of the participants and I would respectfully highlight that this statement does not seem consistent with the information provided in the accompanying table of sample characteristics. This table states that 58.4% of cases and 43.2% of controls were unemployed. The percentages in this table have some inaccurate rounding but more worryingly, contrary to the authors' report, there is a clear statistically significant difference ($P=0.001$ using a z-test for proportions).

This also seems to be a highly relevant and clinically significant difference that may have introduced considerable bias into this study and merited the attention of the 14 authors. In the discussion the authors state 'the increased availability of skunk cannot alone explain why our control group members are less likely to prefer higher-potency types than the cases group across time'. The requirement to hold down a job may be a highly significant reason why controls smoked cannabis of lesser potency less often than the unemployed. Moreover, individuals who are unemployed are highly likely to have poorer social and health status, which further serves to obscure the true role of cannabis in this study.

1 Di Forti M, Morgan C, Dazzan P, Pariante C, Mondelli V, Marques TR, et al. High-potency cannabis and the risk of psychosis. *Br J Psychiatry* 2009; **195**: 488–91.

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doi: 10.1192/bjp.196.4.332b

Authors' reply: Among the sociodemographic variables we reported in Table 1, it is correct to point out that unemployment rates are statistically significantly higher in the cases compared with controls ($P<0.001$). This difference has already been reported in previous epidemiological studies and there is no evidence that this arises from a bias in the sample selection. However, it is rather a potential confounder. In our paper we did not discuss if or how employment status might have influenced our findings, because, together with other relevant variables, we controlled for it in the statistical analyses. Thus, the higher rate of unemployment in cases than controls might partially account for the drop of the crude odds ratio (OR) of 8.1 (95% CI 4.6–13.5) to the adjusted one (OR=6.8, 95% CI 2.6–25.4), which occurred when we controlled for confounders including unemployment. However, the odds ratio still remains strikingly high and statistically significant ($P<0.05$), indicating that our findings cannot be explained by the effect of employment status or by any of the other social variables listed.

Lastly, we wish to comment on the suggestion that controls' preference for low-potency cannabis might be consequent to their need to continue being able to work. Would this not indicate that high-potency cannabis is more likely to negatively affect social functioning perhaps via its detrimental effect on mental health? Exactly what our findings suggest.

Marta M. Di Forti, Department of Psychiatry, Institute of Psychiatry, De Crespigny Park, London, UK. Email: marta.diforti@kcl.ac.uk; **Craig Morgan**, **Robin M. Murray**, Institute of Psychiatry, London, UK

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Corrections

Superior temporal gyrus volume in antipsychotic-naive people at risk of psychosis. *BJP*, 196, 206–211. The second sentence of the Method (p. 206) should read: Those recruited were aged 14–30 years, had not experienced a previous psychotic episode, had never received any psychotropic medication (antipsychotics, antidepressants, mood stabilisers or benzodiazepines) and had an IQ score above 70, assessed with the National Adult Reading Test.

Bringing new life into psychiatry – extra. *BJP*, 196, 248. The doi was printed incorrectly and should be: 10.1192/bjp.196.3.248a. The online version has been corrected in deviation from print and in accordance with this correction.

Recent trends in the incidence of recorded depression in primary care. *BJP*, 195, 520–524. In the key to Fig. 1 (p. 522) 'Depression' and 'Combined' are transposed. The correct figure is reproduced below.

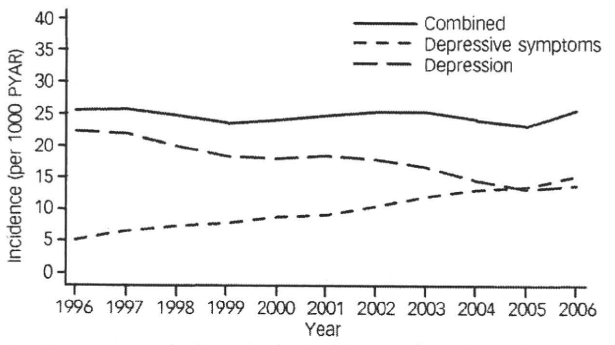

Fig. 1 Incidence of diagnosed depression and depressive symptoms.

PYAR, person-years at risk.

doi: 10.1192/bjp.196.4.333a

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196, 206–211. doi: 10.1192/bjp.bp.109.069732

Data supplement

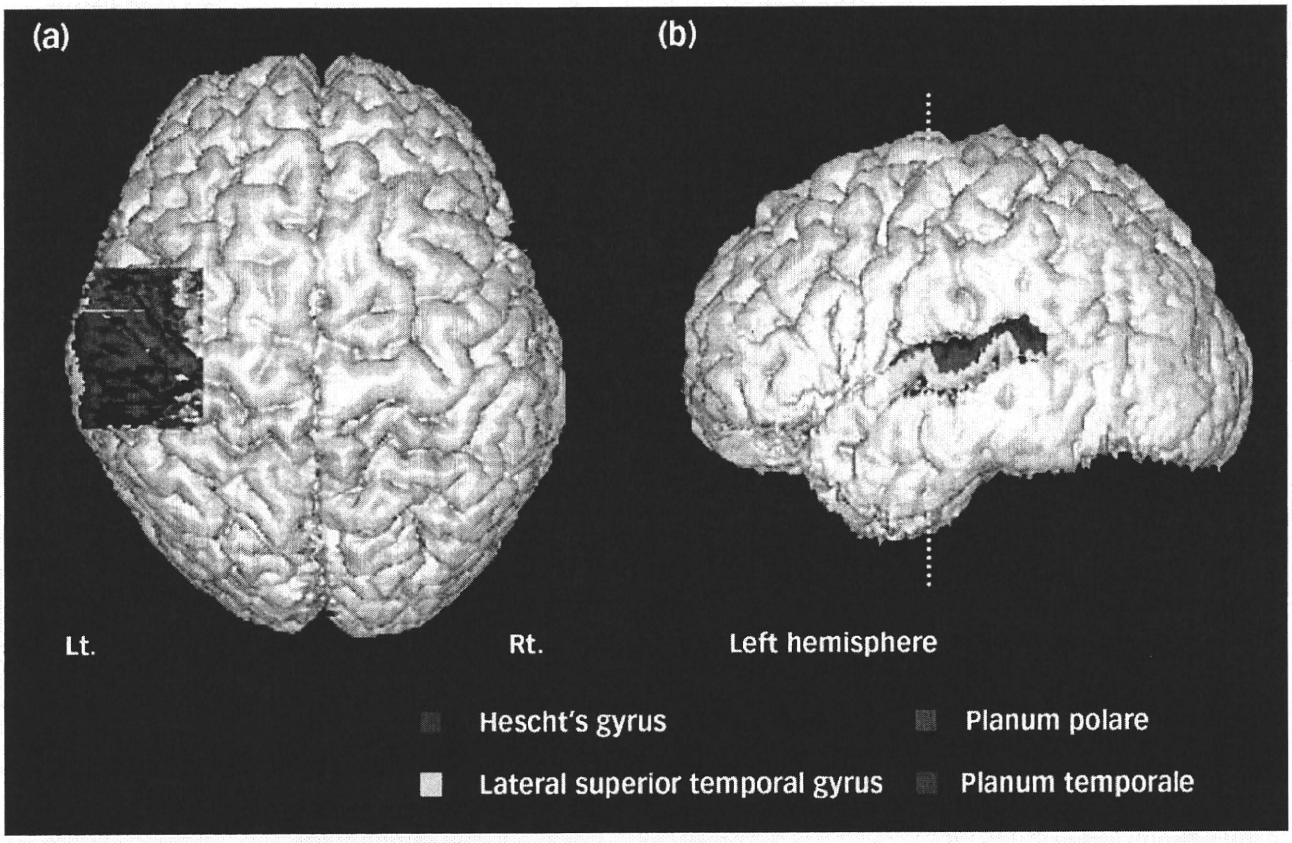

Fig. DS1 Three-dimensional reconstructed images of superior temporal subregions presenting top-down (a) and lateral (b) views of the brain. The frontal and parietal lobes in (a) are partially cut off to disclose the regions examined. The lateral superior temporal gyrus was further subdivided into rostral and caudal regions by a plane containing the anterior end of Heschl's gyrus, shown as dotted line in (b). Lt, left; Rt, right.

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A follow-up MRI study of the superior temporal subregions in schizotypal disorder and first-episode schizophrenia

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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 unknown whether patients with schizotypal features exhibit similar STG changes. In this study, longitudinal MRI data were obtained from 18 patients with first-episode schizophrenia, 13 patients with schizotypal disorder, and 20 healthy controls. The volumes of the STG and its subregions [planum polare (PP), Heschl gyrus (HG), planum temporale (PT), rostral STG, and caudal STG] were measured on baseline and follow-up (mean: 2.7 years) scans and were compared across groups. At the baseline, both the schizophrenia and schizotypal patients had smaller left PT and left caudal STG than the controls. In a longitudinal comparison, the schizophrenia patients showed significant gray matter reduction of the STG over time (left: −2.8%/year; right: −1.5%/year) compared with the schizotypal patients (left: −0.6%/year; right: −0.3%/year) and controls (left: 0.0%/year; right: −0.1%/year) without a prominent effect of subregion or type of antipsychotic (typical/atypical). In the schizophrenia patients, greater annual volume reductions of the left PP and right PT were correlated with less improvement of positive psychotic symptoms. A higher cumulative dose of antipsychotics during follow-up in schizophrenia was significantly correlated with less severe gray matter reductions in the left PT and bilateral caudal STG. Our findings suggest that the left posterior STG subregions are commonly reduced in diseases of the schizophrenia spectrum; whereas, schizophrenia patients exhibit further progressive STG changes associated with overt psychosis in the early years of the illness.

