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A follow-up MRI study of the fusiform gyrus and middle and inferior temporal gyri in schizophrenia spectrum

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ABSTRACT

While longitudinal magnetic resonance imaging (MRI) studies have demonstrated progressive gray matter reduction of the superior temporal gyrus (STG) during the early phases of schizophrenia, it remains largely unknown whether other temporal lobe structures also exhibit similar progressive changes and whether these changes, if present, are specific to schizophrenia among the spectrum disorders. In this longitudinal MRI study, the gray matter volumes of the fusiform, middle temporal, and inferior temporal gyri were measured at baseline and follow-up scans (mean inter-scan interval = 2.7 years) in 18 patients with first-episode schizophrenia, 13 patients with schizotypal disorder, and 20 healthy controls. Both schizophrenia and schizotypal patients had a smaller fusiform gyrus than controls bilaterally at both time points, whereas no group difference was found in the middle and inferior temporal gyri. In the longitudinal comparison, the schizophrenia patients showed significant fusiform gyrus reduction (left, −2.6%/year; right, −2.3%/year) compared with schizotypal patients (left: −0.4%/year; right: −0.2%/year) and controls (left: 0.1%/year; right: 0.0%/year). However, the middle and inferior temporal gyri did not exhibit significant progressive gray matter change in all diagnostic groups. In the schizophrenia patients, a higher cumulative dose of antipsychotics during follow-up was significantly correlated with less severe gray matter reduction in the left fusiform gyrus. The annual gray matter loss of the fusiform gyrus did not correlate with that of the STG previously reported in the same subjects. Our findings suggest regional specificity of the progressive gray matter reduction in the temporal lobe structures, which might be specific to overt schizophrenia within the schizophrenia spectrum.

1. Introduction

Several whole-brain magnetic resonance imaging (MRI) studies have demonstrated progressive gray matter reduction predominantly in the temporal regions in first-episode schizophrenia (Mané et al., 2009; Whitford et al., 2006), suggesting active pathological processes during the early course of the illness. More specifically, longitudinal MRI studies using manual region-of-interest (ROI) method have revealed marked gray matter loss (up to 5%/year) of the superior temporal gyrus (STG) in these patients, which is likely to underlie positive symptomatology (Kasai et al., 2003a,b; Sun et al., 2009; Takahashi et al., 2009, 2010b). On the other hand, patients with schizotypal (personality) disorder (SPD), a prototypic disorder within the schizophrenia spectrum (Siever and Davis, 2004), or affective psychosis are unlikely to exhibit progressive STG changes (Kasai et al., 2003a,b; Takahashi et al., 2010b), suggesting that such active pathological processes are specific to overt schizophrenia among the spectrum disorders. However, whether these progressive changes occur predominantly in the STG or are widely seen in the lateral temporal regions (e.g., the middle and inferior temporal gyri) has yet to be elucidated.

The fusiform gyrus, a spindle-shaped structure located on the ventral surface of the brain, is engaged in face recognition (Haxby et al., 2000, 2002; Kanwisher et al., 1997), which has been reported to be disturbed in the schizophrenia spectrum (Conklin et al., 2002; Larøi et al., 2007; Martin et al., 2005; Morris et al., 2009; Sachs et al., 2004). Previous postmortem (McDonald et al., 2000) and MRI (Lee et al., 2002; Onitsuka et al., 2003, 2005, 2006; Takahashi et al., 2006) studies

Abbreviations: ANCOVA, analysis of covariance; ANOVA, analysis of variance; CASH, Comprehensive Assessment of Symptoms and History; FG, fusiform gyrus; ICV, intracranial volume; ITG, inferior temporal gyrus; MRI, magnetic resonance imaging; MTG, middle temporal gyrus; ROI, region-of-interest; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; SPD, schizotypal personality disorder; STG, superior temporal gyrus.

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in schizophrenia have demonstrated reduced gray matter volume in this region and its relationship to a range of clinical symptoms such as both positive (Nestor et al., 2007) and negative (Nestor et al., 2007) symptoms, lack of insight (Ha et al., 2004), and cognitive deficits (Onitsuka et al., 2006). On the other hand, a few MRI studies of the fusiform gyrus in schizotypal subjects have yielded inconsistent results, with both normal (Dickey et al., 2003) and reduced (Takahashi et al., 2006) gray matter volume. A recent finding of an inverse correlation between the volume of the left fusiform gyrus and the duration of initial untreated period of first-episode psychoses (Bangalore et al., 2009) suggests a regional progressive process in the fusiform gyrus during the early stages of psychosis. To our knowledge, however, no ROI-based MRI studies have undertaken a detailed longitudinal examination of the fusiform gyrus in first-episode schizophrenia or schizotypal patients.

This longitudinal ROI-based MRI study aimed to investigate the gray matter changes of the fusiform gyrus, middle temporal gyrus, and inferior temporal gyrus in first-episode schizophrenia and schizotypal patients compared with healthy controls. On the basis of previous cross-sectional findings in these temporal lobe structures (Takahashi et al., 2006) as well as previous observation suggesting that active pathological processes of the temporal region might be specific to overt schizophrenia (Kasai et al., 2003a,b; Takahashi et al., 2010b), we predicted that only the schizophrenia patients would show progressive gray matter loss in the fusiform gyrus. We also explored possible relationships between the progressive brain changes and clinical variables (e.g., antipsychotic medication, treatment response) in first-episode schizophrenia.

2. Methods

2.1. Participants

Eighteen first-episode schizophrenia patients (12 males, 6 females), 13 schizotypal disorder patients (9 males, 4 females), and 20 control subjects (11 males, 9 females) were included in this study. All subjects were right-handed and physically healthy, and none had a history of serious head trauma, neurological illness, substance abuse disorder, or serious medical disease. Table 1 shows the demographic and clinical data of the subjects. MRI findings of the STG in the same group of subjects have been reported previously (Takahashi et al., 2010b). Of the 51 participants in this study, 48 subjects (17 schizophrenia, 12 schizotypal, and 19 control subjects) were also included in our previous cross-sectional study of temporal lobe structures (Takahashi et al., 2006). This study was approved by the Committee on Medical Ethics of Toyama Medical and Pharmaceutical University. After a complete description of the study was provided, written informed consent was obtained from all subjects.

First-episode schizophrenia patients who fulfilled the ICD-10 research criteria (World Health Organization, 1993) were recruited from inpatient and outpatient clinics of the Department of Neuropsychiatry of Toyama University Hospital. In accordance with the literature (Hirayasu et al., 2000; Kasai et al., 2003a,b; Schooler et al., 2005; Yap et al., 2001), first-episode patients were defined as patients experiencing their first episode of schizophrenia whose illness onset was within 1 year of baseline scanning ($N=14$) or those undergoing their first psychiatric hospitalization ($N=4$). The diagnosis of schizophrenia was confirmed at the follow-up scan for all cases.

Schizotypal disorder patients who met the ICD-10 research criteria (World Health Organization, 1993) were recruited from among patients who visited the clinics of the Department of Neuropsychiatry of Toyama University Hospital. This patient group had exhibited at least four of the schizotypal features (inappropriate affect, odd behavior, social withdrawal, magical thinking, suspiciousness, ruminations without inner resistance, unusual perceptual experiences, stereotyped thinking, and occasional transient quasi-psychotic episodes) over a period of at least two years, accompanied by distress or associated problems in their lives and required clinical care including low-dose antipsychotics. Their characteristics have been described previously (Kawasaki et al., 2004; Suzuki et al., 2005; Takahashi et al., 2006). All available clinical information and data obtained from a detailed review of the patients' 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 a consensus reached by at least two psychiatrists using these data. Although all of the schizotypal subjects in this study also fulfilled the DSM-IV criteria for schizotypal personality disorder

Table 1
Demographic and clinical data of healthy controls, schizotypal disorder patients, and first-episode schizophrenia patients.

	Control subjects ($N=20$)	Schizotypal patients ($N=13$)	Schizophrenia patients ($N=18$)	Group comparisons
Male/female	11/9	9/4	12/6	Chi-square = 0.87, $p=0.649$
Height at first scan (cm)	165.6 (7.2)	166.6 (9.5)	166.1 (6.7)	ANOVA: $F(2,48)=0.08$, $p=0.925$
Education (years)	15.1 (2.4)	12.6 (2.5)	13.0 (1.6)	ANOVA: $F(2,48)=6.58$, $p=0.003$
Parental education (years)	12.9 (2.8)	12.2 (1.7)	12.4 (2.1)	ANOVA: $F(2,48)=0.40$, $p=0.670$
Age at baseline scan (years)	23.2 (5.7) [18.0–38.0]	22.8 (5.0) [16.3–34.4]	23.1 (4.7) [17.9–31.9]	ANOVA: $F(2,48)=0.32$, $p=0.727$
Inter-scan interval (years)	2.6 (0.4) [2.0–3.2]	2.9 (0.8) [1.8–4.4]	2.7 (0.6) [1.3–3.9]	ANOVA: $F(2,48)=0.84$, $p=0.437$
Age of onset (years)	–	–	21.9 (4.7) [16.0–30.0]	–
Illness duration at baseline (months)	–	–	10.8 (9.7) [1–41] (median = 6.6)	–
Duration of medication at baseline (months)	–	38.7 (61.0) [1.2–204] (median = 10.8)	9.1 (10.4) [1–36] (median = 3.6)	ANOVA: $F(1,29)=4.12$, $p=0.052$
Drug dose (haloperidol equivalent[a])				
At baseline (mg/day)	–	4.6 (3.8)	15.7 (11.9)	ANOVA: $F(1,29)=10.36$, $p=0.003$
At follow-up (mg/day)	–	5.7 (5.0)	13.2 (10.4)	ANOVA: $F(1,29)=5.86$, $p=0.022$
Mean dose during follow-up (mg/day)	–	5.4 (4.2)	9.9 (6.8)	ANOVA: $F(1,29)=4.52$, $p=0.042$
Cumulative dose during follow-up (mg)	–	5970 (6307)	10213 (8974)	ANOVA: $F(1,29)=2.13$, $p=0.155$
Total SAPS score[b]				
Baseline	–	17.0 (9.7)	34.3 (25.2)	ANOVA: $F(1,25)=5.00$, $p=0.035$
Follow-up	–	12.1 (10.2)	20.8 (17.7)	ANOVA: $F(1,28)=2.49$, $p=0.126$
Total SANS score[b]				
Baseline	–	52.1 (21.6)	58.8 (24.2)	ANOVA: $F(1,25)=0.56$, $p=0.462$
Follow-up	–	41.8 (17.2)	38.9 (24.4)	ANOVA: $F(1,28)=0.13$, $p=0.718$

Data are presented as mean (SD) [range]. SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms.
[a] The different typical and atypical antipsychotic dosages are converted into haloperidol equivalents using the guideline by Toru (2001).
[b] Data missing for 4 patients (1 schizotypal and 3 schizophrenia patients) at the baseline and for 1 schizophrenia patient at the follow-up.

(SPD) on Axis II, two subjects had previously experienced transient quasi-psychotic episodes fulfilling a DSM Axis I diagnosis of brief psychotic disorder (American Psychiatric Association, 1994). The mental condition of each subject was regularly assessed by experienced psychiatrists to check for the emergence of full-blown psychotic symptoms, and none of the 13 patients has developed overt schizophrenia to date (mean clinical follow-up period after baseline scanning = 5.1 years, SD = 2.1).

