technical support for MRI scanning and data processing. Dr. Velakoulis and Ms. Soulsby developed the tracing protocol and supervised the MRI analysis. Drs. Suzuki, Velakoulis, Lorenzetti, and Pantelis contributed to writing and editing of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

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

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Follow-up MRI study of the insular cortex in first-episode psychosis and chronic schizophrenia

Tsutomu Takahashi [a,b,c,*], Stephen J. Wood [a], Bridget Soulsby [a], Patrick D. McGorry [d], Ryoichiro Tanino [b], Michio Suzuki [b,c], Dennis Velakoulis [a], Christos Pantelis [a]

[a] *Melbourne Neuropsychiatry Centre, Department of Psychiatry, University of Melbourne and Melbourne Health, Victoria, Australia*
[b] *Department of Neuropsychiatry, University of Toyama, Toyama, Japan*
[c] *Core Research for Evolutional Science and Technology, Japan Science and Technology Corporation, Tokyo, Japan*
[d] *ORYGEN Research Centre, University of Melbourne, Victoria, Australia*

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ABSTRACT

Morphologic abnormalities of the insular cortex have been described in psychotic disorders such as schizophrenia, but it remains unknown whether these abnormalities develop progressively over the course of the illness. In the current study, longitudinal magnetic resonance imaging data were obtained from 23 patients with first-episode psychosis (FEP), 11 patients with chronic schizophrenia, and 26 healthy controls. The volumes of the short (anterior) and long (posterior) insular cortices were measured on baseline and follow-up (between 1 and 4 years later) scans and were compared across groups. In cross-sectional comparison at baseline, the FEP and chronic schizophrenia patients had significantly smaller short insular cortex than did controls. In longitudinal comparison, the FEP patients showed significant gray matter reduction of the insular cortex over time (−4.3%/2.0 years) compared with controls (0.3%/2.2 years) without significant subregional effects, but there was no difference between chronic schizophrenia patients (−1.7%/2.4 years) and controls. The gray matter loss of the left insular cortex over time in FEP patients was correlated with the severity of positive and negative symptoms at follow-up. These findings indicate that patients with psychotic disorders have smaller gray matter volume of the insular cortex especially for its anterior portion (short insula) at first expression of overt psychosis, but also exhibit a regional progressive pathological process of the insular cortex during the early phase after the onset, which seems to reflect the subsequent symptomatology.

1. Introduction

Structural brain abnormalities in schizophrenia have already developed by the onset of psychosis (Vita et al., 2006), suggesting a neurodevelopmental pathology (Weinberger, 1987). Recent longitudinal magnetic resonance imaging (MRI) studies in first-episode schizophrenia have demonstrated progressive ventricular expansion (Cahn et al., 2002; DeLisi et al., 1997; Nakamura et al., 2007; Puri et al., 2005) or volume reduction in frontal and temporal regions (Bachmann et al., 2004; Gur et al., 1998; Ho et al., 2003; Kasai et al., 2003a,b; Nakamura et al., 2007) in the initial years subsequent to the onset, possibly reflecting a pathological process in 'late neurodevelopment' (Pantelis et al., 2005, 2007). The few longitudinal studies that directly compare progressive brain changes in first-episode and chronic schizophrenia (Gur et al., 1998; Pantelis et al., 2008) have suggested that such changes are nonlinear and most prominent at the earliest phase of the illness.

The anatomical pattern of progressive brain changes in schizophrenia remains largely unknown. One voxel-based morphometric (VBM) study (Farrow et al., 2005) demonstrated

* Corresponding author: Melbourne Neuropsychiatry Centre, c/o National Neuroscience Facility, 161 Barry St, Carlton South, Victoria 3053, Australia. Tel.: +61 3 8344 1800; fax: +61 3 9348 0469.
E-mail address: tsutomu@med.u-toyama.ac.jp (T. Takahashi).

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that first-episode schizophrenia patients exhibit progressive gray matter reduction in lateral fronto-temporal and left cingulate regions, but a subsequent study by the same group using a modified methodology (Whitford et al., 2006) showed progressive changes predominantly in parietal cortex. Our recent study in first-episode schizophrenia (Sun et al., in press) based on a cortical pattern matching technique, which allows sensitive assessment of regional progressive changes throughout the lateral cortical surface, found increased brain surface contraction mainly in the dorsal prefrontal cortex. However, this approach cannot examine the cortical regions in deep sulci such as the insular cortex.