1. Introduction

Gray matter reductions of the superior temporal gyrus (STG) and its functionally relevant subregions [e.g., the primary auditory cortex (Heschl gyrus, HG), a neocortical language region (planum temporale, PT), and the lateral portion related to social cognition (Gallagher and Frith, 2003)] have been repeatedly described in previous magnetic resonance imaging (MRI) studies of schizophrenia (reviewed by Shenton et al., 2001; Sun et al., 2009). These morphologic changes, which have been implicated in various psychotic symptoms such as auditory hallucinations and thought disorders (Barta et al., 1997; Rajarethinam et al., 2000; Shenton et al., 1992; Sumich et al., 2005; Takahashi et al., 2006) appear to already be present at the onset of the first episode of schizophrenia (Hirayasu et al.,

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1998, 2000; Kasai et al., 2003a,b; Keshavan et al., 1998; Kim et al., 2003; Takahashi et al., 2009b). These observations support a neurodevelopmental pathology (Weinberger, 1987); whereas, recent longitudinal MRI studies have demonstrated marked progressive gray matter reduction of the STG during the early phases of schizophrenia (Kasai et al., 2003a,b; Mané et al., 2009; Takahashi et al., 2009a; Whitford et al., 2006), suggesting a further ongoing pathological process associated with psychosis in this region.

Schizotypal (personality) disorder is a prototypic disorder within the schizophrenia spectrum, which is characterized by odd behavior and attenuated forms of schizophrenic features without manifestation of overt and sustained psychosis (World Health Organization, 1992; American Psychiatric Association, 1994). Such subjects with schizotypal features share genetic, biological, and psychological commonalities with schizophrenia patients and are thought to include individuals with the prodromal phase of schizophrenia (Siever and Davis, 2004). Based on previous studies concerning brain morphologic changes and cognitive characteristics in schizotypal and schizophrenia patients, it is hypothesized that abnormalities in the temporal regions are common to both groups as a neurobiological basis of schizophrenia susceptibility (Dickey et al., 2002a; Kurachi, 2003a,b; Siever and Davis, 2004). In particular, although it has not been consistently replicated (e.g., Dickey et al., 2003), previous cross-sectional MRI studies from our (Kawasaki et al., 2004; Takahashi et al., 2006) and other (Dickey et al., 1999, 2002b; Koo et al., 2006; Goldstein et al., 2009) groups have demonstrated gray matter reduction of the STG in schizotypal subjects to the same degree as that seen in schizophrenia patients. On the other hand, given the evidence of progressive STG changes associated with overt psychosis during the early phases of schizophrenia (Kasai et al., 2003a,b; Takahashi et al., 2009a), it is possible that the absence of such active pathological processes in this region underlies the sparing of schizotypal patients from the development of schizophrenic psychosis. To our knowledge, however, no volumetric MRI studies have examined longitudinal morphologic changes of the STG in subjects with schizotypal features.

This longitudinal MRI study aimed to examine the progressive gray matter changes of the STG and its subregions in schizotypal disorder and first-episode schizophrenia patients compared with healthy controls. On the basis of the differing phenomenology between schizophrenia and schizotypal disorder (World Health Organization, 1992) as well as the potential role of active STG pathological processes in the development of overt psychosis (Kasai et al., 2003b; Takahashi et al., 2009b), we predicted that only the schizophrenia patients would show progressive gray matter loss of this region and that its degree would be related to the severity of positive psychotic symptoms. We also explored the potential ameliorating effect of antipsychotic medication (Scherk and Falkai, 2006) on longitudinal STG changes.

2. Methods

2.1. Subjects

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 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 (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).

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. On the basis of the literature (Hirayasu et al., 1998, 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. 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 family and personal histories, as well as present illness (Takahashi et al., 2008). 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 homogenous control group without eccentric profiles on the MMPI and were excluded if they had an abnormal profile; i.e., any *T*-score on the validity or clinical scales exceeding 70.

The clinical symptoms of the schizotypal and schizophrenia patients were rated at the time of scanning (baseline and follow-up) using the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1984a) and the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984b). 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 patient), 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 (except 2 patients who 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 at the time of the study, and none had a history of serious head trauma, neurological illness, substance abuse disorder, or serious medical disease. All participants were also screened for gross brain abnormalities by the neuroradiologists. Of the 51 participants in this study, 48 subjects (17 schizophrenia, 12 schizotypal, and 19 control subjects) were included in our previous cross-sectional STG study (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, 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, the image data were processed using the Dr View 5 software package (AJS, Tokyo, Japan) on a Unix workstation. 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, of 1-mm thickness, perpendicular to the anterior commissure–posterior commissure line. The whole cerebrum was manually separated from the brain stem and cerebellum. The signal-intensity histogram distributions produced 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 superior temporal subregions

The gray matter of the STG subregions [planum polare (PP), Heschl gyrus (HG), planum temporale (PT), rostral STG, and caudal STG] (Fig. 1) was manually traced on 1-mm consecutive coronal slices as described in detail elsewhere (Takahashi et al., 2006). Briefly, on the basis of the established tracing guidelines (Kim et al., 2000), the first coronal plane containing the temporofrontal junction and the coronal plane containing the posterior end of the posterior horizontal limb of the sylvian fissure were chosen as anterior and posterior boundaries of the STG, respectively. On each coronal slice, the STG was bounded superiorly by the sylvian fissure and inferiorly by the superior temporal sulcus. The STG was then segmented into supratemporal and lateral portions using the lateral limb of the supratemporal plane as the border between the two. The HG was traced posterior to anterior, beginning with the first slice containing the Heschl sulcus and ending anteriorly with the slice containing the most anterior

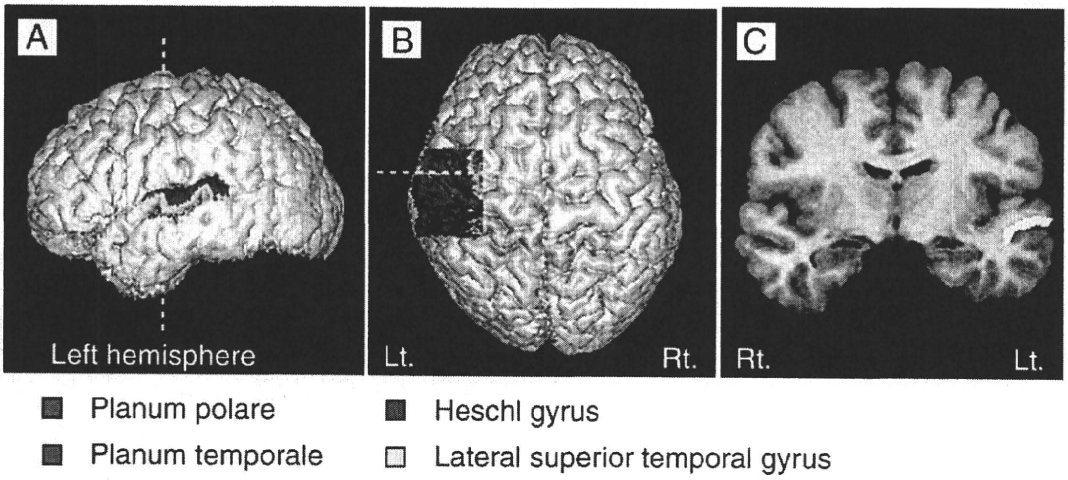

Fig. 1. Three-dimensional reconstructed images presenting lateral (A) and top-down (B) views and a sample coronal image (C) of superior temporal subregions on left hemisphere. The frontal and parietal lobes in panel B have been partially cut off to highlight the regions examined. The lateral superior temporal gyrus (STG) was further subdivided into rostral STG and caudal STG using a plane containing the anterior end of the Heschl gyrus as the border between the two (dotted line).

point of the Heschl sulcus or the sulcus intermedius, if present. On each coronal slice, the HG was bounded medially by the sylvian fissure, inferior circular insular sulcus, or the first transverse sulcus and laterally by the Heschl sulcus. After tracing the HG, which takes a diagonal course on the supratemporal plane, the regions lying anteromedial and posterolateral to the HG within the remaining gray matter of the supratemporal plane were regarded as the PP and PT, respectively. The lateral STG was divided into rostral and caudal STG portions by using the plane containing the anterior tip of the HG as the border between the two.

All volumetric data reported here were measured by one rater (TT), who was blinded to the subjects' identities and the times of their scans. The reliability of these measurements has been established previously, and the intra- and inter-rater (TT and RT) intraclass correlation coefficients in five randomly selected brains were over 0.88 for all STG subregions.

2.4. Statistical analysis

Statistical analysis was carried out using the software package STATISTICA 4.1J for Macintosh (Statsoft, Tulsa, OK, USA). Clinical and demographic differences between groups were examined with one-way analysis of variance (ANOVA) or the chi-square test. The absolute volume of the STG was assessed using a repeated measures analysis of covariance (ANCOVA) with age, ICV, and dosage of antipsychotic medication at scanning as covariates; group (schizophrenia patients, schizotypal patients, and controls) as a between-subject factor; and subregion (PP, HG, PT, rostral STG, and caudal STG) and side (left and right) as within-subject variables. The different typical and atypical antipsychotic dosages are converted into haloperidol equivalents using the guideline by Toru (2001).

The longitudinal volume change of the STG was analyzed using the percentage volume change [100 x (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 between scans as covariates; diagnosis as a between-subject factor; and subregion and side as within-subject factors was performed. Post hoc Neuman–Keuls tests were carried out to follow-up the significant main effects or interactions yielded by these analyses. None of the ANCOVA results for the cross-sectional or longitudinal comparisons reported herein changed, even when we included gender and medication duration at the baseline as covariates.

Since the extent of progressive STG changes during the initial period of psychosis might reflect the severity of subsequent positive symptomatology (Takahashi et al., 2009b), the correlations between the percentage volume change per year of the STG and SAPS subscale scores (absolute score change between scans, score at follow-up) in schizophrenia patients were analyzed using Spearman's rho. To minimize type I errors due to multiple comparisons, we limited the analyses to the severity of three selected positive symptoms (i.e., hallucinations, delusions, and positive formal thought disorder) based on previous observations (e.g., Barta et al., 1997; Shenton et al., 1992; Sumich et al., 2005; Takahashi et al., 2006). The association between the annual STG gray matter loss and cumulative dose of antipsychotics was also analyzed. These analyses were not performed for schizotypal disorder patients because of their very low scores for these subscales and the lack of a significant STG reduction over time. For schizophrenia and schizotypal patients, the association between the relative STG volume (100×absolute volume/ICV) at baseline and medication effect (daily dosage, duration) was analyzed using Spearman's rho. Statistical significance was defined as $p<0.05$ (two tailed).