The clinical symptoms of the schizophrenia and schizotypal patients were rated at the time of scanning (baseline and follow-up) using the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1984) and the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984). At the baseline, 12 schizophrenia and 6 schizotypal patients were treated with atypical antipsychotics, and 6 schizophrenia and 7 schizotypal patients were receiving typical ones. The patients were also receiving benzodiazepines (15 schizophrenia and 8 schizotypal patients), anticholinergics (14 schizophrenia and 9 schizotypal patients), antidepressants (1 schizophrenia and 6 schizotypal patients), and/or mood stabilizers [lithium carbonate (1 schizotypal patient), sodium valproate (1 schizophrenia patient), or carbamazepine (2 schizotypal patients)]. At the follow-up scan, 11 schizophrenia and 10 schizotypal patients were on atypical antipsychotics, and 7 schizophrenia and 3 schizotypal patients were on typical antipsychotics. Some patients were also receiving benzodiazepines (13 schizophrenia and 10 schizotypal patients), anticholinergics (15 schizophrenia and 9 schizotypal patients), antidepressants (1 schizophrenia and 4 schizotypal patients), and/or mood stabilizers [sodium valproate (1 schizophrenia and 1 schizotypal patients), carbamazepine (1 schizophrenia and 2 schizotypal patients), or a combination of lithium and carbamazepine (1 schizophrenia and 1 schizotypal patients)]. During the follow-up period between scans, 9 patients (4 schizophrenia and 5 schizotypal patients) were predominantly treated with typical antipsychotics, 18 patients (11 schizophrenia and 7 schizotypal patients) were treated mostly with atypical antipsychotics (although 2 patients received typical antipsychotics for <1 month), and 4 (3 schizophrenia and 1 schizotypal patients) received substantial amounts of both typical and atypical antipsychotics.

The control subjects consisted of 20 healthy volunteers recruited from members of the community, hospital staff, and university students. They were given a questionnaire consisting of 15 items concerning their personal (13 items; e.g., a history of obstetric complications, substantial head injury, seizures, neurological or psychiatric diseases, impaired thyroid function, hypertension, diabetes, and substance use) and family (2 items) histories of illness. They did not have any personal or family history of psychiatric illness among their first-degree relatives.

2.2. Magnetic resonance imaging procedures

The subjects were scanned twice on 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 as follows: repetition time = 24 ms; echo time = 5 ms; flip angle = 40°; field of view = 256 mm; and matrix size = 256 × 256 pixels. The voxel size was 1.0 × 1.0 × 1.0 mm. The scanner was calibrated weekly with the same phantom to ensure measurement stability.

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 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 described previously (Zhou et al., 2003).

2.3. Volumetric analyses of regions of interest (ROIs)

As described in detail elsewhere (Takahashi et al., 2006), the gray matter volume of the fusiform gyrus, middle temporal gyrus, and inferior temporal gyrus was measured on consecutive 1-mm coronal slices of segmented gray matter images (Fig. 1).

Briefly, 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 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 (Kim et al., 2000; Lee et al., 2002). The fusiform gyrus was then subdivided into anterior and posterior portions by the last slice including the crus of the fornix.

For the middle and inferior temporal gyri, the slice showing the appearance of the temporal stem and that containing the anterior tip of the parieto-occipital sulcus 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

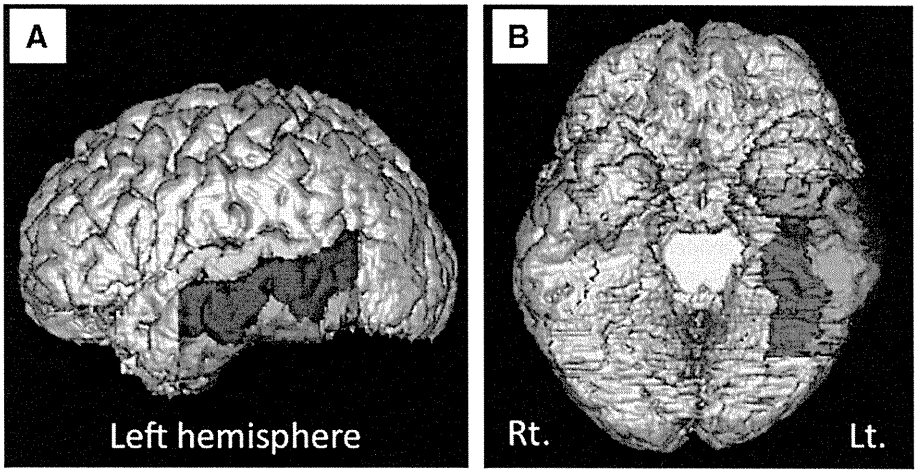

Fig. 1. Sagittal (A) and ventral (B) views of a three-dimensional reconstructed image of the temporal lobe structures. The middle (red) and inferior (green) temporal gyri and the fusiform gyrus (blue) were manually traced in this study. The superior temporal gyrus (yellow) has been measured in our previous study (Takahashi et al., 2010b) but is shown here as a reference for the topography of the temporal lobe structures.

occipitotemporal sulcus or the collateral sulcus in the area rostral to the end of the occipitotemporal sulcus was used as the inferior boundary. The middle and inferior temporal gyri were then 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 (Kim et al., 2000).

All measurements were carried out by one rater (TT) without knowledge of the subjects' identities and the times of their scans. Inter- (TT and TR) and intra-rater intraclass correlation coefficients in a subset of 10 randomly selected brains were over 0.92.

2.4. Statistical analysis

Clinical and demographic differences between groups were examined with one-way analysis of variance (ANOVA) or chi-square test. The absolute ROI volumes were analyzed using a repeated measures analysis of covariance (ANCOVA) with age, ICV, and dosage of antipsychotic medication at scanning as covariates, diagnosis as a between-subject factor, and side as a within-subject variable.

The longitudinal volume changes were analyzed using the percentage volume change [100×(absolute volume at follow-up scan − absolute volume at baseline)/absolute volume at baseline] as the dependent variable. A repeated measures ANCOVA with age at first scan, ICV, inter-scan interval, and cumulative dose of antipsychotics during scans as covariates, diagnosis as a between-subject factor, and side as a within-subject factor was performed. For the fusiform gyrus, subregion (anterior and posterior portions) was also used as a within-subject variable in these ANCOVAs. Post hoc Neumann–Keuls tests were carried out. While gender was not used as a between-subject factor owing to small sample size, especially for females, none of the ANCOVA results reported herein changed when we included gender as a covariate.

As we found significant volume changes over time only in the fusiform gyrus of first-episode schizophrenia group in this study, the correlations between the percentage volume change per year of the fusiform gyrus and the severity of clinical symptoms (absolute score change between scans and score at follow-up period of total or subscale SANS/SAPS scores) as well as cumulative dose of antipsychotics in the schizophrenia patients were analyzed using Spearman's rho. In order to examine the possible relationship of the gray matter reduction over time among temporal lobe structures in first-episode schizophrenia, Spearman's rho was calculated between the annual gray matter loss of the STG subregions (Takahashi et al., 2010b) and fusiform gyrus. For schizophrenia and schizotypal patients, the association between the relative ROI volumes (100×absolute volume/ICV) at baseline and medication effect (daily dosage, duration) was also analyzed. Statistical significance was defined as $p<0.05$.

3. Results

3.1. Demographic and clinical data

The groups were matched for age, gender, height, parental education, and inter-scan interval, but the controls had attained a higher level of education than the patients with either disorder (Table 1). While the baseline SAPS score for the schizophrenia patients was higher than that for the schizotypal patients, no significant group difference was found at follow-up, indicating relatively good response of positive symptoms to medication in our first-episode schizophrenia group (Table 1). There were significant differences in medication dosage at both time points; the schizotypal patients took significantly smaller amounts of antipsychotics than the schizophrenia patients. As ANCOVA with age as a covariate showed that the schizotypal patients had a larger ICV compared with the schizophrenia patients ($p=0.015$) and controls ($p=0.017$) [$F(2, 47)=3.65$, $p=0.034$], we controlled for ICV for all group comparisons of the ROIs examined in this study.

3.2. Cross-sectional comparison

ANCOVAs of the fusiform gyrus showed significant main effect of diagnosis at both time points [baseline, $F(2, 45)=5.75$, $p=0.006$; follow-up, $F(2, 45)=4.51$, $p=0.016$], but there were no significant interactions involving side ($p>0.369$) or subregion ($p>0.263$). Post-hoc analyses showed that both schizophrenia (baseline, $p=0.014$; follow-up, $p<0.001$) and schizotypal (baseline, $p=0.017$; follow-up, $p=0.010$) patients had significantly smaller fusiform gyrus volume than the controls, whereas no difference was found between these patient groups (baseline, $p=0.658$; follow-up, $p=0.170$).

For the middle and inferior temporal gyri, ANCOVAs revealed no main effect of diagnosis or side-by-diagnosis interaction at both baseline and second scan ($F=0.01$ to 1.03, $p=0.363$ to 0.994).

3.3. Longitudinal comparison

For the fusiform gyrus, ANCOVA showed a significant group difference [$F(2, 44)=10.03$, $p<0.001$], with the schizophrenia patients having a greater gray matter loss over time than the controls ($p<0.001$) or schizotypal patients ($p<0.001$) (Table 2, Fig. 2). However, no difference was found between the schizotypal patients and controls ($p=0.337$). There were no main effects of side [$F(1, 48)=0.39$, $p=0.533$] and subregion [$F(1, 48)=0.50$, $p=0.482$] or interactions involving these factors (all $p>0.254$), suggesting that volume changes of the fusiform gyrus were not highly localized to specific subregions. The fusiform gyrus volume changes over time did not differ between the patients who were predominantly treated with typical ($N=9$) and atypical ($N=18$) antipsychotics during the follow-up period [$F(1, 21)=0.18$, $p=0.679$].

There was no group difference for the middle [$F(2, 44)=0.05$, $p=0.949$] and inferior [$F(2, 44)=0.36$, $p=0.701$] temporal gyri.

When we used all available temporal ROI volumes (superior, middle, and inferior temporal gyri and fusiform gyrus) as the within-subject variable in a repeated measures ANCOVA model, there were significant main effects of diagnosis [$F(2, 44)=3.90$, $p=0.028$] and ROI [$F(3, 144)=2.93$, $p=0.036$] and a diagnosis-by-ROI interaction [$F(6, 144)=4.28$, $p<0.001$]. Post-hoc analyses showed that the fusiform gyrus and STG exhibited greater gray matter reduction over time compared with middle (fusiform gyrus, $p<0.001$; STG, $p=0.006$) and inferior (fusiform gyrus, $p<0.001$; STG, $p=0.006$) temporal gyri in first-episode schizophrenia. However, there was no significant difference in their progressive volume changes between the fusiform gyrus and STG ($p=0.518$) (see Table 2).

3.4. Correlational analysis

In the schizophrenia patients, annual gray matter reduction of the left posterior fusiform gyrus was correlated with higher total SANS score at follow-up (rho $=0.56$, $p=0.019$), but this correlation did not survive Bonferroni correction for multiple comparisons. A higher cumulative dose of antipsychotics during follow-up was significantly correlated with less severe gray matter reduction in the left fusiform gyrus (rho $=-0.55$, $p=0.019$). There was no medication effect (duration and daily dosage at scanning) on the baseline volume of the temporal lobe structures in the schizophrenia patients (rho $=-0.21$ to 0.20, $p=0.43$ to 0.97), while medication duration at the baseline in the schizotypal group was correlated with left middle temporal gyrus volume (rho $=-0.66$, $p=0.014$).

We also examined the association between the annual gray matter loss of the fusiform gyrus and STG subregions for first-episode

Table 2
Absolute gray matter volume of the whole brain and temporal lobe structures at the baseline and the second scan and the annual percent change.

