22.1	50.9±22.1	43.4±24.4

The 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 to females.

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

[c] $p<0.05$: compared to schizotypal patients.

[d] The different typical and atypical neuroleptic dosages were converted into haloperidol equivalents using the guideline by Toru (2001).

[e] $p<0.01$: compared to schizotypal patients.

or associated problems in their lives and who needed to receive clinical care including medication with low-dose antipsychotics for these problems. The sample characteristics of the clinic-based schizotypal disorder patients in our laboratory have been described previously (Kawasaki et al., 2004; Suzuki et al., 2004, 2005b; Takahashi et al., 2005, 2006). The mental condition of each subject was assessed by experienced psychiatrists to check for the emergence of overt psychotic symptoms, and none of the 39 patients has developed overt schizophrenia to date (mean follow-up period after MRI scanning=2.7 years, SD=2.2). All available clinical information and data obtained from a detailed review of the clinical records and structured interviews for Comprehensive Assessment of Symptoms and History (CASH) including the chapter on premorbid or intermorbid personality (Andreasen et al., 1992) were stored in a database. The subjects were diagnosed by consensus reached by at least two psychiatrists based on these data. Although all of the schizotypal subjects in this study also fulfilled the DSM-IV criteria of the SPD on Axis II, 10 subjects had experienced in past transient quasi-psychotic episodes fulfilling the diagnosis of a brief psychotic disorder on Axis I (American Psychiatric Association, 1994). At the time of MRI scanning, 34 of the 39 patients were treated with low-dose antipsychotics, of which eleven were treated with typical neuroleptics and twenty-three received atypical neuroleptics. The remaining five patients were neuroleptic-naïve. Thus, our clinic-based sample was considered to comprise patients more severely ill than schizotypal individuals among the general population.

The schizophrenia patients fulfilled the ICD-10 diagnostic criteria for research on schizophrenia (World Health Organization, 1993). All but one of the schizophrenia patients were on neuroleptic medication; 30 were being treated with typical neuroleptics and 34 were receiving atypical neuroleptics. Clinical symptoms of schizotypal disorder and schizophrenia patients were rated at the time of scanning using the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1984a) and the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984b).

The control subjects consisted of healthy volunteers recruited from members of the community, hospital staff, and university students. They were given a questionnaire consisting of 15 items concerning their family and past histories, as well as present illness. They did not have any personal or family history of psychiatric illness among their first-degree relatives. All controls were interviewed and administered the Minnesota Multiphasic Personality Inventory (MMPI) by experienced psychologists to obtain a rather homogenous control group without eccentric profiles on the MMPI, and were excluded if they had an abnormal profile with any T-score for the validity scales or the clinical scales exceeding 70.

All subjects were physically healthy at the time of the study, and none had a lifetime history of serious head trauma, neurological illness or substance abuse disorder. The three groups were matched for age, gender, height, and parental education, but the control subjects had attained a higher mean level of education than had the patients with either disorder. The total SAPS score for

the schizophrenia patients was significantly higher than that for the schizotypal patients. There were significant differences in medication dosage and duration of neuroleptic medication; the patients with schizotypal disorder took significantly smaller amounts of neuroleptics than did the patients with schizophrenia. This study was approved by the Committee on Medical Ethics of Toyama Medical and Pharmaceutical University. After a complete description of the study, written informed consent was obtained from all subjects.

2.2. Magnetic resonance imaging procedures

Magnetic resonance images were obtained by utilizing a 1.5-T Magnetom Vision (Siemens Medical System, Inc, Erlangen, Germany) with a three-dimensional gradient-echo sequence FLASH (fast low-angle shots) yielding 160–180 contiguous T1-weighted slices of 1.0-mm thickness in the sagittal plane. 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 $1.0 \times 1.0 \times 1.0$ mm^3.

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 (Asahi Kasei Joho System Co, Ltd, 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 (Takahashi et al., 2006).

2.3. Volumetric analyses of regions of interest (ROIs)

As presented in Fig. 1, the volume of gray matter in the fusiform gyrus, the parahippocampal gyrus, the middle temporal gyrus, and the inferior temporal gyrus was measured in this study. Each ROI was traced manually on consecutive 1-mm coronal slices. The fusiform gyrus and the middle and inferior temporal gyri were delineated on the segmented gray matter images based on the tracing guidelines established by Kim et al. (2000).