3. Results

3.1. Sample characteristics

The three groups were matched for age, gender, height, parental education, and inter-scan interval, but the control subjects had attained a higher mean level of education than the patients with either disorder (Table 1). While the baseline SAPS score for the schizophrenia patients was significantly higher than that for the schizotypal patients, no significant group difference was found at follow-up potentially due to 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. The schizotypal patients had a significantly larger ICV compared with the schizophrenia patients ($p=0.015$) and controls ($p=0.017$).

3.2. Cross-sectional comparison

An ANCOVA of the STG at baseline showed significant main effects for group [$F(2, 45)=9.42$, $p<0.001$], side [$F(1, 48)=35.40$, $p<0.001$], and subregion [$F(4, 192)=240.39$, $p<0.001$] and significant group-by-subregion [$F(8, 192)=2.09$, $p=0.039$], side-by-subregion [$F(4, 192)=2.99$, $p=0.020$], and group-by-side-by-subregion [$F(8, 192)=2.76$, $p=0.007$] interactions. Post hoc analyses showed that both the schizophrenia and schizotypal patients had significantly smaller volumes of the PT (schizophrenia, $p=0.008$; schizotypal, $p=0.046$) and caudal STG ($p<0.001$ for both patient groups) in the left hemisphere than the controls.

An ANCOVA at follow-up showed significant main effects for group [$F(2, 45)=12.61$, $p<0.001$], side [$F(1, 48)=31.80$, $p<0.001$], and subregion [$F(4, 192)=255.66$, $p<0.001$] and significant group-by-subregion [$F(8, 192)=3.33$, $p=0.001$], side-by-subregion [$F(4, 192)=2.55$, $p=0.041$], and group-by-side-by-subregion [$F(8, 192)=3.06$, $p=0.003$] interactions. At the follow-up scan, in addition to the volume reduction of the left PT (schizophrenia, $p<0.001$; schizotypal, $p=0.018$) and left caudal STG ($p<0.001$ for both patient groups), the schizophrenia patients had a smaller right caudal STG compared with the controls ($p=0.003$). No significant difference in the STG volume was found between the schizophrenia and schizotypal patients for either time point.

3.3. Longitudinal comparison

ANCOVA of the percentage volume change showed a significant group difference [$F(2, 44)=4.69$, $p=0.014$], with the schizophrenia patients having a greater STG reduction over time compared with the schizotypal patients ($p=0.039$) or controls ($p=0.034$) (Table 2, Fig. 2). However, there was

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: $F(1, 28)=0.13$, $p=0.718$
Intracranial volume (cm^3)	1494 (142)	1593 (104)	1477 (137)	ANCOVA [c]: $F(2, 46)=3.94$, $p=0.026$

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.
[c] Age and gender were used as covariates.

no difference between the schizotypal patients and controls ($p=0.653$). There was no group × subregion [$F(8, 192)=0.792$, $p=0.627$] or group × side × subregion [$F(8, 192)=0.884$, $p=0.531$] interaction, implying that the group differences in longitudinal STG volume reduction were not highly localized to a particular subregion. When we examined each STG subregion separately, however, significant group differences were found only for the HG [group effect, $F(2, 44)=4.11$, $p=0.023$; group × side interaction, $F(2, 48)=3.54$, $p=0.037$] and caudal STG [group effect, $F(2, 44)=5.31$, $p=0.009$]. Compared with the other groups, the schizophrenia patients showed greater gray matter loss of the left HG (versus controls, $p=0.001$; versus schizotypal patients, $p=0.003$) and bilateral caudal STG (versus controls, $p=0.024$; versus schizotypal patients, $p=0.061$).

There was no significant difference in the STG gray matter reduction over time between the patients who were predominantly treated with typical ($n=9$) and atypical ($n=18$) antipsychotics during the follow-up period [$F(1, 21)=2.81$, $p=0.108$]. No significant effect of between-scan medication type (typical versus atypical) on gray matter changes was found, even when we examined each STG subregion separately.

We also examined the longitudinal volume change of the whole gray matter using the same ANCOVA model, but there was no significant difference between the schizophrenia, schizotypal, and control groups [$F(2, 44)=0.43$, $p=0.653$].

3.4. Correlational analysis

In the schizophrenia patients, greater annual volume reductions of the left PP and right PT were correlated with less improvement of hallucinations (rho = 0.71, $p=0.004$) and delusions (rho = 0.73, $p=0.002$), respectively (Fig. 3). While correlations were also found between greater reduction of the rostral STG over time and higher scores for delusions (right, rho = 0.54, $p=0.026$) and thought disorders (left, rho = 0.59, $p=0.013$) at the follow-up, these were not significant after Bonferroni correction. A higher cumulative dose of antipsychotics during follow-up was significantly correlated with less severe gray matter reductions in the left PT (rho = −0.72, $p<0.001$) and bilateral caudal STG (left, rho = −0.64, $p=0.004$; right, rho = −0.75, $p<0.001$) (Fig. 4) as well as greater improvement of hallucinations (rho = −0.57, $p=0.035$). When we examined only the schizophrenia patients treated with atypical antipsychotics during follow-up ($n=11$), relation to the cumulative dose was found only for the caudal STG (left, rho = −0.61, $p=0.047$; right, rho = −0.80, $p=0.003$).

There was no medication effect on the baseline STG volume in the schizophrenia patients (duration, rho = −0.26 to 0.43, $p=0.082$ to 0.971; daily dosage, rho = −0.20 to 0.27, $p=0.093$ to 0.964), but medication duration at the baseline in the schizotypal group was negatively correlated with left HG volume (rho = −0.689, $p=0.009$).

4. Discussion

To the best of our knowledge, this is the first volumetric MRI study to examine progressive gray matter changes of the STG subregions in schizotypal disorder patients compared with first-episode schizophrenia patients and healthy controls. In a baseline comparison, both patient groups had smaller left PT and left caudal STG volumes than the controls, indicating that the left posterior STG subregions are commonly reduced in the

Table 2
Absolute gray matter volume of the whole brain and superior temporal sub-regions 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	697069 (69538)	693464 (77687)	−0.3 (1.2)	743076 (71627)	723953 (50955)	−0.9 (2.1)	684184 (83120)	664053 (67613)	−0.9 (1.8)
Whole STG									
Left	12443 (1800)	12397 (1762)	0.0 (1.3)	10808 (1406)	10563 (1356)	−0.6 (3.6)	10795 (1992)	10023 (1701)	−2.8 (2.8)
Right	10631 (1219)	10650 (1347)	−0.1 (1.5)	9926 (1272)	9732 (898)	−0.3 (3.3)	9356 (1658)	8972 (1436)	−1.5 (2.7)
Planum polare									
Left	1495 (506)	1486 (534)	−0.3 (3.6)	1531 (368)	1517 (287)	0.4 (3.7)	1539 (468)	1487 (394)	−0.8 (5.3)
Right	1800 (491)	1780 (467)	−0.3 (3.3)	1373 (340)	1366 (367)	0.4 (3.7)	1404 (612)	1353 (588)	−0.9 (4.2)
Heschl gyrus									
Left	2061 (432)	2055 (434)	0.2 (2.5)	1867 (429)	1828 (403)	−0.6 (4.7)	1947 (514)	1750 (492)	−3.6 (3.3)
Right	1410 (348)	1426 (357)	0.5 (3.4)	1641 (435)	1585 (424)	−1.2 (2.3)	1420 (426)	1370 (398)	−0.9 (3.9)
Planum temporale									
Left	2972 (576)	2965 (553)	0.1 (2.0)	2585 (530)	2522 (613)	−0.4 (5.5)	2393 (600)	2227 (603)	−2.9 (2.6)
Right	2215 (501)	2236 (546)	0.4 (4.2)	2276 (629)	2265 (559)	0.4 (4.8)	2143 (638)	2116 (582)	−0.4 (3.8)
Rostral STG									
Left	1377 (734)	1364 (724)	−0.1 (3.6)	1281 (538)	1240 (474)	−1 (5.3)	1455 (631)	1323 (576)	−3.9 (4.5)
Right	1374 (619)	1329 (582)	−1.1 (2.7)	946 (455)	916 (408)	−0.1 (4.6)	964 (725)	887 (646)	−1.7 (5.8)
Caudal STG									
Left	4502 (998)	4495 (901)	0.1 (2.0)	3529 (874)	3399 (745)	−0.5 (5.6)	3446 (933)	3153 (753)	−3.2 (4.1)
Right	3862 (1024)	3870 (1014)	0.1 (2.1)	3663 (605)	3578 (516)	−0.4 (3.7)	3399 (726)	3221 (755)	−2.5 (4.0)

Data are presented as mean (SD). Values indicate absolute volumes (mm3) except % change/year values. STG, superior temporal gyrus.
% change/year was calculated as follows: [100 × (absolute volume at follow-up − absolute volume at baseline)/absolute volume at baseline]/interscan interval. Negative value indicates decrease in volume.