Brain region	Control subjects			Schizotypal patients			Schizophrenia patients		
	Baseline	Second Scan	% change/y	Baseline	Second Scan	% change/y	Baseline	Second Scan	% change/y
Whole gray matter	697,069 (69,538)	693,464 (77,687)	−0.3 (1.2)	743,076 (71,627)	723,953 (50,955)	−0.9 (2.1)	684,184 (83,120)	664,053 (67,613)	−0.9 (1.8)
Whole FG									
Left	9197 (1622)	9193 (1478)	0.1 (2.2)	8245 (1315)	8133 (1433)	−0.4 (1.8)	7685 (1605)	7184 (1495)	−2.6 (2.3)
Right	9024 (1792)	9004 (1671)	0.0 (1.2)	7819 (1391)	7786 (1408)	−0.2 (1.1)	7993 (1487)	7557 (1493)	−2.3 (2.3)
Anterior FG									
Left	5157 (991)	5155 (903)	0.1 (2.2)	5103 (1300)	5048 (1457)	−0.5 (2.3)	4649 (1295)	4297 (1133)	−2.9 (2.4)
Right	5127 (1082)	5108 (1004)	0.0 (1.5)	4655 (900)	4665 (929)	−0.1 (1.1)	4756 (1071)	4467 (1033)	−2.5 (2.7)
Posterior FG									
Left	4039 (1084)	4038 (1084)	0.0 (2.7)	3142 (736)	3084 (643)	−0.3 (2.1)	3036 (918)	2887 (868)	−2.1 (2.9)
Right	3897 (909)	3896 (874)	0.1 (1.3)	3164 (764)	3121 (763)	−0.4 (1.7)	3237 (799)	3090 (817)	−2.0 (2.7)
STG									
Left	12,443 (1800)	12,397 (1762)	0.0 (1.3)	10,808 (1406)	10,563 (1356)	−0.6 (3.6)	10,795 (1992)	10,023 (1701)	−2.8 (2.8)
Right	10,631 (1219)	10,650 (1347)	−0.1 (1.5)	9926 (1272)	9732 (898)	−0.3 (3.3)	9356 (1658)	8972 (1436)	−1.5 (2.7)
MTG									
Left	14,462 (2467)	14,483 (2713)	−0.2 (1.6)	15,517 (1892)	15,442 (1707)	0.1 (2.0)	14,794 (2929)	14,681 (2951)	−0.2 (1.6)
Right	15,323 (2180)	15,186 (2152)	−0.4 (1.2)	16,693 (2007)	16,545 (1952)	−0.2 (1.8)	15,182 (2800)	15,003 (2493)	−0.3 (1.8)
ITG									
Left	12,814 (2288)	12,749 (2611)	−0.5 (2.0)	13,596 (3046)	13,454 (3130)	−0.1 (2.0)	12,377 (2419)	12,285 (2223)	−0.3 (1.7)
Right	12,026 (1746)	11,921 (1936)	−0.4 (1.6)	12,752 (1601)	12,626 (1650)	−0.4 (1.1)	11,526 (2059)	11,366 (1744)	−0.3 (2.0)

Data are presented as mean (SD). Values indicate absolute volumes (mm3) except % change/year values. FG, fusiform gyrus; ITG, inferior temporal gyrus; MTG, middle temporal gyrus; STG, superior temporal gyrus.
% change/year was calculated as follows: [100 × (absolute volume at follow-up − absolute volume at baseline)/absolute volume at baseline]/inter-scan interval. Negative value indicates decrease in volume. To demonstrate the regional volume changes within the temporal lobe structures, the previously published data of the STG (Takahashi et al., 2010b) are also shown here.

schizophrenia, but no significant correlation was found (rho = −0.12 to 0.42, $p = 0.08$ to 0.83).

4. Discussion

This longitudinal ROI-based MRI study examined the gray matter changes of the temporal lobe structures including the fusiform gyrus in first-episode schizophrenia and schizotypal disorder patients. Both patient groups had significantly smaller fusiform gyrus, but not middle and inferior temporal gyri, as compared with healthy controls at baseline, possibly reflecting a common neurobiological basis of schizophrenia susceptibility. In a longitudinal comparison, only schizophrenia patients showed further ongoing gray matter reduction in the fusiform gyrus, which might be related to the differences in phenomenology between schizophrenia and a milder form of the spectrum disorders. While we have previously reported marked STG gray matter reduction over time specifically in first-episode schizophrenia (Takahashi et al., 2010b), the middle and inferior temporal gyri did not exhibit progressive changes in the same group of subjects. The present findings thus support the regional specificity of the

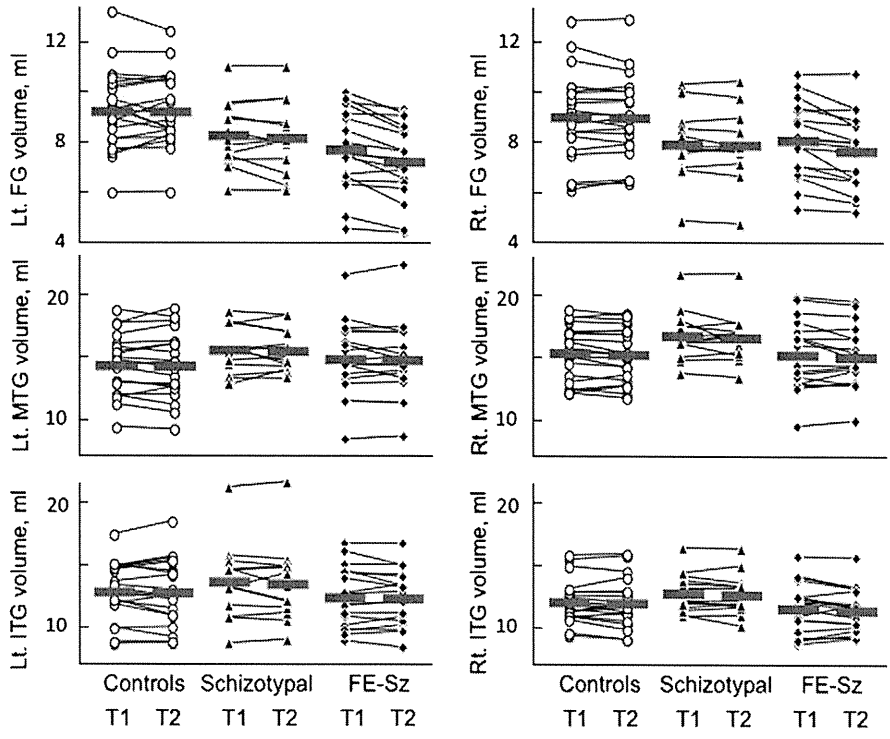

Fig. 2. Progressive volume changes of the temporal lobe structures in healthy controls, patients with schizotypal disorder, and first-episode patients with schizophrenia (FE-Sz). Values of baseline (T1) and follow-up (T2) scans in each subject are connected with a straight line. Horizontal bars indicate the means of each group. FG, fusiform gyrus; ITG, inferior temporal gyrus; MTG, middle temporal gyrus.

progressive gray matter reduction in the temporal lobe structures, which might be specific to overt schizophrenia within the schizophrenia spectrum.

Previous longitudinal studies using whole-brain voxel-based morphometric (VBM) analyses demonstrated progressive gray matter reduction predominantly in the left STG among temporal regions in first-episode schizophrenia (Mané et al., 2009; Whitford et al., 2006), which has been supported by several ROI studies showing approximately 2–6%/year reduction in this region during early phases of schizophrenia (Kasai et al., 2003a,b; Takahashi et al., 2010b). In accordance with these localized brain changes in schizophrenia, we found no cross-sectional and longitudinal gray matter changes in non-STG lateral temporal regions (middle and inferior temporal gyri) in our first-episode cohort. However, a cross-sectional MRI study by Onitsuka et al. (2004) reported gray matter reduction in these regions, which contribute to visual recognition and speech perception (Hickok and Poeppel, 2004) and are also related to auditory hallucination (Jardri et al., 2011), in male chronically medicated schizophrenia patients. The possibilities of non-STG gray matter changes later in the course of schizophrenia and potential medication effect on these regions seem worthy of further examination.

This study generally supports previous cross-sectional MRI findings of bilateral fusiform gyrus gray matter reduction in first-episode (Lee et al., 2002) and chronic (Onitsuka et al., 2003; Takahashi et al., 2006) schizophrenia. Our finding of marked ongoing gray matter reduction in the fusiform gyrus during first-episode schizophrenia is also consistent with an inverse correlation between the fusiform gyrus gray matter volume and initial untreated (Bangalore et al., 2009) or total (Premkumar et al., 2008) illness duration. No fusiform gray matter changes in previous longitudinal VBM studies might be partly attributable to methodological issues of these analyses such as problems of brain registration (Crum et al., 2003). Since our data of a significant correlation between a higher cumulative dose of antipsychotics and less severe gray matter reduction in the fusiform gyrus support the potential ameliorating effect of antipsychotics (Scherk and Falkai, 2006), different sample characteristics (e.g., medication status) might also partly explain these discrepancies. Although the pathological mechanisms underlying these progressive fusiform gray matter changes remain unknown, one postmortem study in the fusiform gyrus of schizophrenia reported reduced neuron density, enlarged minicolumn, and lack of minicolumn thinning that occurs during normal aging (Di Rosa et al., 2009), partly consistent with the hypothesis that anomalies of synaptic plasticity, abnormal brain maturation, and other factors may be relevant (Pantelis et al., 2005).

Despite the notion that dynamic brain changes during the early phases are likely to be related to clinical manifestations of schizophrenia (Takahashi et al., 2009), we did not find a significant relationship of the fusiform gyrus morphologic changes to clinical symptoms, which has been suggested by previous cross-sectional MRI studies (Ha et al., 2004; O'Daly et al., 2007; Nestor et al., 2007). This might be partly due to the small sample size of this study, as annual gray matter loss of the left posterior fusiform gyrus, which contains a core region of social cognition called the "fusiform face area" (Kanwisher et al., 1997), was non-significantly correlated with the severity of negative symptoms. It is also possible that fusiform gyrus abnormalities are more closely related to cognitive deficits, which were not comprehensively assessed in this study.

In this study, the reduction rate of the fusiform gyrus in first-episode schizophrenia (left, −2.6%/year; right, −2.3%/year) was comparable with that found in the STG (left, −2.8%/year; right, −1.5%/year) in the same group of subjects (Table 2). However, we found no direct association between the gray matter changes over time of these structures. Furthermore, whereas progressive changes of the STG were highly correlated with positive symptoms (Takahashi et al., 2010b), those of fusiform gyrus might be related to the severity of negative symptoms. Interestingly, a cross-sectional MRI study found similar dissociable brain structure–function relationships; Nestor et al. (2007) reported that (1) reduced left STG volume was related to positive symptoms and executive deficits and that (2) reduced left fusiform gyrus was related to negative symptoms and facial memory deficits in the same subjects with chronic schizophrenia. Taken together, these findings suggest the regional specificity of the temporal lobe pathology in schizophrenia in showing that the STG and fusiform gyrus might have distinct contributions to different facets of the illness. Previous MRI studies of the STG suggested a period of intense gray matter reduction during early phases of schizophrenia (Takahashi et al., 2009, 2010a,b), but it remains unclear whether other brain regions have similar nonlinear pattern of progressive changes. Thus, further longitudinal follow-up of first-episode patients as well as additional patients with chronic disease would be required to examine the nature (including the regional specificity) of the progressive gray matter reduction in the course of schizophrenia.

For schizotypal subjects, to our knowledge, only two cross-sectional MRI studies have specifically delineated the fusiform gyrus; we previously reported gray matter reduction in its posterior region in a larger sample of ICD-10 schizotypal disorder patients (Takahashi et al., 2006), whereas another group reported normal fusiform gyrus volume in male subjects with SPD (Dickey et al., 2003). Despite the inconsistencies among the reports possibly due to differences in sample characteristics (e.g., community- or clinic-based, medication status, gender ratio) or imaging techniques, our findings support the notion that schizotypal patients partly share temporal abnormalities with schizophrenia patients, which presumably underlie the attenuated forms of schizophrenic features seen in these patients (Kurachi, 2003; Siever and Davis, 2004; Suzuki et al., 2005). Recent MRI studies using sophisticated Brodmann area (BA)-based analysis in unmedicated SPD (Goldstein et al., 2009; Hazlett et al., 2008) have generally supported our results of ICD-10 schizotypal disorder in showing that SPD patients have temporal gray matter reductions but frontal areas are relatively preserved in schizotypal subjects. In the present longitudinal comparison, only the schizophrenia patients showed progressive gray matter changes of the fusiform gyrus, suggesting that, in combination with lack of frontal changes (Hazlett et al., 2008; Suzuki et al., 2005), the absence of active pathological processes in the fusiform gyrus might be partly related to the sparing of schizotypal patients from the development of full-blown schizophrenia.