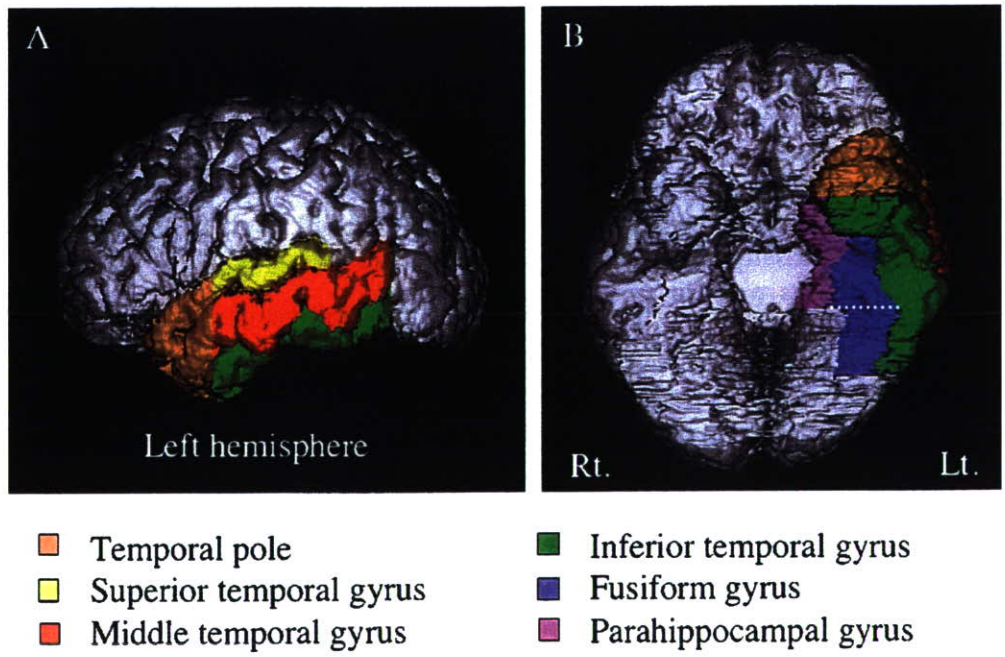

Fig. 1. Lateral (A) and ventral (B) views of a three-dimensional reconstructed image of the temporal lobe structures. The middle and inferior temporal gyri, the fusiform gyrus, and the parahippocampal gyrus were manually traced in this study. The temporal pole and the superior temporal gyrus have been measured in our previous study (Takahashi et al., 2006) but are shown here as a reference for the topography of the temporal lobe structures. The dotted line in panel B indicates the boundary between the anterior and posterior fusiform gyri.

2.3.1. Fusiform gyrus

The fusiform gyrus was traced from rostral to caudal, beginning with the slice containing the anterior tip of the parieto-occipital sulcus as seen on the midsagittal plane for each hemisphere and ending caudally with the most anterior slice that contains the occipitotemporal sulcus. On each coronal slice, the medial and lateral boundaries were the collateral sulcus and the occipitotemporal sulcus, respectively. When these sulci were interrupted or duplicated particularly in the caudal area, the more prominent one or the lateral one if equal was used as the border (Kim et al., 2000; Lee et al., 2002). If the collateral sulcus disappeared prior to the anterior end of the occipitotemporal sulcus, the medial border was changed to the rhinal sulcus. The fusiform gyrus was then subdivided into anterior and posterior portions by the last slice including the crus of the fornix.

2.3.2. Parahippocampal gyrus

The procedure for delineation of the parahippocampal gyrus was described in detail elsewhere (Suzuki et al., 2005a,b). Briefly, the gyrus was separated laterally by using the line drawn from the most lateral border of the hippocampal flexure to the collateral sulcus, and superiorly by the inferior gray border of the hippocampal formation. The slice showing the appearance of the temporal stem and that showing the last appearance of the fiber of the fornix were chosen as anterior and posterior boundaries, respectively. In this study, we obtained the gray matter volume by using the above-mentioned segmentation procedure in spite of tracing the volumes of the gray and white matter together as in previous studies (Suzuki et al., 2005a,b).

2.3.3. Middle and inferior temporal gyri

First, the middle and inferior temporal gyri as a whole were demarcated from the other parts of the brain. The slice showing the appearance of the temporal stem and that containing the anterior tip of the parieto-occipital sulcus as seen on the midsagittal plane were chosen as anterior and posterior boundaries, respectively. The superior temporal sulcus or the anterior occipital sulcus was used as the superior boundary, and the occipitotemporal sulcus or the collateral sulcus in the area rostral to the end of the occipitotemporal sulcus was used as the inferior boundary. After extracting previously traced ROIs of the temporal lobe [the fusiform gyrus, the parahippocampal gyrus, and the superior temporal gyrus (Takahashi et al., 2006)] and the inferior parietal gyrus (Zhou et al., in submission), the middle and inferior temporal gyri were readily delineated with minimal manual editing.

Next, the middle and inferior temporal gyri were divided into each gyrus by the inferior temporal sulcus. The course of the inferior temporal sulcus was carefully followed in three dimensions because of its frequent interruptions. In these interrupted cases, the more prominent one or the lowest one on the lateral surface if equal was used as the boundary.

The fusiform gyrus and the middle and inferior temporal gyri were traced by one rater (TT), and the parahippocampal gyrus was measured by another rater (LN). All measurements were carried out without knowledge of the subjects' identity, gender, and diagnosis. Intra- and inter-rater (TT and RT, LN and HH) intraclass correlation coefficients in a subset of five randomly selected brains were over 0.92 for all ROIs.

2.4. Statistical analysis

Statistical differences in the regional volumetric measurements were analyzed using the repeated measures multivariate analysis of covariance (MANCOVA) with ICV and age as covariates for each region, with diagnosis (schizophrenia patients, schizotypal disorder patients, and controls) and gender (male, female) as between-subject factors, and side (left, right) as a within-subject variable. Post hoc Scheffé's tests were carried out to follow-up the significant main effects or interactions yielded by MANCOVAs. Spearman's rank correlations were calculated to examine relationships between relative volume [(absolute volume/ICV) × 100] for each ROI and the clinical variables. For these analyses, statistical significance was defined as $p < 0.05$. To prevent a possible type I error due to multiple tests, a Bonferroni correction was applied for correlation analyses.

3. Results

3.1. Volumes of ROIs

Table 2 shows the gray matter volumes for measured ROIs and results of MANCOVAs for the main effect of diagnosis. The effect involving gender was not significant for any region measured in this study. To demonstrate the regional volume changes within the temporal lobe in schizophrenia spectrum disorders, the previously published data of the hippocampus (Suzuki et al., 2005a,b), the amygdala (Niu et al., 2004; Suzuki et al., 2005a,b), the temporal pole (Takahashi et al., 2006), and the superior temporal gyrus (Takahashi et al., 2006) are also shown in Table 2.