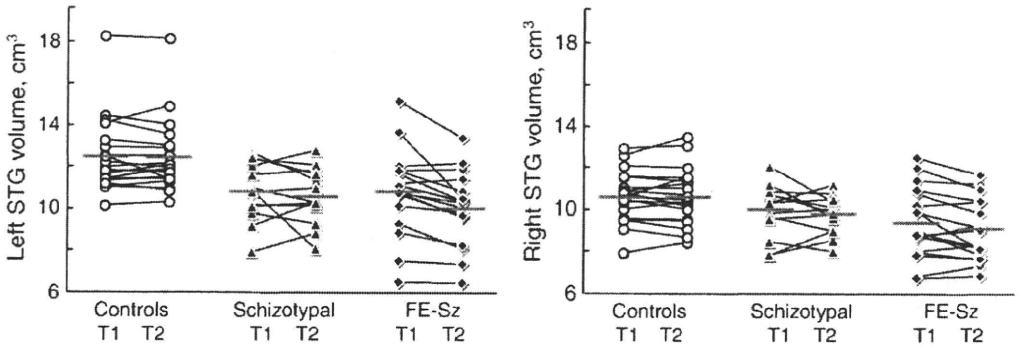

Fig. 2. Progressive gray matter changes of the superior temporal gyrus (STG) in healthy controls, patients with schizotypal disorder, and first-episode patients with schizophrenia (FE-Sz). Values of baseline (T1) and follow-up (T2) scans in each subject are connected with a straight line. Horizontal bars indicate the means of each group.

schizophrenia spectrum as a neurobiological basis of schizophrenia susceptibility. In a longitudinal comparison, only the first-episode schizophrenia patients showed further ongoing STG reduction without a prominent subregional effect, which was associated with the severity and course of psychotic symptoms. These findings suggest a role for the active pathological process of the STG in the development of overt psychosis, which might partly underlie the differences in phenomenology between schizophrenia and a milder form of schizophrenia spectrum disorder.

Largely consistent with previous cross-sectional (Hirayasu et al., 2000; Kim et al., 2003; Takahashi et al., 2009b) and longitudinal (Kasai et al., 2003a,b; Mané et al., 2009) MRI studies, our results demonstrate that schizophrenia patients have STG changes especially in the left posterior regions at illness onset, with further ongoing gray matter reduction in these and other subregions including the HG during early phases of the illness. Given the role of the caudal STG in auditory speech perception (Price, 2004) and mentalizing tasks (Gallagher and Frith, 2003), these observations support the notion that schizophrenia involves disruption to regions subserving primary auditory, speech, and language processes (Kasai et al., 2003b; Sumich et al., 2005) as well as social cognitive function (Brüne, 2005; Frith and Frith, 1999), which may account for the varying range of clinical presentations in schizophrenia. In addition, while previous cross-sectional findings in schizophrenia have implicated the role of the STG in the severity of positive psychotic symptoms (e.g., Barta et al., 1997; Shenton et al., 1992), our findings further suggest that the progressive STG changes during initial years after onset are relevant to the early course (e.g., treatment response) of these symptoms. The reduction rate of the STG in our schizophrenia sample (Table 2) was comparable with but somewhat less than that found in an earlier study by Kasai et al. (2003b) (left HG: −4.8%/year; right HG: 1.5%/year; left PT: −5.1%/year; right PT: −0.6%/year); this might reflect longer inter-scan interval in our sample (mean = 2.7 years) compared with theirs (mean = 1.4 years), as progressive STG reduction appears to be most prominent around psychosis onset with subsequent less marked changes during the first psychotic episode (Takahashi et al., 2009a). Taken together, these STG findings in first-episode schizophrenia support the model of psychosis that morphologic abnormalities seen in the patients reflect a combination of pre-existing vulnerability and changes associated with the first expression of psychotic symptoms (Pantelis et al., 2005).

The principal focus of this study was on the similarities and differences in the STG gray matter changes between schizophrenia and schizotypal patients. Our cross-sectional STG finding, which is similar to that observed in a larger sample of ICD-10 schizotypal disorder patients including most of the current subjects (Takahashi et al., 2006), is also in

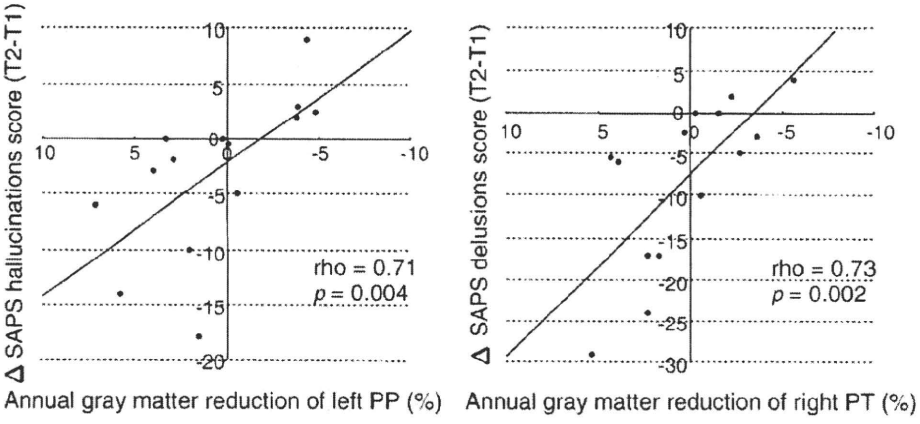

Fig. 3. Correlations between annual gray matter reduction of the superior temporal subregions and absolute score changes between the baseline (T1) and follow-up (T2) scans on the Scale for the Assessment of Positive Symptoms (SAPS) in 14 patients with first-episode schizophrenia. Annual gray matter reduction was calculated as follows: [100 × (absolute volume at T2 − absolute volume at T1)/absolute volume at T1]/inter-scan interval (in years). Negative values indicate decreases in volume. Abbreviations: PP = planum polare; PT = planum temporale.

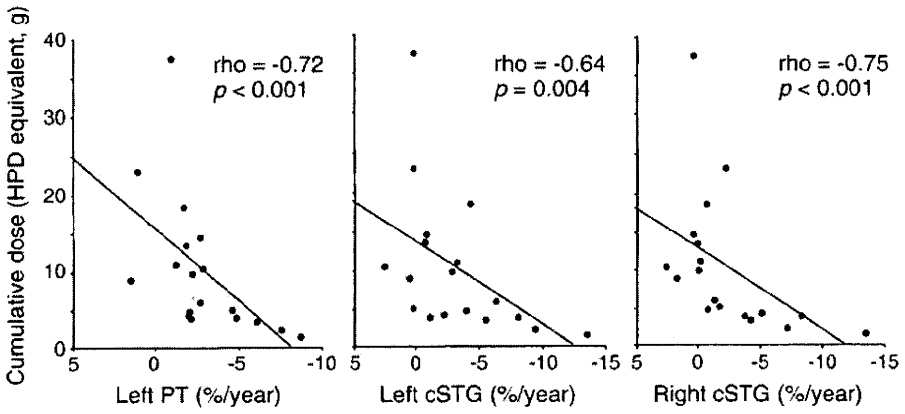

Fig. 4. Correlations between annual gray matter reduction of the superior temporal subregions and cumulative dose of antipsychotics (haloperidol equivalent, g) in 18 patients with first-episode schizophrenia. Annual gray matter reduction was calculated as follows: [100 × (absolute volume at T2 − absolute volume at T1)/absolute volume at T1]/inter-scan interval (in years). Negative values indicate decreases in volume. Abbreviations: cSTG = caudal superior temporal gyrus; HPD, haloperidol; PT = planum temporale.

line with previous reports from other groups showing reduced STG volume, especially in the left hemisphere, in patients with SPD (Dickey et al., 1999, 2002b; Goldstein et al., 2009; Hazlett et al., 2008; Koo et al., 2006). Despite some differences in the degree of change [e.g., milder STG changes compared to schizophrenia (Hazlett et al., 2008)] or subregional effect [e.g., significant HG changes (Dickey et al., 2002b)] among reports, possibly due to differences in sample characteristics (e.g., community- or clinic-based, medication status) or image analysis techniques, these STG findings support the hypothesis that schizotypal patients partly share temporal abnormalities with schizophrenia patients, which presumably underlie the attenuated forms of schizophrenic features seen in these patients (Kurachi, 2003a,b; Siever and Davis, 2004). In sharp contrast to these cross-sectional findings, our longitudinal comparison demonstrated progressive STG changes associated with psychosis in the schizophrenia patients only, suggesting that the absence of active pathological processes in this region might be related to the sparing of schizotypal patients from the development of florid psychosis. This view is consistent with a recent longitudinal study that demonstrated progressive STG reduction in high-risk subjects who later developed psychosis during the transition phase (left: −5.0%/year; right: −3.9%/year) but not in those who did not (left: 0.1%/year; right: −0.5%/year) (Takahashi et al., 2009a), since none of the 13 schizotypal patients in this study developed overt and sustained psychosis during the follow-up period.

In this study, a higher cumulative dose of antipsychotics between scans was significantly correlated with less severe gray matter reduction in the posterior STG regions and greater improvement of hallucinations in schizophrenia patients, supporting the assertion that antipsychotics ameliorate the progressive structural changes caused by the active disease processes during the first episode of schizophrenia (Scherk and Falkai, 2006). Although the pathological mechanisms underlying these progressive STG changes remain unknown, anomalies of synaptic plasticity, abnormal brain maturation, stress, and other environmental factors may be relevant (Pantelis et al., 2005). Glutamatergic excess due to hypofunction of the N-methyl-D-aspartate receptors on corticolimbic gamma-aminobutyric acid (GABA)-ergic interneurons may also lead to adverse neurotoxic effects in the early stages of schizophrenia (Coyle et al., 2003; Stone et al., 2007). Although further analyses in a larger sample are required as described below, potential ameliorating effects of antipsychotics on these hypothesized active processes and the significant relation of the progressive STG reduction to the early course of psychosis may implicate the role of the STG changes as a potential therapeutic target during the early phases of schizophrenia.