A few possible confounding factors in this study should be taken into account. First, this study was partly limited by the small sample size in terms of the study participants. We found no subregional effect in the fusiform findings despite the presumable differences in the functions of the anterior versus posterior portions (Kanwisher et al., 1997). We also failed to detect a significant relationship between the fusiform gyrus volume changes and clinical symptoms in first-episode schizophrenia. The limited statistical power due to small sample size might partly explain these unexpected results. On the other hand, given the small effect size of longitudinal fusiform changes in the schizotypal patients [Cohen's $d = 0.25$ (left) and 0.17 (right)], merely a lack of statistical power could not fully explain disease specific fusiform reduction in schizophrenia [Cohen's $d = 1.20$ (left) and 1.23 (right)]. Second, given the weak correlation between the left middle temporal gyrus volume and medication duration in the schizotypal subjects, the possibility exists that the medication effects have biased our results. However, the effect of medication alone could not explain our main finding of progressive fusiform changes specific to schizophrenia patients, who received larger amounts of antipsychotics than schizotypal patients, as correlation analyses suggested potential ameliorating effects of antipsychotics. The effect of medication on brain morphology has been controversial; a recent animal study suggests a toxic effect of antipsychotics on brain volumes

(Vernon et al., 2011), whereas previous *in vivo* data suggest both toxic (Ho et al., 2011) and protective (Lieberman et al., 2005; Molina et al., 2005) effects. As antipsychotic may act regionally rather than globally (Borgwardt et al., 2009) and typical and atypical antipsychotics are likely to have different effects (Dazzan et al., 2005) on the brain morphology, the association of detailed medication data (e.g., type, cumulative dose) and longitudinal changes in several brain regions should be further examined in a larger sample. Finally, although we focused on the temporal gray matter changes in this study, assessment of other key brain regions (e.g., prefrontal cortex) would be required to clarify the diagnostic and regional specificity of active brain changes early in the course of schizophrenia.

5. Conclusion

In combination with our previous findings of the temporal lobe structures in a larger cross-sectional sample (Takahashi et al., 2006) as well as longitudinal findings of the STG in the same group of subjects (Takahashi et al., 2010b), the present findings support the model that both schizophrenia and schizotypal patients partly share temporal lobe abnormalities as a morphologic substrate for the schizophrenia spectrum, with only schizophrenia patients exhibiting further ongoing pathological processes. These temporal lobe abnormalities are likely to be localized to specific regions (i.e., the STG and fusiform gyrus) and each temporal region might be differentially involved in the clinical manifestations of schizophrenia.

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Longitudinal volume changes of the pituitary gland in patients with schizotypal disorder and first-episode schizophrenia

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ABSTRACT

An enlarged volume of the pituitary gland has been reported in the schizophrenia spectrum, possibly reflecting the hypothalamic–pituitary–adrenal (HPA) hyperactivity. However, it remains largely unknown whether the pituitary size longitudinally changes in the course of the spectrum disorders. In the present study, longitudinal magnetic resonance imaging (MRI) data were obtained from 18 patients with first-episode schizophrenia, 13 patients with schizotypal disorder, and 20 healthy controls. The pituitary volume was measured at baseline and follow-up (mean, 2.7 years) scans and was compared across groups. The pituitary volume was larger in the schizophrenia patients than controls at baseline, and both patient groups had significantly larger pituitary volume than controls at follow-up. In a longitudinal comparison, both schizophrenia (3.6%/year) and schizotypal (2.7%/year) patients showed significant pituitary enlargement compared with controls (−1.8%/year). In the schizophrenia patients, greater pituitary enlargement over time was associated with less improvement of delusions and higher scores for thought disorders at the follow-up. These findings suggest that the pituitary gland exhibits ongoing volume changes during the early course of the schizophrenia spectrum as a possible marker of state-related impairments.

1. Introduction

Hypothalamic–pituitary–adrenal (HPA) axis hyperactivity is thought to reflect stress-related hormonal dysregulation and has been described in schizophrenia and related disorders (Phillips et al., 2006; Walker et al., 2008). Neuroendocrine studies in schizophrenia and schizotypal (personality) disorder (SPD), a prototypic disorder within the schizophrenia spectrum (Siever and Davis, 2004), have demonstrated that these disorders might share similar HPA axis dysfunctions, such as higher salivary cortisol level (Mittal et al., 2007; Walker et al., 2001) or blunted cortisol response to acute metabolic stress (Mitropoulou et al., 2004), as a potential indicator of common stress vulnerability. Furthermore, the association of HPA axis dysfunction with symptom severity (Goyal et al., 2004; Walder et al., 2000; Walker et al., 2001), medication (Cohrs et al., 2006; Scheepers et al., 2001), and illness stages (Phillips et al., 2006; Walker et al., 2008) in these disorders suggests that HPA activity reflects state-related impairments in the course of the schizophrenia spectrum.

The pituitary gland, an integral part of the HPA axis, may be one of the brain regions most affected by the hormonal stress response (Phillips et al., 2006). Recent magnetic resonance imaging (MRI) findings of increased pituitary volume in first-episode psychosis (Pariante et al., 2004, 2005), recent onset schizophrenia or schizotypal disorder (Takahashi et al., 2009), and individuals at high risk of developing psychosis (Garner et al., 2005) have been attributed to HPA hyperactivity in the early stages of these disorders, whereas normal (Tournikioti et al., 2007) or even decreased (Pariante et al., 2004) pituitary volume in chronically medicated schizophrenia patients could be explained by the notion that pituitary size is reduced over time as a result of prolonged HPA activation (Pariante et al., 2004; Sassi et al., 2001). However, the few longitudinal MRI studies of pituitary volume in psychotic disorders have yielded inconsistent findings from non-significant decrease (<2% over a 3-month period) (Nicolo et al., 2010) to 12% increase over 12 months (MacMaster et al., 2007b) during the first episode of illness. The effect of medication is also an important consideration for the pituitary

Abbreviations: ANCOVA, analysis of covariance; ANOVA, analysis of variance; CASH, Comprehensive Assessment of Symptoms and History; HPA axis, hypothalamic–pituitary–adrenal axis; ICV, intracranial volume; MMPI, Minnesota Multiphasic Personality Inventory; MRI, magnetic resonance imaging; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; SPD, schizotypal personality disorder.

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findings (MacMaster et al., 2007b; Nicolo et al., 2010; Phillips et al., 2006), but a cross-sectional finding of decreased pituitary volume in antipsychotic-naïve schizophrenia patients with relatively recent onset (Upadhyaya et al., 2007) suggests that factors other than illness stages or medication, such as early treatment response (Garner et al., 2009), might also affect the pituitary volume. However, the precise effect of these clinical factors in schizophrenia remains unclear, especially for pituitary volume changes over time. In addition, no longitudinal MRI studies have examined the pituitary volume in schizotypal subjects, who have no overt and sustained psychosis but partly share stress vulnerability with full-blown schizophrenia (Siever and Davis, 2004).

This longitudinal MRI study investigated the pituitary volume changes over time in patients with first-episode schizophrenia and schizotypal disorder compared with those in healthy equivalents. On the basis of the potential role of the pituitary volume as an indicator of HPA dysfunction in the schizophrenia spectrum (Takahashi et al., 2009), which could reflect state influences of the disorders (Garner et al., 2009; Phillips et al., 2006; Walker et al., 2008), we predicted that both schizophrenia and schizotypal patients would show progressive pituitary enlargement. We also explored the relationship between the pituitary volume changes over time and several clinical factors (e.g., antipsychotic medication and early treatment response) in these disorders.

2. Methods

2.1. Participants

Eighteen first-episode schizophrenia patients who fulfilled the ICD-10 research criteria (World Health Organization, 1993) were recruited from inpatient and outpatient clinics of the Department of Neuropsychiatry of Toyama University Hospital. In accordance with the literature (Hirayasu et al., 2000; Kasai et al., 2003; Schooler et al., 2005; Takahashi et al., 2009; Yap et al., 2001), first-episode patients were defined as patients experiencing their first episode of schizophrenia whose illness onset was within 1 year of baseline scanning ($N=14$) or those undergoing their first psychiatric hospitalization ($N=4$). The diagnosis of schizophrenia was confirmed at the follow-up scan for all cases.

Schizotypal disorder patients ($N=13$) who met the ICD-10 research criteria (World Health Organization, 1993) were recruited from among patients who visited the clinics of the Department of Neuropsychiatry of Toyama University Hospital. This patient group had exhibited at least four of the schizotypal features (inappropriate affect, odd behavior, social withdrawal, magical thinking, suspiciousness, ruminations without inner resistance, unusual perceptual experiences, stereotyped thinking, and occasional transient quasi-psychotic episodes) over a period of at least 2 years, accompanied by distress or associated problems in their lives and required clinical care including low-dose antipsychotics. Their characteristics have been described previously (Kawasaki et al., 2004; Suzuki et al., 2005; Takahashi et al., 2006). All available clinical information and data obtained from a detailed review of the patients' 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 a consensus reached by at least two psychiatrists using these data. Although all of the schizotypal subjects in this study also fulfilled the DSM-IV criteria for SPD on Axis II, two subjects had previously experienced transient quasi-psychotic episodes fulfilling a DSM Axis I diagnosis of brief psychotic disorder (American Psychiatric Association, 1994). The mental condition of each subject was regularly assessed by experienced psychiatrists to check for the emergence of full-blown psychotic symptoms, and none of the 13 patients has developed overt schizophrenia to date (mean clinical follow-up period after baseline scanning = 5.1 years, SD = 2.1).

The control subjects consisted of 20 healthy volunteers recruited from members of the community, hospital staff, and university students. They were given a questionnaire consisting of 15 items concerning their personal (13 items; e.g., a history of obstetric complications, substantial head injury, seizures, neurological or psychiatric diseases, impaired thyroid function, hypertension, diabetes, and substance use) and family (2 items) histories of 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 relatively homogeneous control group without eccentric profiles on the MMPI and were excluded if they had an abnormal profile, namely, any T-score on the validity or clinical scales exceeding 70.

The clinical symptoms of the schizophrenia and schizotypal patients were rated at the time of scanning (baseline and follow-up) using the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1984) and the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984). At the baseline, 12 schizophrenia and 6 schizotypal patients were treated with atypical antipsychotics, and 6 schizophrenia and 7 schizotypal patients were receiving typical antipsychotics. The patients were also receiving benzodiazepines (15 schizophrenia and 8 schizotypal patients), anticholinergics (14 schizophrenia and 9 schizotypal patients), antidepressants (1 schizophrenia and 6 schizotypal patients), and/or mood stabilizers [lithium carbonate (1 schizotypal patient), sodium valproate (1 schizophrenia patient), or carbamazepine (2 schizotypal patients)]. At the follow-up scan, 11 schizophrenia and 10 schizotypal patients were on atypical antipsychotics, and 7 schizophrenia and 3 schizotypal patients were on typical antipsychotics. Some patients were also receiving benzodiazepines (13 schizophrenia and 10 schizotypal patients), anticholinergics (15 schizophrenia and 9 schizotypal patients), antidepressants (1 schizophrenia and 4 schizotypal patients), and/or mood stabilizers [sodium valproate (1 schizophrenia and 1 schizotypal patients), carbamazepine (1 schizophrenia and 2 schizotypal patients), or a combination of lithium and carbamazepine (1 schizophrenia and 1 schizotypal patients)]. During the follow-up period between scans, 9 patients (4 schizophrenia and 5 schizotypal patients) were predominantly treated with typical antipsychotics, 18 patients (11 schizophrenia and 7 schizotypal patients) were treated mostly with atypical antipsychotics (although 2 patients received typical antipsychotics for <1 month), and 4 (3 schizophrenia and 1 schizotypal patients) received substantial amounts of both typical and atypical antipsychotics.