Neuroimaging investigations have shown that the pathological process in schizophrenia predominantly affects the fronto-temporolimbic-paralimbic regions, including insular cortex bilaterally (Glahn et al., 2008). Gray matter reduction of the insular cortex, which plays crucial roles in emotional and various cognitive functions as a component of the 'limbic integration cortex' (Augustine, 1996), has been repeatedly described in schizophrenia (Crespo-Facorro et al., 2000; Kasai et al., 2003c; Kim et al., 2003; Makris et al., 2006; Saze et al., 2007; Takahashi et al., 2004, 2005), although its pattern of topographically specific localization [i.e., sulcally defined and functionally different short (anterior) versus long (posterior) insular cortex (Augustine, 1996; Türe et al., 1999)] is still unclear. Gray matter reduction or dysfunction of the insula has been implicated in manifesting psychotic symptoms (Crespo-Facorro et al., 2000; Shapleske et al., 2002; Shergill et al., 2000) and cognitive impairments (Crespo-Facorro et al., 2001a,b; Curtis et al., 1998). An inverse correlation between insular cortex volume and illness duration in schizophrenia (Takahashi et al., 2004, 2005) suggests a regional progressive pathological process in the course of the illness. Negative insular findings in the above-mentioned longitudinal studies based on statistical imaging techniques (Farrow et al., 2005; Whitford et al., 2006) might be due to lower sensitivity compared with manual region of interest (ROI) methods (Giuliani et al., 2005).

This study aimed to examine the progressive gray matter changes of the insular subregions in psychotic disorders using ROI analysis of longitudinal MRI data in both first-episode psychosis (FEP) and chronic schizophrenia patients compared with healthy controls. Based on previous studies, we predicted that both patient groups would show progressive insular cortex atrophy, but its degree would be greater in the FEP patients.

2. Methods

2.1. Subjects

Twenty-three first-episode psychotic (FEP) inpatients were recruited from the Early Psychosis Preventions and Intervention Centre (McGorry et al., 1996). Inclusion criteria for FEP patients have been previously described (Velakoulis et al., 1999); all patients were age at onset between 16 and 30 years and psychotic at intake as reflected by the presence of at least one symptom (delusions, hallucinations, disorder of thinking or speech other than simple acceleration or retardation, or disorganized, bizarre, or markedly inappropriate behavior). DSM-IV diagnoses (American Psychiatric Association, 1994) were based on chart review, Structured Clinical Interview for DSM-IV Disorders (SCID) (First et al., 1997) and the Royal Park Multidiagnostic Instrument for Psychosis (McGorry et al., 1989) administered during the initial treatment episode (median illness duration = 29.0 days). All FEP patients were neuroleptic-naïve prior to admission but 17 had received neuroleptics for a short period prior to first scanning. Accurate values for duration of medication were not available, but mean duration of such a period in our centre is about 30 days (Velakoulis et al., 1999). The final diagnoses of these patients during the follow-up were as follows: schizophrenia (n = 16), schizoaffective disorder (n = 3), schizophreniform disorder (n = 1), and other psychoses (e.g., delusional disorder, n = 3).

Eleven chronic schizophrenia patients, who had more than 18 months of continuous illness, were recruited from the Adult Mental Health Rehabilitation services of the North Western Mental Health Program, Melbourne. Diagnoses were based on SCID and chart review. Twenty-six healthy volunteers without any personal or family history of psychiatric illness were recruited from similar socio-demographic areas as the patients by approaching ancillary hospital staff and through advertisements.