Several limitations of this study need to be addressed. First, even at the baseline scan, the first-episode schizophrenia patients had already experienced a substantial exposure to antipsychotics (median = 3.6 months), and the schizotypal group had a longer medication duration (median = 10.8 months). Significant differences in medication status (i.e., larger amounts of antipsychotics in the schizophrenia patients) might also have affected our results. In fact, although there was no medication effect (e.g., duration, daily dosage) on the baseline STG volume in the schizophrenia patients, medication duration at the baseline in the schizotypal group was negatively correlated with left HG volume. We therefore used these medication factors as a covariate for all ANCOVA. Furthermore, the effect of medication alone could not explain our main finding of greater STG reduction over time in schizophrenia than in schizotypal patients, as correlation analyses suggested potential ameliorating effects of antipsychotics. Second, we could not reliably assess the effects of the type of antipsychotic medication (typical versus atypical) or gender due to the small sample size. Typical and atypical antipsychotic agents may differentially affect brain morphology early in the course of schizophrenia (Lieberman et al., 2005; Scherk and Falkai, 2006; Thompson et al., 2009). While this study is strengthened by the completeness of the medication data (e.g., type and cumulative dose of antipsychotics) concerning the patients during follow-up, we failed to find a significant effect of antipsychotic type on the longitudinal STG changes, possibly due to limited statistical power. On the other hand, given that most of the schizotypal and schizophrenia patients were also receiving benzodiazepines and anticholinergics, the effects of these other psychotropics on brain morphology need to be further examined. Gender is also thought to affect brain morphology in schizophrenia (Leung and Chue, 2000), although our previous MRI study in a large sample balanced by gender did not find any gender specific STG changes

in the schizophrenia or schizotypal disorder patients (Takahashi et al., 2006). As the schizotypal patients had a larger ICV compared with other groups, we controlled for ICV for all group comparisons of the STG volume. Third, the possibility exists that the current schizotypal patients exhibited progressive STG changes prior to the baseline scan. Thus, the timing and course of brain changes in schizotypal disorder should be tested further in a larger sample at earlier stages, ideally in medication naïve patients. Finally, since other key brain regions in the pathophysiology of schizophrenia (e.g., prefrontal cortex; Goldman-Rakic and Selemon, 1997) were not assessed in this study, regional specificity of our findings needs to be examined in future studies.

In conclusion, the present findings indicate that both first-episode schizophrenia and schizotypal patients have smaller left posterior STG regions compared with controls at baseline potentially as a common neurobiological basis within the schizophrenia spectrum, whereas only schizophrenia patients exhibit further ongoing STG changes in the initial years of the illness, which could be relevant to the severity and early course of positive psychotic symptoms. In addition, our findings support the notion that antipsychotics may ameliorate progressive brain structural changes during the first episode of schizophrenia.

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Contibutors

MS and MK conceived the idea and methodology of the study. TT conducted the statistical analyses and wrote the manuscript. TT, MS, RT, KN, YK, and MK recruited the subjects, were involved in clinical and diagnostic assessments and for MRI scanning. TT, SYZ, and RT analyzed the MRI data. HS provided technical support for the MRI scanning and data processing. All authors contributed to the writing of the manuscript and have approved the final draft.

Conflict of interest

There are no conflicts of interest for any of the authors.

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Differentiation of first-episode schizophrenia patients from healthy controls using ROI-based multiple structural brain variables

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ABSTRACT

Background: Brain morphometric measures from magnetic resonance imaging (MRI) have not been used to discriminate between first-episode patients with schizophrenia and healthy subjects.
Methods: Magnetic resonance images were acquired from 34 (17 males, 17 females) first-episode schizophrenia patients and 48 (24 males, 24 females) age- and parental socio-economic status-matched healthy subjects. Twenty-nine regions of interest (ROI) were measured on 1-mm-thick coronal slices from the prefrontal and central parts of the brain. Linear discriminant function analysis was conducted using standardized *z* scores of the volumes of each ROI.
Results: Discriminant function analysis with cross-validation procedures revealed that brain anatomical variables correctly classified 75.6% of male subjects and 82.9% of female subjects, respectively. The results of the volumetric comparisons of each ROI between patients and controls were generally consistent with those of the previous literature.
Conclusions: To our knowledge, this study provides the first evidence of MRI-based successful classification between first-episode patients with schizophrenia and healthy controls. The potential of these methods for early detection of schizophrenia should be further explored.

1. Introduction

A number of neuroimaging studies have demonstrated subtle but significant structural changes in multiple brain regions in schizophrenia (McCarley et al., 1999; Wright et al., 2000; Shenton et al., 2001; Honea et al., 2005). Although magnetic resonance imaging (MRI), which provides stable and reliable information of brain structure, has brought about increasing understanding of the pathophysiology of schizophrenia, relatively few efforts have been made in the clinical application of MRI. Several studies have attempted to discriminate between schizophrenia patients and healthy subjects using brain anatomical structures obtained by MRI (Suddath et al., 1990; Leonard et al., 1999; Nakamura et al., 2004). Recently, some studies reported voxel-based morphometry (VBM)-based classification approaches (Davatzikos et al., 2005; Kawasaki et al., 2007; Fan et al., 2007). Although VBM is an unbiased, rater-independent technique, there are several criticisms of VBM and discrepancies between VBM and manually-traced region of interest (ROI) measurements (Bookstein 2001; Gitelman et al., 2001; Good et al., 2002; Mehta et al., 2003).

In our previous classification study, we investigated how brain anatomical measures based on ROI methods could distinguish mostly chronic schizophrenia patients from control subjects (Nakamura et al., 2004). Discriminant function analysis of 14 anatomical variables measured in a small number of coronal slices at the level of the mammillary body correctly classified 80% of male schizophrenia patients, 77.8% of female patients, 80% of male controls, and 86.4% of female controls. The relatively high specificity and sensitivity of the

Abbreviations: ANOVA, Analysis of variance; AZ, Area under the receiver operating characteristics curve; BPRS, Brief Psychiatric Rating Scale; DTI, Diffusion tensor imaging; DUP, Duration of untreated psychosis; ICC, Intraclass correlation coefficients; ICD-10, International Classification of Diseases, 10th edition; JART, Japanese version of the National Adult Reading Test; MRI, Magnetic resonance imaging; ROC, Receiver operating characteristics curve; ROI, Region of interest; SD, Standard deviation; VBM, Voxel-based morphometry.

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obtained classifiers revealed the validity of the use of anatomical measures from limited slices of MRI in discriminant function analysis. In the study, however, the medial temporal and prefrontal structures were not included as ROI, despite the fact that volume reduction of these structures has been repeatedly demonstrated in schizophrenia patients and these regions have been strongly implicated in the pathophysiology of schizophrenia (McCarley et al., 1999; Wright et al., 2000; Shenton et al., 2001; Suzuki et al., 2005b). Involvement of the hippocampal formation has been related to psychotic symptoms and verbal memory deficits in schizophrenia patients (Friston et al., 1992; Liddle et al., 1992; Goldberg et al., 1994), while prefrontal abnormalities have been implicated in negative symptoms and cognitive impairments such as deficits in working memory, executive and problem solving functions (Goldman-Rakic and Selemon, 1997). Thus, inclusion of medial temporal and prefrontal measures would enhance the accuracy of the classifiers.

A shorter duration of untreated psychosis (DUP) has consistently been associated with greater therapeutic outcome and better prognosis in schizophrenia (Marshall et al., 2005; Perkins et al., 2005). Given the chronic and disabling nature of schizophrenia for most affected individuals, the link between shorter DUP and better outcome suggests the critical importance of early detection and intervention. Accurate diagnosis of schizophrenia in the early stage is important for specific early intervention, although some instability of the clinical diagnosis over time has been demonstrated in patients with first-episode psychosis (Haahr et al., 2008; Salvatore et al., 2008). There have been replicated findings of structural brain changes in first-episode patients with schizophrenia, which may be less marked than those in chronic patients (Steen et al., 2006; Vita et al., 2006; Ellison-Wright et al., 2008). For the early detection of schizophrenia, structural neuroimaging techniques might be useful as a biological marker adjunct to clinical diagnosis. However previous classification studies were conducted in mixed samples of chronic and first-episode patients (Nakamura et al., 2004; Davatzikos et al., 2005; Kawasaki et al., 2007; Fan et al., 2007). To our knowledge, no MRI-based study has ever attempted to discriminate between first-episode schizophrenia patients and healthy subjects.

In the present study, we primarily intended to distinguish between first-episode patients with schizophrenia and healthy subjects by MRI-based structural measures. The secondary aim was to investigate regional brain volumetric differences between patients and controls to compare our results with those of previous studies. We generally followed the method of our previous classification study, in which ROI were taken from the central part of MRI images (Nakamura et al., 2004). Additionally, we included eight prefrontal lobe ROI and four medial temporal lobe ROI for use in discriminant function analysis. We predicted that the inclusion of the additional variables from these regions would enhance the potency of the classifiers to yield good classification rates, even in first-episode patients.

2. Methods

2.1. Subjects

Table 1 presents the demographic and clinical characteristics of the subjects. Thirty-four patients (17 males, 17 females) with first-episode schizophrenia (characterized as the first hospitalization for psychiatric illness) were recruited from the inpatient population at the Tokyo Metropolitan Matsuzawa Hospital. All but four males were right-handed. All patients fulfilled the ICD-10 research criteria for schizophrenia (World Health Organization, 1993) and were diagnosed by a consensus of at least two experienced psychiatrists based on a direct interview as well as a chart review. All patients had already been treated with neuroleptics at the time of scanning. Sixteen patients were treated with only atypical antipsychotics, and 18 patients received both typical and atypical antipsychotics. Clinical symptoms were assessed using the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962).

The age- and gender-matched control subjects consisted of forty-eight healthy volunteers (24 males, 24 females) recruited from the hospital staff and college students (Table 1). All of the controls except one female were right-handed. Control subjects with a personal or family history of psychiatric illness were excluded.

Premorbid IQ for schizophrenia patients and present IQ for control subjects were estimated using the shortened version of the Japanese version of the National Adult Reading Test (JART) (Matsuoka et al., 2006; Uetsuki et al., 2007). Socio-economic status as well as parental socio-economic status was assessed (Hollingshead, 1965).

All participants were physically healthy, and none had a lifetime history of serious head trauma, neurological illness, serious medical or surgical illness, or significant alcohol or substance abuse disorder. All subjects participated in this study after providing written informed consent. This study was approved by the Committee on Medical Ethics of Tokyo Metropolitan Matsuzawa Hospital.

2.2. Magnetic resonance imaging procedures

Magnetic resonance images were obtained using a Philips Intera 1.5-T scanner (Philips Medical Systems, Best, The 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.

Table 1
Demographic and clinical characteristics of the subjects.