All subjects were right-handed and physically healthy, and none of the participants were pregnant or taking exogenous estrogens at the time of the study. None had a history of serious head trauma, neurological illness, substance abuse disorder, or serious medical disease (e.g., primary hypothyroidism). All participants were also screened for gross brain abnormalities (e.g., pituitary or hypothalamic tumor) by neuroradiologists. However, hormonal levels as well as menstrual cycle in females were not assessed at scanning. Of the 51 participants in this study, 48 subjects (17 schizophrenia, 12 schizotypal, and 19 control subjects) were included in our previous cross-sectional study of pituitary volume (Takahashi et al., 2009). This study was approved by the Committee on Medical Ethics of Toyama Medical and Pharmaceutical University. After a complete description of the study was provided, written informed consent was obtained from all subjects.

2.2. Magnetic resonance imaging procedures

The subjects were scanned twice on 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. The scanner was calibrated weekly with the same phantom to ensure measurement stability.

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 signal-intensity histogram distributions from the T1-weighted images across the whole cerebrum were then used to semi-automatically segment the voxels into brain tissue components and cerebrospinal fluid. The intracranial volume (ICV) was measured to correct for differences in head size as described previously (Zhou et al., 2003).

2.3. Pituitary measurements

The volume of the pituitary gland was manually traced on consecutive 1-mm coronal slices on the basis of a method used by Garner et al. (2005). Briefly, we traced around the usually well-defined borders of anterior and posterior pituitary: the diaphragma sellae, superiorly; the sphenoid sinus, inferiorly; and the cavernous sinuses, bilaterally. As presented in Fig. 1, the pituitary stalk was excluded from the tracings, but we included a posterior bright spot, corresponding to the posterior pituitary (the intensity of which is thought to reflect vasopressin concentration). All measurements were carried out by a trained rater (TT) without knowledge of the subjects' identities and the times of their scans. Inter- (TT and VL) and intra-rater intraclass correlation coefficients in a subset of 10 randomly selected brains were over 0.93.

2.4. Statistical analysis

Clinical and demographic differences between groups were examined with one-way analysis of variance (ANOVA) or chi-square test. The absolute volume of the pituitary gland was analyzed using a repeated measures analysis of covariance (ANCOVA) with age at first scan, ICV, inter-scan interval, and cumulative dose of antipsychotics during scans as covariates, diagnosis as a between-subject factor, and time of scan (baseline and follow-up) as a within-subject variable. We also investigated the pituitary volume change over time using ANCOVA with the percentage volume change [100 × (absolute volume at follow-up scan − absolute volume at baseline)/absolute volume at baseline] as the dependent variable. Post hoc Tukey honestly significant difference test was used. While gender was not used as a between-subject factor owing to the small sample size, especially for females, none of the ANCOVA results reported herein changed when we included gender as a covariate.

While our previous cross-sectional study in a larger sample (Takahashi et al., 2009) found no significant correlation between pituitary volume and clinical variables (including onset age, illness duration, daily dosage or duration of antipsychotic medication, and the severity of both positive and negative symptoms), longitudinal changes in HPA activity in psychosis have been implicated in the manifestation of clinical symptoms (Phillips et al., 2006; Walker et al., 2010). We therefore examined the correlation between the percentage pituitary volume change per year and SANS/SAPS subscale scores (absolute score change between scans and score at follow-up) using Spearman's rho. The association between the annual pituitary volume change and cumulative dose of antipsychotics as well as illness (schizophrenia) or medication (schizophrenia and schizotypal disorder) duration at baseline was also analyzed. Statistical significance was defined as $p<0.05$.

3. Results

3.1. Demographic and clinical data

The groups were matched for age, gender, height, parental education, and inter-scan interval, but the controls had attained a higher level of education than the patients with either disorder (Table 1). While the baseline SAPS score for the schizophrenia patients was higher than that for the schizotypal patients, no significant group difference was found at follow-up, indicating relatively good response of positive symptoms to medication in our first-episode schizophrenia group (Table 1). There were significant differences in medication dosage at both time points; the schizotypal patients took significantly smaller amounts of antipsychotics than the schizophrenia patients. ANCOVA with age as a covariate showed that the schizotypal patients had a larger ICV compared with the schizophrenia patients ($p=0.015$) and controls ($p=0.017$) [$F(2, 47)=3.65$, $p=0.034$].

3.2. Comparison of absolute pituitary volume

ANCOVA showed a significant effect of time [$F(1, 48)=11.87$, $p=0.001$] and a time-by-diagnosis interaction [$F(2, 48)=14.01$, $p<0.001$]. The pituitary volume was larger in the schizophrenia patients than controls at baseline ($p=0.021$), and both patient groups

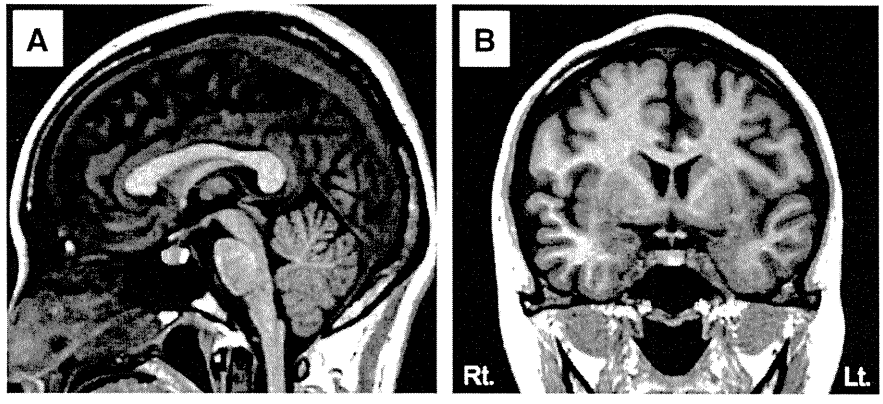

Fig. 1. Sagittal (A) and coronal (B) views of the pituitary gland manually traced in this study (blue). The pituitary stalk was excluded from the tracings, but we included a posterior bright spot.

had significantly larger pituitary volume than controls at follow-up ($p<0.001$) (Table 2). The schizophrenia patients had a larger pituitary volume compared with schizotypal patients (baseline, $p=0.004$; second scan, $p=0.002$).

While no significant difference was found between the pituitary volume at baseline and follow-up for the controls ($p=0.250$), the pituitary gland exhibited a significant volume enlargement (follow-up>baseline) in both patient groups (schizophrenia, $p=0.002$; schizotypal, $p=0.020$).

3.3. Comparison of pituitary percentage volume change

ANCOVA of the longitudinal volume change showed a significant group difference [$F(2, 44)=11.92$, $p<0.001$], with both schizophrenia ($p<0.001$) and schizotypal ($p<0.001$) patients having a greater pituitary enlargement over time than the controls (Table 2, Fig. 2). However, there was no difference between the schizophrenia and schizotypal patients ($p=0.984$).

The pituitary volume changes over time did not differ between the patients who were predominantly treated with typical ($N=9$) and atypical ($N=18$) antipsychotics during the follow-up period [$F(1, 21)=2.23$, $p=0.150$].

3.4. Correlational analysis

In the schizophrenia patients, greater pituitary enlargement over time was correlated with less improvement of delusions ($N=14$, rho$=0.59$, $p=0.026$) and higher scores for thought disorders at the follow-up ($N=17$, rho$=0.73$, $p<0.001$) (Fig. 3), although the former result did not reach statistical significance after Bonferroni correction for multiple comparisons. There was an outlier with a high SAPS thought disorder score at the follow-up (Fig. 3, *right*), but the result did not change even when we excluded this patient ($N=16$, rho$=0.70$, $p=0.002$). No such correlations were found for the schizotypal patients (all $p>0.427$). The SANS subscale scores did not correlate with pituitary changes over time in both patient groups (all $p>0.100$).

A higher cumulative dose of antipsychotics during follow-up was significantly correlated with greater improvement of hallucinations (rho$=-0.57$, $p=0.035$) in schizophrenia, but there was no significant correlation between the cumulative dose and pituitary volume changes over time in the schizophrenia patients (rho$=-0.33$, $p=0.179$), schizotypal patients (rho$=-0.31$, $p=0.306$), or in the patient group as a whole (rho$=-0.25$, $p=0.175$). When we examined only the patients treated with atypical antipsychotics during follow-up ($n=18$), a higher cumulative dose of antipsychotics tended to correlate with less severe pituitary enlargement (rho$=-0.43$, $p=0.075$). The longitudinal pituitary changes did not correlate with illness (schizophrenia, rho$=0.25$, $p=0.312$) or medication (schizophrenia, rho$=0.21$, $p=0.406$; schizotypal, rho$=0.00$, $p=1.000$) duration.

Table 2
Intracranial and pituitary volumes in the study participants.

Brain region	Controls (11 males, 9 females)		Schizotypal patients (9 males, 4 females)		Schizophrenia patients (12 males, 6 females)	
	Mean	SD	Mean	SD	Mean	SD
ICV (cm^3)	1494	142	1593[a]	104	1477	137
Pituitary gland (mm^3)						
Baseline	719	159	703	141	768[b]	125
Second scan	688	164	762[c]	162	830[b]	134
% change/year	−1.8	2.0	2.7[c]	1.7	3.6[c]	5.0

Values indicate absolute volumes except % change/year values.
% change/year was calculated as follows: [100×(absolute volume at follow-up − absolute volume at baseline)/absolute volume at baseline]/inter-scan interval. Negative value indicates a decrease in volume.
The statistical analyses for longitudinal changes reported herein were based on % changes covarying with inter-scan interval.
For the results of analyses of covariance and post hoc tests, see text.
[a] Significantly larger than controls and schizophrenia patients.
[b] Significantly larger than controls and schizotypal patients.
[c] Significantly larger than controls.

4. Discussion

In the present longitudinal MRI study, we found a significant pituitary enlargement over time in both first-episode schizophrenia and schizotypal disorder patients compared with age- and gender-matched

Table 1
Demographic and clinical data of healthy controls, schizotypal disorder patients, and first-episode schizophrenia patients.

	Control subjects ($N=20$)	Schizotypal patients ($N=13$)	Schizophrenia patients ($N=18$)	Group comparisons
Male/female	11/9	9/4	12/6	Chi-square$=0.87$, $p=0.649$
Height at first scan (cm)	165.6 (7.2)	166.6 (9.5)	166.1 (6.7)	ANOVA: $F(2,48)=0.08$, $p=0.925$
Education (years)	15.1 (2.4)	12.6 (2.5)	13.0 (1.6)	ANOVA: $F(2,48)=6.58$, $p=0.003$
Parental education (years)	12.9 (2.8)	12.2 (1.7)	12.4 (2.1)	ANOVA: $F(2,48)=0.40$, $p=0.670$
Age at baseline scan (years)	23.2 (5.7) [18.0–38.0]	22.8 (5.0) [16.3–34.4]	23.1 (4.7) [17.9–31.9]	ANOVA: $F(2,48)=0.32$, $p=0.727$
Inter-scan interval (years)	2.6 (0.4) [2.0–3.2]	2.9 (0.8) [1.8–4.4]	2.7 (0.6) [1.3–3.9]	ANOVA: $F(2,48)=0.84$, $p=0.437$
Age of onset (years)	–	–	21.9 (4.7) [16.0–30.0]	–
Illness duration at baseline (months)	–	–	10.8 (9.7) [1–41] (median$=6.6$)	–
Duration of medication at baseline (months)	–	38.7 (61.0) [1.2–204] (median$=10.8$)	9.1 (10.4) [1–36] (median$=3.6$)	ANOVA: $F(1,29)=4.12$, $p=0.052$
Drug dose (haloperidol equivalent[a])				
At baseline (mg/day)	–	4.6 (3.8)	15.7 (11.9)	ANOVA: $F(1,29)=10.36$, $p=0.003$
At follow-up (mg/day)	–	5.7 (5.0)	13.2 (10.4)	ANOVA: $F(1,29)=5.86$, $p=0.022$
Mean dose during follow-up (mg/day)	–	5.4 (4.2)	9.9 (6.8)	ANOVA: $F(1,29)=4.52$, $p=0.042$
Cumulative dose during follow-up (mg)	–	5970 (6307)	10,213 (8974)	ANOVA: $F(1,29)=2.13$, $p=0.155$
Total SAPS score[b]				
Baseline	–	17.0 (9.7)	34.3 (25.2)	ANOVA: $F(1,25)=5.00$, $p=0.035$
Follow-up	–	12.1 (10.2)	20.8 (17.7)	ANOVA: $F(1,28)=2.49$, $p=0.126$
Total SANS score[b]				
Baseline	–	52.1 (21.6)	58.8 (24.2)	ANOVA: $F(1,25)=0.56$, $p=0.462$
Follow-up	–	41.8 (17.2)	38.9 (24.4)	ANOVA: $F(1,28)=0.13$, $p=0.718$

Data are presented as mean (SD) [range]. SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms.
[a] The different typical and atypical antipsychotic dosages are converted into haloperidol equivalents using the guideline by Toru (2001).
[b] Data missing for 4 patients (1 schizotypal and 3 schizophrenia patients) at the baseline and for 1 schizophrenia patient at the follow-up.