	Schizophrenia patients		Control subjects		Analysis of variance[a]			
					Diagnosis		Gender	
	Male ($n=17$)	Female ($n=17$)	Male ($n=24$)	Female ($n=24$)	F	p	F	p
Age (years)	29.3 ± 6.6	28.8 ± 6.1	30.8 ± 5.4	29.8 ± 5.8	0.89	0.344	0.32	0.572
Handedness (number of right-handed subjects)	14	17	24	23				
Socio-economic status	2.3 ± 0.9	3.1 ± 1.2	1.7 ± 0.5	1.6 ± 0.5	34.20	<0.001	3.90	0.051
Parental socio-economic status	2.3 ± 0.8	2.7 ± 0.7	2.4 ± 0.6	2.3 ± 0.5	1.47	0.230	0.41	0.520
Estimated IQ[b]	102.4 ± 9.7	102.1 ± 7.6	109.6 ± 7.2	108.6 ± 7.9	13.50	<0.001	0.12	0.734
Duration of untreated psychosis (month)	7.8 ± 8.7	12.2 ± 15.5						
Duration of illness (month)	10.1 ± 10.4	14.6 ± 15.5						
Duration of medication (days)	49.0 ± 73.0	75.4 ± 69.1						
Medication (mg/day, chlorpromazine equiv.)	1055.6 ± 472.4	864.6 ± 431.0						
Total BPRS score	40.1 ± 9.3	37.9 ± 9.4						

BPRS, Brief Psychiatric Rating Scale.
[a] For the results of the post hoc tests, see the text.
[b] Estimated IQ was measured using the shortened version of the Japanese version of the National Adult Reading Test (JART) (Matsuoka et al., 2006; Uetsuki et al., 2007).

The MRI data were transferred to a UNIX work station (Silicon Graphics, Inc., Mountain View, CA) and were randomly coded and analyzed with the software package Dr.View 5.0 (Asahi Kasei Joho System, Tokyo, Japan). Before reconstruction of the MR images, they were realigned in three dimensions to standardize for differences in head tilt during MR image acquisition. Head tilt in the sagittal plane was corrected by aligning the anterior commissure–posterior commissure (AC–PC) plane. Correction in the axial and coronal planes was achieved by aligning the longitudinal third ventricle and the interhemispheric fissure by reference to the symmetry of the eyeballs and optic nerves. After correction, the entire contiguous coronal images of 1-mm thickness vertical to the AC–PC line were reconstructed. The signal-intensity histogram distributions from the T1-weighted images across the whole brain for each subject were used to segment the voxels semi-automatically into brain tissue and cerebrospinal fluid (CSF) according to the Alpert algorithm (Alpert et al., 1996). The gray and white matter of each ROI were manually separated because of the slight non-uniformity of intensity observed in most of the cases.

2.3. Volumetric measurements of ROI

The ROI were measured in the following two regions as presented in Fig. 1.

2.3.1. Prefrontal region

The delineation of the ROI of the prefrontal region was based on the work of Crespo-Facorro et al. (1999) and Ballmaier et al. (2004). The three contiguous coronal slices posterior to the first appearance of the genu of the corpus callosum were chosen for measurement. The genu of the corpus callosum was used as a landmark for the following reasons. First, the present delineation methods can be easily reproduced among different subjects using this procedure. Second, the inferior frontal gyrus, which is a relatively short structure, can be observed adequately within these slices. Third, the anatomical boundary of the anterior cingulate gyrus can be readily determined posterior to the genu of the corpus callosum.

In the prefrontal slices, the areas of the following structures were measured in each slice and summed to obtain volumes: the prefrontal part of the whole cerebrum; the anterior interhemispheric fissure; and the gray matter of the anterior cingulate gyrus, superior frontal gyrus, middle frontal gyrus, inferior frontal gyrus, and orbitofrontal gyrus. The prefrontal part of the whole cerebrum included all the brain tissue of the three chosen slices and was used in the following regression analysis. The boundaries of each ROI were defined as described in Table 2.

2.3.2. Central region

The three contiguous coronal slices in which the mammillary body was most clearly seen were chosen for measurement. The central part of the whole cerebrum and the following ROI were measured: the body and inferior horn of the lateral ventricle, third ventricle, Sylvian fissure, central interhemispheric fissure, whole temporal lobe, gray and white matter of the superior temporal gyrus, amygdala–hippocampal complex, and parahippocampal gyrus. The central part of the whole cerebrum included all the brain tissue of the three chosen slices and was used in the subsequent regression analysis. The detailed delineation of these ROI was based on the method of our previous studies (Nakamura et al., 2004; Niu et al., 2004; Suzuki et al., 2005a). The boundaries of each ROI were defined as described in Table 2.

2.4. Reliability

All measurements were performed by one rater (Y.T.) who was blind to the subjects' gender and diagnosis. The intrarater reliability was established by remeasuring all regions in five randomly selected subjects. The intraclass correlation coefficient (ICC) ranged from 0.91 to 0.99 for all ROI. A second rater (E.T.) blinded to the subjects' identity measured all regions in five randomly selected samples to evaluate the interrater reliability. The interrater ICC was 0.83 for the left parahippocampal gyrus, 0.86 for the right amygdala–hippocampal complex, 0.88 for white matter of the right superior temporal gyrus, and between 0.90 and 0.99 for all other ROI.

2.5. Statistical analysis

All statistical analyses were performed using the software package SPSS 11.01J (SPSS, Chicago, IL, USA).

Demographic and clinical variables were compared by analysis of variance (ANOVA).

The volumes of each ROI were expressed as standardized z scores corrected by regression analysis for the variations in head size and age of the control subjects (Zipursky et al., 1992; Pfefferbaum et al., 1993; Mathalon et al., 1993; Sullivan et al., 2000). Briefly, the prefrontal ROI value for the control group was regressed against prefrontal whole cerebral volume and age, yielding a residual value for each control subject. The prefrontal ROI value for the patient group was 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

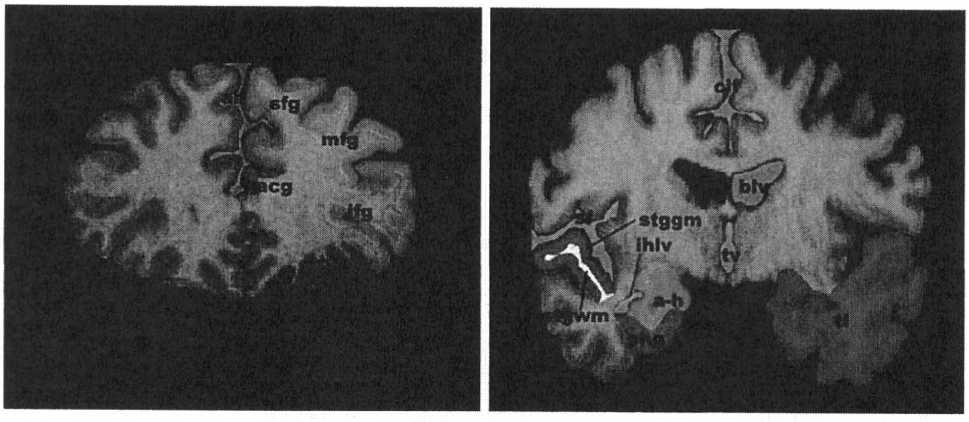

Fig. 1. Examples of the prefrontal regions of interest (left) and central regions of interest (right) traced manually in this study. acg: anterior cingulate gyrus; a–h: amygdala–hippocampal complex; aif: anterior interhemispheric fissure; blv: body of the lateral ventricle; cif: central interhemispheric fissure; ifg: inferior frontal gyrus; ihlv: inferior horn of the lateral ventricle; mfg: middle frontal gyrus; orb: orbitofrontal gyrus; phg: parahippocampal gyrus; sf: Sylvian fissure; sfg: superior frontal gyrus; stggm: gray matter of the superior temporal gyrus; stgwm: white matter of the superior temporal gyrus; tl: temporal lobe; tv: third ventricle.

Table 2
Anatomical boundaries of the regions of interest.

Region	Anatomical landmark
Prefrontal region	
Anterior cingulate gyrus	Superior border: cingulate sulcus Inferior border: callosal sulcus
Superior frontal gyrus[a]	Lateral inferior border: superior frontal sulcus Medial inferior border: cingulate sulcus
Middle frontal gyrus	Superior border: superior frontal sulcus Inferior border: inferior frontal sulcus
Inferior frontal gyrus	Superior border: inferior frontal sulcus Inferior border: lateral orbital sulcus or superior circular sulcus
Orbitofrontal gyrus	Lateral border: lateral orbital sulcus or inferior circular sulcus Medial border: olfactory sulcus
Anterior interhemispheric fissure	Superior border: a line connecting the outer limb of the left superior frontal gyrus with the right one
Central region	
Temporal lobe	Demarcated by a line perpendicular to the axis of the temporal stem from the inferior aspect of the insula
Superior temporal gyrus	Superior border: Sylvian fissure Inferior border: superior temporal sulcus
Amygdala–hippocampal complex	Superior border: cerebrospinal fluid overlying the semilunar gyrus and its medial extension Lateral border: temporal lobe white matter and extension of the inferior horn of the lateral ventricle Inferior border: white matter of the parahippocampal gyrus
Parahippocampal gyrus	Superior border: inferior gray border of the hippocampal formation Inferior border: a line drawn from the most lateral border of the hippocampal flexure to the collateral sulcus
Central interhemispheric fissure	Superior border: a line connecting the outer limb of the left superior frontal gyrus with the right one
Sylvian fissure	Lateral border: a line connecting the outer limb of the postcentral gyrus with the outer limb of the superior temporal gyrus

[a] The paracingulate gyrus was included in the superior frontal gyrus when present (Takahashi et al., 2002; Suzuki et al., 2005a; Zhou et al., 2005).

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. The central ROI value was also processed in the same way as the prefrontal ROI.

In order to see whether volumetric changes in our sample were comparable with those in previous literature, the volumes of each ROI were compared across the diagnostic groups. The z scores of each ROI were analyzed by repeated measures ANOVA with diagnosis as a between-subject factor and hemisphere (left, right) as a within-subject factor. The one-way ANOVA for the z scores of the third ventricle and the anterior and central interhemispheric fissures was carried out without using the within-subject factors. For post hoc pairwise comparisons, Fisher's Least Significant Difference (LSD) tests were employed.