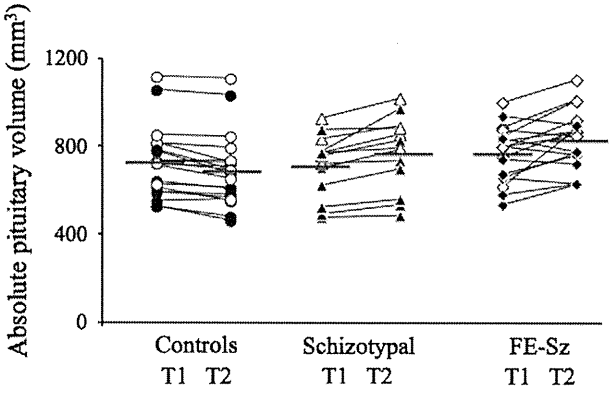

Fig. 2. Progressive volume changes of the pituitary gland in healthy controls, patients with schizotypal disorder, and first-episode patients with schizophrenia (FE-Sz). Values of baseline (T1) and follow-up (T2) scans in each subject are connected with a straight line. Horizontal bars indicate the means of each group. Male and female participants in each group were colored in black and white, respectively.

healthy controls. Our baseline findings replicated the findings by Pariante et al. (2004) in showing that first-episode schizophrenia patients had significantly larger pituitary volume compared with controls. Furthermore, in the schizophrenia group, greater pituitary enlargement over time was associated with less improvement of delusions and higher scores for thought disorders at the follow-up. These findings provide evidence that the pituitary gland exhibits ongoing volume changes during the early course of the schizophrenia spectrum, which might be a marker of state-related impairments.

To date, longitudinal volume changes of the pituitary gland have not been well documented, even for healthy subjects. Consistent with previous cross-sectional observations suggesting normal age-related pituitary atrophy after puberty (Lurie et al., 1990; MacMaster et al., 2007a; Takano et al., 1999), which are considered to reflect endocrinological change and ischemic degeneration of the anterior lobe (Kato et al., 2002), we directly demonstrated pituitary volume reduction over time in medically and psychiatrically healthy controls (mean = 23.2 years, 18 to 38 years of age) during a follow-up period of approximately 2.6 years. The rate of reduction in our sample (− 1.8%/year) was less than but comparable to that in an earlier study by MacMaster et al. (2007b), who demonstrated a 3% decrease of pituitary volume in healthy controls (mean = 23.8 years, 12 to 32 years of age) over a 12-month follow-up.

In sharp contrast to the findings in healthy controls, both schizophrenia (3.6%/year) and schizotypal (2.7%/year) patients exhibited a substantial degree of ongoing pituitary enlargement over an approximately 3-year period. Pituitary volume changes in psychotic disorders might reflect HPA axis hyperactivity and a subsequent increase in the size and number of corticotrophs [cells producing adrenocorticotropic hormone (ACTH)], which could be explained by an activation of the hormonal stress response during psychotic experience (Pariante et al., 2004, 2005). The most common causes of pituitary enlargement [i.e., administration of estrogens, hypothalamic tumor, pregnancy, and primary hypothyroidism (Elster, 1993; Miki et al., 2005)] were excluded in our subjects. Age and gender have been reported to affect pituitary volume (Kato et al., 2002; MacMaster et al., 2007a), but the participants in this study were matched for these variables. The present findings might be consistent with the model of ongoing active pathological process related to HPA axis dysregulation in the course of schizophrenia spectrum disorders (Walker et al., 2008, 2010).

To our knowledge there have been only two MRI studies of longitudinal pituitary volume changes in psychotic disorders, which have yielded inconsistent findings such as a non-significant decrease (<2% over a 3-month period) in one study (Nicolo et al., 2010) and a 12% increase over 12 months in another study (MacMaster et al., 2007b) during the first episode of illness. Our finding of 3.6%/year pituitary enlargement in first-episode schizophrenia is similar to that of MacMaster et al. (2007b), although considerably less pronounced. These discrepancies could be the result of methodological and sample differences across studies [e.g., imaging techniques, gender ratios, and schizophrenia (MacMaster et al., 2007b) versus psychosis in general (Nicolo et al., 2010), medication, and other clinical factors]. As for the effect of medication, Nicolo et al. (2010) demonstrated a cumulative 3-month dose of atypical antipsychotics to be *negatively* correlated with pituitary volume changes in first-episode psychosis. Although not statistically significant, our results of correlational analyses are in line with their finding, suggesting that atypical antipsychotics may reduce pituitary volume in a dose-dependent manner in psychotic disorders (Nicolo et al., 2010), possibly due to suppression of HPA axis activity (Phillips et al., 2006; Scheepers et al., 2001; Walker et al., 2008). In contrast, MacMaster et al. (2007b) explained their finding of pituitary enlargement in drug-naïve patients following antipsychotic medication (especially prolactin-elevating drugs) as a consequence of an activation of prolactin-secreting cells. Owing to the lack of hormonal measures, however, it remains unclear whether pituitary expansion in their sample predominantly reflects the pathological

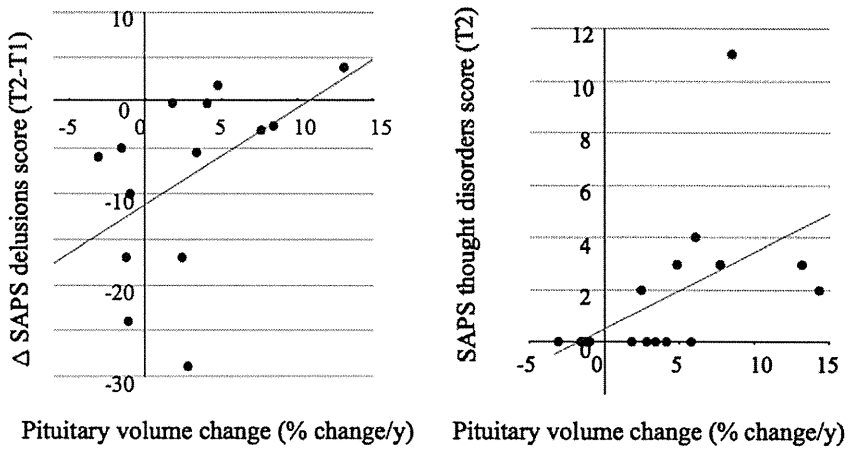

Fig. 3. Correlations between annual pituitary volume changes and absolute score changes of delusions between the baseline (T1) and follow-up (T2) scans on the Scale for the Assessment of Positive Symptoms (SAPS) (rho = 0.59, $p = 0.026$) (*left*) and SAPS thought disorder score at T2 (rho = 0.73, $p < 0.001$) (*right*) in first-episode schizophrenia patients. Annual pituitary volume change was calculated as follows: [100 × (absolute volume at T2 − absolute volume at T1)/absolute volume at T1]/inter-scan interval (in years). Positive values indicate increases in volume.

process of the disease itself or medication effects. Furthermore, a different breakdown of antipsychotics within the atypical group (Nicolo et al., 2010) as well as other psychotropics such as lithium (Bschor et al., 2002; Peiffer et al., 1991) or carbamazepine (Watson et al., 2004; Zobel et al., 2001) could differentially affect HPA function. On the other hand, our findings demonstrated that treatment response and severity of positive psychotic symptoms are also related to pituitary volume changes during the first episode of schizophrenia, consistent with recent cross-sectional MRI findings (Garner et al., 2009). Although the assessment of stress, anxiety, and cognitive or social impairments was not comprehensively undertaken in this sample, a possible effect of medication, positive psychotic symptomatology, and these other mediating factors on pituitary volume seem worthy of further examination. Furthermore, cross-sectional studies in chronic patients (illness duration>15 years) demonstrated normal (Tournikioti et al., 2007) or even decreased (Pariante et al., 2004) pituitary volume, suggesting its atrophy in the later course of the illness. Thus, it would be also worthwhile studying the pituitary changes over time in the chronic phase of psychosis.

In this study, schizotypal disorder patients exhibited similar pituitary enlargement over time to that of established schizophrenia patients, partly consistent with previous neuroendocrine investigations showing HPA hyperactivity in SPD (Mitropoulou et al., 2004; Mittal et al., 2007) and cross-sectional findings of pituitary enlargement in a larger schizotypal cohort (Takahashi et al., 2009). In combination with an association between elevated cortisol levels in SPD subjects and the severity of their clinical schizotypal signs (Walker et al., 2001), these findings suggest that the social distress related to schizotypal features (Dickey et al., 2005) could activate the stress response even without florid psychosis. On the other hand, a recent study of cortisol levels demonstrated longitudinal HPA changes in "at-risk" adolescents who subsequently developed psychosis (Walker et al., 2010). As schizotypal subjects have a higher incidence of developing psychosis (e.g., brief psychotic disorder) than the general population (Nordentoft et al., 2006), further study of the association of longitudinal pituitary volume changes with clinical course in a larger sample would allow us to test the hypothesis that HPA activity could trigger the expression of psychotic symptoms in vulnerable individuals (Walker et al., 2010).

A few possible confounding factors in this study should be taken into account. First, although our findings of ongoing pituitary volume changes might reflect state-related HPA axis dysregulation, we did not directly assess pituitary function. While our findings support the notion that atypical antipsychotics may reduce the pituitary volume, the pituitary gland is also considered to be sensitive especially to prolactin-elevating antipsychotics (MacMaster et al., 2007b; Mondelli et al., 2008). Thus, additional assessment of both pituitary volume and hormonal levels (e.g., cortisol, ACTH, and prolactin) is required. Second, the tracing protocol we used did not enable us to distinguish the anterior from the posterior lobe of the pituitary gland. However, the posterior pituitary that secretes oxytocin and vasopressin (Elster, 1993) constitutes less than 20% of the total pituitary gland and only tumors are associated with its enlargement (Krishnan et al., 1991; Mondelli et al., 2008). Third, despite sexual dimorphism of pituitary volume (males<females) reported in both healthy subjects and psychotic patients (MacMaster et al., 2007a; Takahashi et al., 2009), we could not reliably assess the effect of gender owing to the small sample size, especially for females. We found no overall effect of gender on longitudinal pituitary changes [males ($N=32$), mean = −1.0%/year; females ($N=19$), mean = −1.7%/year; ANCOVA, $F(1, 45)=2.27$, $p=0.139$], and the ANCOVA results for the longitudinal comparison reported herein did not alter even when we examined males and females separately [diagnosis effect for males, $F(2, 25)=5.04$, $p=0.015$; diagnosis effect for females, $F(2, 12)=5.03$, $p=0.026$]. However, further studies should examine the diagnosis-by-gender interaction on pituitary volume in a larger longitudinal sample. In addition, the current pituitary findings in schizotypal patients (no significant enlargement at baseline, smaller as compared with schizophrenia patients) are partly inconsistent with those in our previous cross-sectional study (Takahashi et al., 2009), which could be partly related to the small sample size. No correlations between the clinical symptoms and pituitary changes in schizotypal patients might be attributed to small sample size, mild and attenuated psychotic symptoms in this group, or substantial exposure to antipsychotics prior to the baseline scanning (median = 10.8 months). Finally, given that HPA axis functioning appears to be affected in various psychiatric populations, such as major depressive disorders (Axelson et al., 1992; Krishnan et al., 1991; MacMaster and Kusumakar, 2004), further investigation of the disease specificity of the pituitary findings is warranted, ideally in a longitudinal design across various stages.

5. Conclusion

In contrast to age-related pituitary volume reduction in healthy controls, we demonstrated ongoing volume expansion of the pituitary gland in both first-episode schizophrenia and schizotypal disorder patients. Furthermore, greater pituitary enlargement appears to be related to less improvement of positive psychotic symptoms during the early phases of schizophrenia. Although the effects of medication as well as hormonal levels should be further examined, the present longitudinal study complements and extends previous neuroendocrine and cross-sectional MRI findings in suggesting that the pituitary gland exhibits ongoing volume changes early in the course of the schizophrenia spectrum as a possible state-related marker.

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PLoS one

Classification of First-Episode Schizophrenia Patients and Healthy Subjects by Automated MRI Measures of Regional Brain Volume and Cortical Thickness

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Abstract

Background: Although structural magnetic resonance imaging (MRI) studies have repeatedly demonstrated regional brain structural abnormalities in patients with schizophrenia, relatively few MRI-based studies have attempted to distinguish between patients with first-episode schizophrenia and healthy controls.

Method: Three-dimensional MR images were acquired from 52 (29 males, 23 females) first-episode schizophrenia patients and 40 (22 males, 18 females) healthy subjects. Multiple brain measures (regional brain volume and cortical thickness) were calculated by a fully automated procedure and were used for group comparison and classification by linear discriminant function analysis.

Results: Schizophrenia patients showed gray matter volume reductions and cortical thinning in various brain regions predominantly in prefrontal and temporal cortices compared with controls. The classifiers obtained from 66 subjects of the first group successfully assigned 26 subjects of the second group with accuracy above 80%.

Conclusion: Our results showed that combinations of automated brain measures successfully differentiated first-episode schizophrenia patients from healthy controls. Such neuroimaging approaches may provide objective biological information adjunct to clinical diagnosis of early schizophrenia.

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Introduction

Schizophrenia is a disabling psychiatric disorder which usually begins to affect individuals during their adolescence or early adulthood and most patients continue to suffer social, economic, and psychological difficulties from the first manifestation of the illness. Currently, diagnoses of psychiatric disorders are made on the basis of clinical manifestations and associated psycho-social disturbances [1,2]. However, there is an evidence for diagnostic instability in psychotic patients at an early stage of illness [3,4]. Although an accurate diagnosis is considered a prerequisite for appropriate physical/psychological treatment for each patient, no objective biomarker has been identified.

Previous structural magnetic resonance imaging (MRI) studies have demonstrated gray matter reductions of fronto-temporolimbic brain regions in schizophrenia patients compared with those of healthy subjects [5–11]. Several MRI-based studies have attempted to distinguish schizophrenia patients from healthy subjects using a variety of approaches such as manually traced regions of interest (ROI) [12,13], voxel-based morphometry (VBM) [14–16], cortical pattern matching [17], and cortical thickness obtained by a surface-based approach [18]. These studies have generally reported high classification accuracies (ranging from 75% to 92%), suggesting the potential clinical (i.e., diagnostic) utility of structural MRI. The majority of such classification studies employed chronic schizophrenia patients [12,14–16,18]. To date, only two studies [13,17] have attempted to distinguish between first-episode patients and healthy subjects by structural MRI.

Recently, an automated surface-based approach which can reliably measure local mean cortical thickness has been developed [19]. Several MRI studies applying this technique to schizophrenia have yielded robust findings such as cortical thinning especially in prefrontal and temporal regions [20–25]. This surface-based approach also enables to perform cortical parcellation and

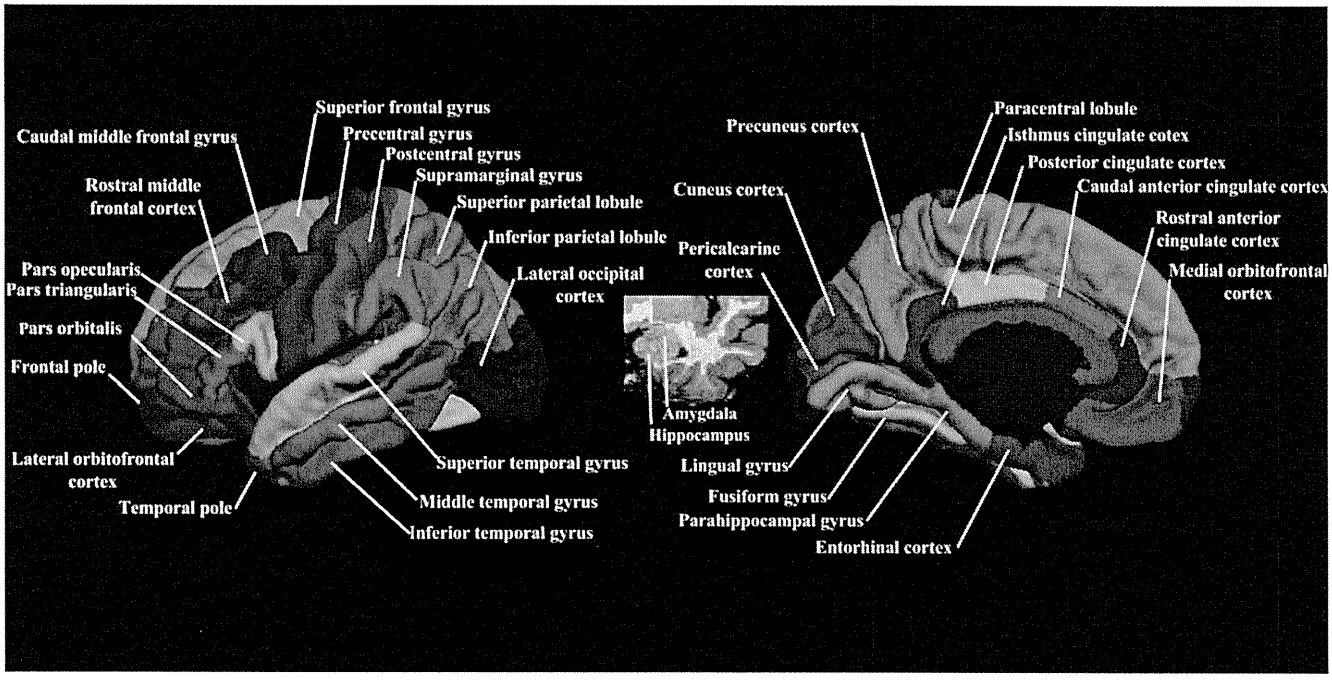

Figure 1. Representations of ROIs examined in this study on the left hemisphere. Cortical ROIs are shown in lateral view (left) and medial view (right). Two subcortical ROIs (i.e., amygdala and hippocampus) are visible in coronal view (middle).
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Table 1. Demographic and clinical characteristics of the male subjects.

A. First group	Control subjects		Schizophrenia patients		Analysis of variance	
	n = 16		n = 20			
	Mean	SD	Mean	SD	F	p
Age (years)	29.9	5.6	27.8	6.0	1.19	0.28
Handedness (number of right-handed)	16.0		19.0			
Socio-economic status	1.6	0.5	2.7	1.0	13.07	0.001
Parental socio-economic status	2.3	0.6	2.4	0.8	0.23	0.63
Estimated IQ	108.8	7.9	103.0	9.7	3.68	0.06
Duration of illness (months)			9.9	11.1		
Total BPRS score			40.2	11.5		
Antipsychotic medication (mg/day, chlorpromazine equiv.)			1074.5	487.9		
B. Second group	**Control subjects**		**Schizophrenia patients**		**Analysis of variance**	
	n = 6		n = 9			
	Mean	SD	Mean	SD	F	p
Age (years)	30.8	6.0	27.9	6.8	0.74	0.41
Handedness (number of right-handed)	6.0		7.0			
Socio-economic status	1.8	0.5	3.9	1.6	9.68	0.01
Parental socio-economic status	2.3	0.4	2.3	0.7	0.37	0.56
Estimated IQ	111.7	5.1	106.2	10.6	1.38	0.26
Duration of illness (months)			12.5	13.0		
Total BPRS score			42.5	9.9		
Antipsychotic medication (mg/day, chlorpromazine equiv.)			864.4	637.7		

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measurement of regional cortical volumes [25–27]. These approaches have been validated by several studies [21,26,28,29]. By using these newly developed automated methods to assess brain morphology (i.e., cortical thickness and regional brain volumes). Desikan et al. [30] demonstrated successful classification of subjects with mild cognitive impairment, patients with Alzheimer's disease, and controls. To our knowledge, however, no studies have attempted to classify patients with schizophrenia and healthy subjects with this fully automated MRI-based analysis.

In this study, we intended to classify schizophrenia patients and healthy subjects using discriminant analysis with automated MRI-based measures of regional brain volume and cortical thickness. On the basis of findings of previous studies, we hypothesized that (1) cortical thinning and gray matter volume reductions in prefrontal and temporal regions would be seen in schizophrenia patients compared with controls, (2) and these MRI measures would differentiate schizophrenia patients from healthy subjects with good accuracy.

Materials and Methods

Subjects

Fifty-two patients (29 males, 23 females) with first-episode schizophrenia were recruited from the inpatient population at Tokyo Metropolitan Matsuzawa Hospital. Inclusion criteria for first-episode schizophrenia patients were (1) first psychiatric hospitalization, (2) younger than 45 years old, (3) currently psychotic as reflected by the presence of at least one "positive" symptom, and (4) fulfilling the ICD-10 research criteria for schizophrenia. Two experienced psychiatrists separately examined the patients within two weeks of admission and diagnostic consensus was confirmed. Furthermore, thorough medical record review was performed to confirm the diagnostic stability for all the patients during the follow-up periods (1 to 5 years) after first admission. All but three male patients with schizophrenia were right-handed. All patients had received antipsychotic medications at the time of scanning.

The control subjects consisted of 40 healthy volunteers (22 males, 18 females) who were recruited from the hospital staff and college students. All of the control subjects were right-handed. All control subjects were interviewed by psychiatrists using the questionnaire concerning their family and past histories, and present illness. Individuals who had a personal history of psychiatric illness or a family history of psychiatric disorders in their first degree relatives were excluded.

For the discriminant analysis described below, the subjects were randomly assigned to two independent groups. The first group consisted of 36 males (16 healthy subjects and 20 schizophrenia patients) and 30 females (13 healthy subjects and 17 schizophrenia patients). The second group for the prospective validation consisted of 15 males (6 healthy subjects and 9 schizophrenia patients) and 11 females (5 healthy subjects and 6 schizophrenia patients). Since the sample size of the present study is relatively modest, we assigned more subjects to the first group (i.e., about 70%) than to the second group to enhance the discriminating ability of the classifier.

In the schizophrenia patients, clinical symptoms were assessed using the Brief Psychiatric Rating Scale (BPRS) [31]. The premorbid IQ for schizophrenia patients and the present IQ for control subjects were estimated using the shortened version of the

Table 2. Demographic and clinical characteristics of the female subjects.