Discriminant function analysis was conducted using z scores as independent variables to assess the possibility of differentiating the schizophrenia patients from the control subjects by a combination of brain anatomical variables. The variables were entered in a stepwise manner using the Wilks method. For the stepwise selection, the inclusion criterion was set at $p \leq 0.25$ according to the recommendation by Costanza and Afifi (1979). This liberal cutoff p value for entry was chosen to avoid the exclusion of potentially important variables (Bendel and Afifi, 1977; Costanza and Afifi, 1979). Such liberal criteria have been employed in a number of previous studies (Carter et al., 1999; Shaw et al., 2000; Nakamura et al., 2004).

To validate the present discriminant function, we used the Jackknife (leave-one-out) approach. Using this, we were able to estimate the potency of the obtained classifier when it was adopted for new subjects. We also performed a receiver operating characteristic curve (ROC) analysis and calculated the area under the ROC curve (Az).

Pearson's correlation coefficients were calculated to examine relationships between z scores of each ROI and DUP, duration of illness, daily medication dosage, duration of neuroleptic medication, total BPRS score, and estimated IQ. To prevent a possible type I error due to multiple tests, a Bonferroni correction was applied for correlation analyses.

Transformation of ROI volumes into z scores, ANOVA comparisons, discriminant function analyses and correlation analyses were carried out separately for each gender because of the evidence for gender differences in brain morphology among healthy subjects (Cosgrove et al., 2007) and gender-specific brain structural changes in schizophrenia patients (Goldstein et al., 2002; Takahashi et al., 2002).

Statistical significance was defined as $p < 0.05$ (two-tailed).

3. Results

3.1. Demographic and clinical characteristics

There were no significant group differences in age or parental socio-economic status. There were significant main effects on diagnosis of socio-economic status (ANOVA, $F = 34.20$, df = 1,79, $p < 0.001$) and estimated IQ (ANOVA, $F = 13.50$, df = 1,74, $p < 0.001$). Post hoc tests showed that the schizophrenia patients had a significantly lower socio-economic status ($p < 0.001$) and estimated premorbid IQ ($p < 0.001$) (Table 1).

3.2.1. Comparison of the ROI volumes in male subjects

One-way ANOVA revealed a significant main effect of diagnosis for the third ventricle ($F = 5.63$, df = 1,39, $p = 0.023$). The post hoc test showed that the third ventricle was significantly larger in the schizophrenia patients than in the controls ($p = 0.023$).

Repeated measures ANOVA revealed significant main effects of diagnosis for the middle frontal gyrus ($F = 4.65$, df = 1,39, $p = 0.037$), the amygdala–hippocampal complex ($F = 4.10$, df = 1,39, $p = 0.049$), and the inferior horn of the lateral ventricle ($F = 4.07$, df = 1,39, $p = 0.049$). Post hoc tests showed that the left amygdala–hippocampal complex volume was significantly reduced ($p = 0.038$) and the left inferior horn of the lateral ventricle was significantly enlarged in the schizophrenia patients ($p = 0.019$). The difference in the volume of the middle frontal gyrus did not reach statistical significance.

There were significant main effects of hemisphere ($F = 4.46$, df = 1,39, $p = 0.041$) and diagnosis × hemisphere interaction ($F = 4.46$, df = 1,39, $p = 0.041$) for the parahippocampal gyrus. Post hoc tests showed that the parahippocampal gyrus was significantly smaller in the left hemisphere ($p = 0.041$) than in the right and that the parahippocampal gyrus was significantly unilaterally reduced in the schizophrenia patients ($p = 0.039$ for the left hemisphere) (Fig. 2).

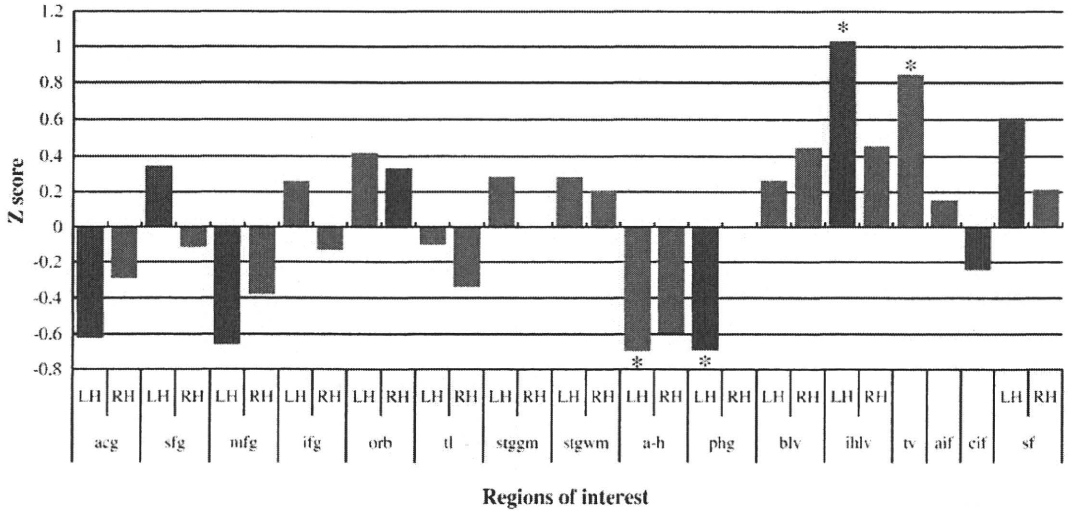

Fig. 2. Standardized *z* scores for each ROI of male patients with schizophrenia. For the control subjects, the expected mean *z* score was 0. LH: left hemisphere; RH: right hemisphere; acg: anterior cingulate gyrus; a–h: amygdala–hippocampal complex; aif: anterior interhemispheric fissure; blv: body of the lateral ventricle; cif: central interhemispheric fissure; ifg: inferior frontal gyrus; ihlv: inferior horn of the lateral ventricle; mfg: middle frontal gyrus; orb: orbitofrontal gyrus; phg: parahippocampal gyrus; sf: Sylvian fissure; sfg: superior frontal gyrus; stggm: gray matter of the superior temporal gyrus; stgwm: white matter of the superior temporal gyrus; tl: temporal lobe; tv: third ventricle. $^{*}p < 0.05$, post hoc analysis. Red bar indicates inclusion in the discriminant model.

There were no significant differences in any ROI volume between patients receiving only atypical antipsychotics and those treated with both typical and atypical antipsychotics.

3.2.2. Comparison of the ROI volumes in female subjects

One-way ANOVA revealed a significant main effect of diagnosis for the third ventricle ($F = 5.03$, df = 1,39, $p = 0.030$). The post hoc test showed that the third ventricle was significantly enlarged in the schizophrenia patients ($p = 0.030$).

Repeated measures ANOVA revealed significant main effects of diagnosis for the body of the lateral ventricle ($F = 6.45$, df = 1,39, $p = 0.015$) and the Sylvian fissure ($F = 8.03$, df = 1,39, $p = 0.007$). Post hoc tests showed that the body of the lateral ventricle ($p = 0.022$ for the left hemisphere, $p = 0.016$ for the right hemisphere) and the Sylvian fissure ($p = 0.013$ for the left hemisphere, $p = 0.025$ for the right hemisphere) were significantly bilaterally enlarged in the schizophrenia patients (Fig. 3).

No ROI volumes differed between the patients treated with only atypical antipsychotics and those treated with both typical and atypical antipsychotics.

3.3. Discriminant function analysis

Among the male subjects, the following eight variables were entered in a stepwise manner: the left anterior cingulate gyrus, the left superior frontal gyrus, the left middle frontal gyrus, the right orbitofrontal gyrus, the left parahippocampal gyrus, the left inferior horn of the lateral ventricle, the central interhemispheric fissure, and the left Sylvian fissure. The use of these variables resulted in correct classification rates of 95.8% in the control subjects, 76.5% in the

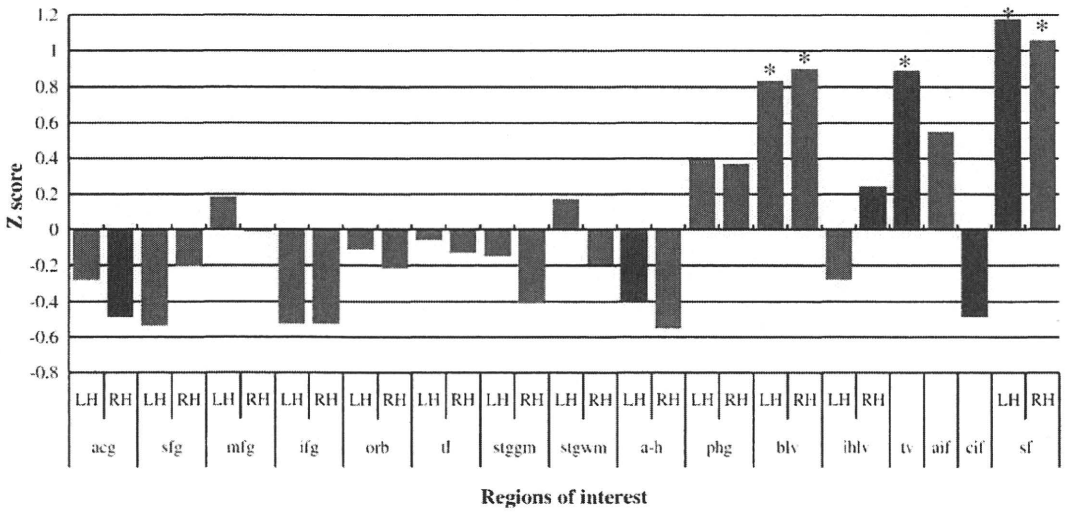

Fig. 3. Standardized *z* scores for each ROI of female patients with schizophrenia. For the control subjects, the expected mean *z* score was 0. LH: left hemisphere; RH: right hemisphere; acg: anterior cingulate gyrus; a–h: amygdala–hippocampal complex; aif: anterior interhemispheric fissure; blv: body of the lateral ventricle; cif: central interhemispheric fissure; ifg: inferior frontal gyrus; ihlv: inferior horn of the lateral ventricle; mfg: middle frontal gyrus; orb: orbitofrontal gyrus; phg: parahippocampal gyrus; sf: Sylvian fissure; sfg: superior frontal gyrus; stggm: gray matter of the superior temporal gyrus; stgwm: white matter of the superior temporal gyrus; tl: temporal lobe; tv: third ventricle. $^{*}p < 0.05$, post hoc analysis. Red bar indicates inclusion in the discriminant model.

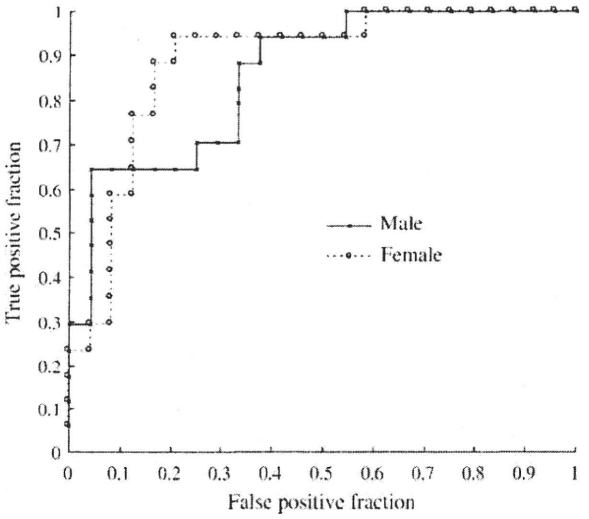

Fig. 4. Receiver operating characteristic (ROC) curves for male and female subjects. The area under the ROC curve (Az) was 0.858 for male subjects and 0.885 for female subjects. Greater Az value indicates better diagnostic performance of the classifier. True positive fraction and false positive fraction indicate sensitivity and 1 − specificity, respectively.

schizophrenia patients, and 87.8% in all male subjects ($F = 4.53$; df = 8,32; $p = 0.001$; Wilks lambda = 0.469).

Among the female subjects, the following six variables were entered in a stepwise manner: the right anterior cingulate gyrus, the left amygdala–hippocampal complex, the third ventricle, the right inferior horn of the lateral ventricle, the central interhemispheric fissure, and the left Sylvian fissure. By using these variables, 83.3% of the control subjects, 94.1% of the schizophrenia patients, and 87.8% of all female subjects were correctly classified ($F = 6.11$; df = 6,34; $p < 0.001$; Wilks lambda = 0.481).

After a cross-validation procedure using the Jackknife approach, the correct classification rates were 75.6% in the male subjects (83.3% specificity and 64.7% sensitivity) and 82.9% in the female subjects (83.3% specificity and 82.4% sensitivity). The area under the ROC curve (Az) was 0.858 for the male subjects and 0.885 for the female subjects, respectively (Fig. 4).

3.4. Correlation analysis

Pearson's correlation coefficients did not reveal any significant correlation between ROI volumes and clinical variables after the Bonferroni correction [Twenty-nine ROI; $p < 0.0017$ (0.05/29)].

4. Discussion

To our knowledge, this study is the first that differentiated first-episode schizophrenia patients from healthy subjects by the discriminant function analysis using ROI-based brain structural variables from MRI. The stepwise discriminant function analysis identified the combinations of ROI that characterized brain anatomical features distinguishing first-episode patients from healthy controls with fairly good sensitivity and specificity. As to the correct classification rates, our results were comparable to those of previous MRI-based classification studies conducted among mainly chronic patients (Leonard et al., 1999; Nakamura et al., 2004; Davatzikos et al., 2005; Kawasaki et al., 2007; Fan et al., 2007). Considering the smaller magnitude of brain volume changes observed in first-episode schizophrenia patients relative to chronic patients (Steen et al., 2006; Vita et al., 2006; Ellison-Wright et al., 2008), the classification accuracy in the present study comparable to that obtained in our previous study (Nakamura et al., 2004) may be accounted by the additional inclusion of the prefrontal and medial temporal components in the analyses.

The results of the present study suggest that the combinations of brain structural measures may provide objective biological information adjunct to the clinical diagnosis of schizophrenia even in the early stage. However it is too early to draw a conclusion that the MRI-based classification methods can be applied directly to the diagnosis of first-episode schizophrenia, since we have not included patients with other types of psychosis such as first-episode affective psychosis in the analyses. Further studies are needed to examine whether first-episode patients who later become clearly diagnosed with schizophrenia would be discriminated from those with some other types of psychosis. For the detection at the earliest stage, it must be tested if our methods would help to predict whether subjects in a prodromal phase will later go on to develop schizophrenia.

Among male patients, the volumes of the third ventricle and the left inferior horn of the lateral ventricle were significantly enlarged, and the left amygdala–hippocampal complex and the left parahippocampal gyrus were significantly reduced compared to those of the controls. Significant enlargements of the third ventricle, the bilateral body of the lateral ventricle, and the bilateral Sylvian fissure were observed in female patients. These results are consistent with those of a number of previous studies (McCarley et al., 1999; Wright et al., 2000; Shenton et al., 2001; Honea et al., 2005). Gray matter volume reduction of the superior temporal gyrus is one of the most consistently reported abnormalities in the brain structure of schizophrenia patients (Shenton et al., 2001). Moreover, the smaller gray matter volume of the superior temporal gyrus and its progressive volume reduction were demonstrated in first-episode schizophrenia patients (Hirayasu et al., 1998, 2000; Gur et al., 2000; Kasai et al., 2003; Sumich et al., 2005; Takahashi et al., 2009). However, no significant volume differences in the superior temporal gyrus were observed in the present study. Although the validity of using a limited number of slices was demonstrated in our previous studies (Kurokawa et al., 2000; Nakamura et al., 2004), a larger number of slices for measurement may be required to detect significant volume changes in the superior temporal gyrus in patients.

In the stepwise discriminant function analyses, eight ROI were entered among the male subjects whereas six ROI were selected for entry among the female subjects. Some of ROI which showed volume differences between diagnostic groups in ANOVA were not included in the discriminant model because their p values for entry varied during the stepwise processes and consequently exceeded the criterion for inclusion. ROI included in the discriminant function analysis in the male subjects appeared more lateralized to the left hemisphere relative to those in the female subjects, as were similarly seen in the volume changes of many ROI (see Figs. 2 and 3). Several previous studies demonstrated more left-lateralized volume reductions specific to male schizophrenia patients in the whole temporal lobe (Bryant et al., 1999), planum temporale (Goldstein et al., 2002), hippocampus (Bogerts et al., 1990) and amygdala (Niu et al., 2004), while right-sided abnormalities such as the lack of normal leftward asymmetry of the planum temporale (Goldstein et al., 2002) and smaller right anterior cingulate gyrus (Takahashi et al., 2002) were reported in female patients. Although our results were not fully consistent with those of the previous studies, gender differences in lateralization of selected ROI for the discriminant function analyses might reflect such sexually dimorphic changes in schizophrenia patients.

The lack of significant correlations between brain structural measures and clinical variables in the patients might be explained from several aspects. Structural changes associated with schizophrenia may probably consist of the consequences of multiple processes including premorbid vulnerability, progressive changes during and/or after onset, effects of antipsychotic medication, and influence of other non-specific factors (Pantelis et al., 2005; Lieberman et al., 2005). Meanwhile, severity of clinical symptoms can be variable, in particular, under the influence of pharmacotherapy. These complexities may

make it difficult to see simple correlations of brain measures with clinical variables. Furthermore the volumes of ROI measured from the limited number of slices may not necessarily have represented those of the whole structures. The conservative Bonferroni correction taking account of the multiple measured ROI (29 ROI) might have also affected the results.

Discrimination of schizophrenia patients from healthy subjects has been attempted by several studies employing variables derived from positron emission tomography (Levy et al., 1992), neuropsychological tests (Arango et al., 1999; Fleck et al., 2001), MMPI scales (Carter et al., 1999), and neurophysiological measures (Gerez and Tello, 1995; Knott et al., 1999; Kojima et al., 2001). These functional measures have been reported to successfully distinguish between schizophrenia patients and controls, although they are considered more susceptible to the subjects' condition than brain structural measures, which provide stable biological information. Pardo et al. (2006) demonstrated successful classification of the three diagnostic groups (schizophrenia, bipolar disorder, and controls) by employing discriminant function analysis with variables obtained by structural brain measures and neuropsychological tests. Combinations of different modalities would contribute to the enhancement of classification accuracy.

There are several limitations of this study that should be taken into account. First, the sample size was not so large, although fairly good correct classification rates were obtained between the patients and controls. Second, the effects of lower premorbid intelligence in the patients on brain morphometric changes were not fully investigated in the present study, although treating the premorbid IQ as a covariate in the statistical analysis did not essentially affect the results (data not shown). Third, the structured interview such as SCID was not used for diagnosis in this study. However we have confirmed the diagnostic stability of all the patients included in the present study during the follow-up periods (1 to 4 years) after the scans. Fourth, all patients were exposed to antipsychotic medications before scanning even for a short period. In a recent study, schizophrenia patients treated with the typical antipsychotic drug haloperidol showed gray matter volume reduction over time, while olanzapine-treated patients did not (Lieberman et al., 2005). Although there were no significant differences in all ROI volumes between the patients receiving typical antipsychotics and those treated with both typical and atypical antipsychotics, future research should be designed to analyze drug-naïve patients to exclude the influence of antipsychotic medication. Finally, as discussed above, since other psychiatric disorders such as mood disorder were not included in the present study, the current classification methods cannot be applied to separate patients with schizophrenia from those with different psychiatric diagnoses.

In conclusion, our results showed that the discriminant function analysis using brain structural variables successfully distinguished between first-episode schizophrenia patients and healthy subjects with good accuracy. Such techniques may provide objective biological information adjunct to the clinical diagnosis of schizophrenia, although further studies are needed to see if they could contribute to early detection.

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