A. First group	Control subjects		Schizophrenia patients		Analysis of variance	
	n = 13		n = 17			
	Mean	SD	Mean	SD	F	p
Age (years)	27.5	4.8	28.1	5.8	0.16	0.69
Handedness (number of right-handed)	14.0		17.0			
Socio-economic status	1.6	0.5	3.1	1.1	17.14	<0.001
Parental socio-economic status	2.4	0.8	2.9	0.8	3.03	0.09
Estimated IQ	107.0	8.1	103.5	7.8	2.55	0.12
Duration of illness (months)			13.0	12.6		
Total BPRS score			37.4	9.7		
Antipsychotic medication (mg/day, chlorpromazine equiv.)			930.8	451.6		
B. Second group	**Control subjects**		**Schizophrenia patients**		**Analysis of variance**	
	n = 5		n = 6			
	Mean	SD	Mean	SD	F	p
Age (years)	28.4	3.8	28.3	8.6	0.05	0.83
Handedness (number of right-handed)	4.0		6.0			
Socio-economic status	1.6	0.5	2.5	1.0	4.65	0.06
Parental socio-economic status	2.0	0.0	2.6	0.9	2.25	0.17
Estimated IQ	108.1	10.8	103.0	8.1	0.18	0.68
Duration of illness (months)			14.5	19.8		
Total BPRS score			36.5	4.4		
Antipsychotic medication (mg/day, chlorpromazine equiv.)			483.3	263.9		

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Japanese version of the National Adult Reading Test (JART) [32]. The subjects' socio-economic status (SES) as well as parental SES was assessed using the Hollingshead's Index [33].

All subjects were physically healthy at the time of the study, and none had a lifetime history of serious head trauma, neurological illness, or serious medical or surgical illness. Individuals who met the ICD-10 research criteria for mental and behavioral disorders due to psychoactive substance use were excluded. All schizophrenia patients participated in this study after providing written informed consent. In addition, regal representatives of schizophrenia patients gave written informed consent. In case of unable to directly access to a patient's legal representative, oral informed consent was obtained using telephone, and this procedure was witnessed by at least two hospital staff and recorded in the medical chart. All control subjects also provided written informed consent. Since control group of this study consisted of only healthy adults, their legal representatives were not asked to give informed consents. This study was approved by the Committee on Medical Ethics of Tokyo Metropolitan Matsuzawa Hospital.

MRI data acquisition

MR images were obtained using a Philips Intera 1.5-T scanner (Philips Medical Systems, Best, Netherlands) with a three-dimensional sequence yielding 192 contiguous T1-weighted slices of 1.0-mm thickness in the axial plane. The imaging parameters were as follows: repetition time = 21 ms, echo time = 9.2 ms, flip angle = 30°, field of view = 256 mm, matrix size = 256×256 pixels, voxel size = 1.0×1.0×1.0 mm^3.

Automated MRI data processing

Cortical reconstruction and volumetric segmentation were performed with the Freesurfer image analysis suite (version 4.5), which is documented and freely available for download online (http://surfer.nmr.mgh.harvard.edu/). This processing includes motion correction and averaging of multiple volumetric T1-weighted images, removal of non-brain tissue using a hybrid watershed/surface deformation procedure [34], automated Talairach transformation, segmentation of the subcortical white matter and deep gray matter volumetric structures (including hippocampus and amygdala) [35,36], intensity normalization [37], tessellation of the gray matter/white matter boundary, automated topology correction [38,39], and surface deformation following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid (CSF) borders at the location where the greatest shift in intensity defines the transition to the other tissue class [19,40,41]. Once the cortical models are completed, a number of deformable procedures can be performed for further data processing and analysis.

Cortical thickness measurements were obtained by calculating the shortest distance from the gray/white boundary to the gray/CSF boundary at each vertex on the tessellated surface [19]. The cerebral cortex of each MRI scan was automatically parcelled into regions of interest (ROIs) based on gyral and sulcal structure [26,42]. Both automated cortical thickness measurements and cortical parcellation have already been validated [21,26,28,29]. Figure 1 presents the neocortical ROIs and two limbic ROIs (hippocampus and amygdala) examined in this study. To control for head size in statistical analyses, the total intracranial volume (ICV) was calculated automatically [43].

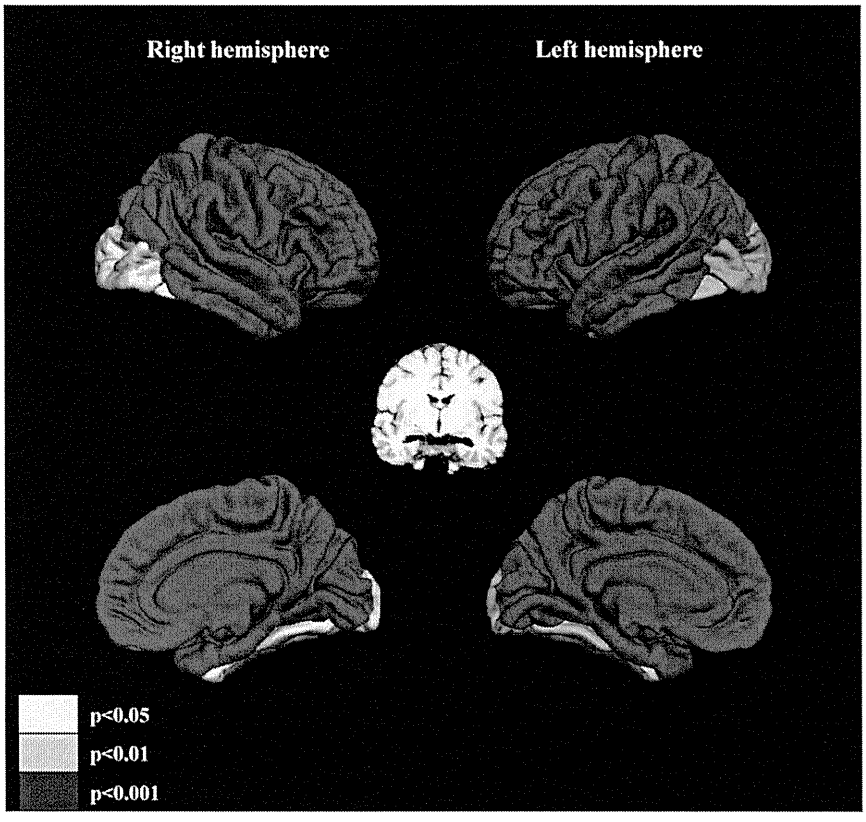

Figure 2. ROIs for which the volumes were significantly reduced in schizophrenia patients compared with those of healthy subjects. ROIs were differentially colored according to the p values of the post hoc tests.
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Statistical analysis-1 Group comparison

Demographic and clinical variables were compared by analysis of variance (ANOVA). The ROI volumes and the mean cortical thickness of ROIs were analyzed by repeated measures analysis of covariance (ANCOVA) with diagnosis and gender as between-subject factors, hemisphere (left, right) as a within-subject factor, and age and ICV as covariates. To prevent possible type 1 error, we used false positive discovery rate (FDR) correction. For variables of which p-values remained significant even after the FDR correction, post hoc Scheffe's tests were used to follow up significant main effects or interactions.

Statistical analysis-2 Classification by brain measures

The following statistical procedures were carried out separately for each gender, as was the case in our previous studies [12,13], on the basis of the gender differences in brain morphology found in this study (described below) as well as the evidence for gender differences in brain morphology among healthy subjects [44] and gender-specific brain structural changes in schizophrenia patients [45,46].

Transformation of brain measures into z scores. The volumes and mean cortical thickness of ROIs were expressed as standardized z scores corrected by regression analysis for the variations in head size and age of the control subjects, as described in our previous studies [12,13]. Briefly, the ROI volume and mean cortical thickness for the control group were regressed against ICV and age, yielding a residual value for each control subject. The ROI volume and mean cortical thickness for the patient groups were entered into the same equation as for the control group to calculate the residual value for each patient. The mean residual values and standard deviation (SD) derived from the control subjects were used to calculate z scores (z = [residual value - mean residual value for control subjects]/SD). For the control subjects, the expected mean z score was 0 with an SD of 1. The use of standardized z scores allows analysis of disease-related changes independent of head size and normal aging.

Linear discriminant function analysis. For the first group, discriminant function analysis was conducted using z scores as independent variables to assess the possibility of classifying diagnostic groups by a combination of brain measures. The variables were entered in a stepwise manner. Since we employed a stepwise variable selection, the number of variables which were entered into the discriminant analysis varied depending on the inclusion and exclusion criteria. In this study, relatively conservative inclusion criteria were used for the stepwise selection, which were set at $p<0.05$ to enter and $p>0.1$ to remove. If we used a more liberal criterion, more variables could be used for the discriminant function, vice versa. For each step, always a measure whose p-value is the smallest and smaller than 0.05 is entered to the discriminant function. Similar to a stepwise linear regression analysis, however, p-values of variables vary for each step. If a p-value of a measure that has already been entered to the model exceeds 0.1, this variable is removed at this step. If a p-value of the measure is 0.06 (i.e., <0.1), it remains in the model. However, if a measure with a p-value of 0.06 has yet to be entered in the model, it is still out of the model at this step. For each subject of the second group, the discriminant score was calculated using the discriminant function derived from the first group and his/her diagnosis was predicted based on the discriminant score. Since the p-value for the stepwise variable selection was computed

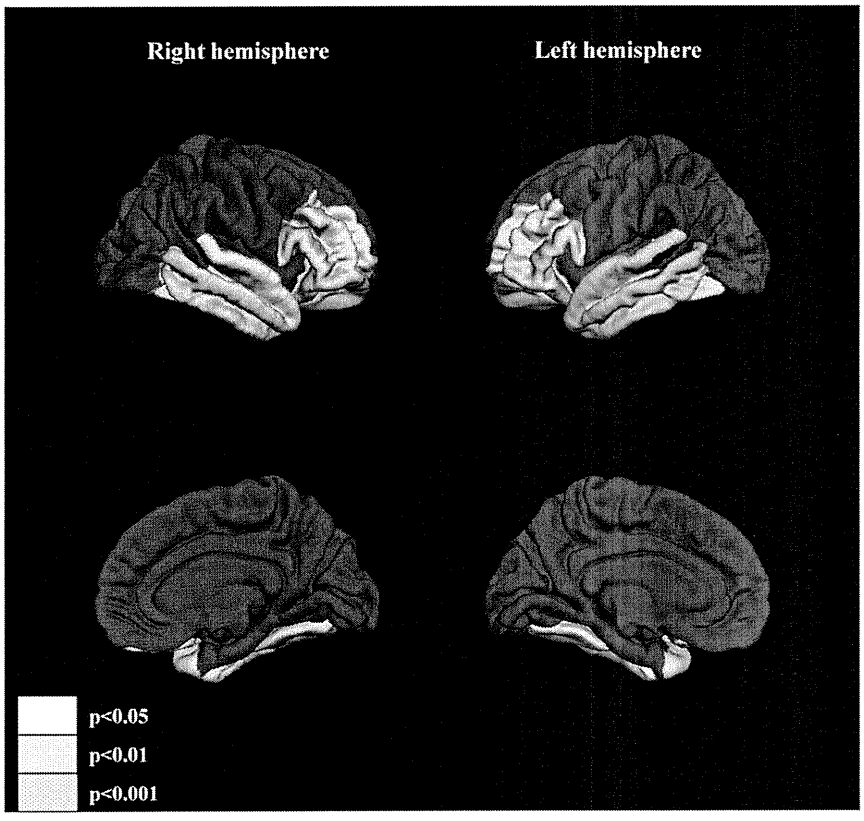

Figure 3. Significant cortical thinning of ROIs in schizophrenia patients compared with that of healthy subjects observed in this study. ROIs were differentially colored according to the p values of the post hoc tests.
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