Clinical information including handedness, onset date, IQ as assessed by the National Adult Reading Test (Nelson and O'Connell, 1978), and medication data was obtained from patient interview and chart review. Patients' symptoms at baseline and second scan (where available) were assessed using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). At baseline, 8 FEP and 5 chronic schizophrenia patients were treated with atypical antipsychotics, and 9 FEP and 4 chronic patients were receiving typical ones. Patients were also receiving benzodiazepines (10 FEP and 3 chronic patients), antidepressants (2 FEP and 2 chronic patients), anticholinergics (3 chronic patients), and/or mood stabilizers [lithium carbonate (3FEP and 1 chronic patients), sodium valproate (1 chronic patient), or combination of carbamazepine and sodium valproate (1 chronic patient)]. Two FEP and one chronic patients were prescribed no medication at baseline. At follow-up scanning, 8 FEP and 4 chronic patients were on atypical antipsychotics and 7 FEP and 4 chronic patients were on typical antipsychotics. They were also receiving benzodiazepines (4 FEP and 2 chronic patients), antidepressants (2 FEP and 2 chronic patients), anticholinergics (2 chronic patients), and/or mood stabilizers [lithium carbonate (2 FEP and 1 chronic patients), carbamazepine (one chronic patient), or combination of lithium carbonate and sodium valproate (1 FEP patient)]. Eight FEP and one chronic patients were either non-compliant with treatment or prescribed no medication at follow-up. The medication status was unknown for 4 FEP and one chronic patient at baseline and for 2 chronic patients at follow-up.

All participants were screened for co-morbid medical and psychiatric conditions by clinical assessment, physical and neurological examination. Exclusion criteria were a history of head injury, neurological diseases, impaired thyroid function, corticosteroid use, or DSM-IV criteria of alcohol or substance abuse or dependence. This study was approved by local research and ethics committees. Written informed consent was obtained from all subjects.

2.2. MRI procedures

Subjects were scanned twice on a 1.5-T GE Signa scanner (GE, Milwaukee, Wisconsin). A three-dimensional volumetric spoiled gradient recalled echo in the steady state sequence generated 124 contiguous 1.5 mm coronal slices. Parameters were: echo time, 3.3 ms; repetition time, 14.3 ms; flip angle, 30°; matrix size, 256×256; field of view, 24×24-cm matrix; and voxel dimensions, 0.938×0.938×1.5 mm. The scanner was calibrated fortnightly with the same phantom to ensure stability of measurements.

The image data were coded randomly and analyzed with the Dr View software (AJS, Tokyo, Japan). Brain images were realigned in three dimensions and reconstructed into contiguous coronal images, with a 0.938-mm thickness, perpendicular to the AC–PC line. The whole brain was manually separated from the brainstem and cerebellum. The signal-intensity histogram distributions from the T1-weighted images across the whole brain were used to semi-automatically segment the voxels into gray matter, white matter, and cerebrospinal fluid. The whole brain volume was then calculated by summing the voxels for tissue components across all brain slices. The intracranial volume (ICV) was measured on a sagittal reformat of the original 3-dimensional data set using the dura mater, undersurface of the frontal lobe, dorsum sellae, clivus, and C1 vertebra as major landmarks (Eritaia et al., 2000) to correct for differences in head size; the groups did not differ significantly in their ICVs (Table 1).

2.3. Insular cortex measurements

Based on the segmented gray matter images, the insular cortex was traced on 0.938-mm consecutive coronal slices as described elsewhere (Takahashi et al., 2005). Briefly, the most rostral coronal slice containing the insular cortex and the coronal plane containing the fusion of the superior and inferior circular insular sulci were chosen as anterior and posterior boundaries, respectively. On each coronal slice, the insular cortex was bounded superiorly by the superior circular insular sulcus and inferiorly by the inferior circular insular sulcus or the orbitoinsular sulcus. The insular cortex was then divided into the short and long insular cortices by the central insular sulcus, which was readily identified using both coronal and sagittal views (Fig. 1).

All volumetric data reported here were measured by one rater (TT), who was blinded to subjects' identities or time of scan. The volumes of the short and long insular cortices in a subset of 5 randomly selected brains were measured independently by two raters (TT and RT), and these volumes in 10 randomly selected brain images were remeasured by the first rater; intra/inter-rater intraclass correlation coefficients (ICCs) of the short and long insular cortex measurements were 0.96/0.98 and 0.98/0.93, respectively.

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 insular cortex volume at baseline and follow-up was assessed using a repeated measures analysis of covariance with age, gender, and ICV as covariates (ANCOVA), with diagnosis as a between-subject factor, and side and subregion (short, long) as within-subject variables.

The longitudinal volume change of the insular cortex was analyzed using the percent volume change [100×(absolute volume at second scan−absolute volume at baseline)/

Table 1
Demographic and clinical characteristics of the sample

	Control subjects (n=26)	FEP patients (n=23)	Chronic Sz patients (n=11)	Group comparisons
Age at baseline scan (years)	25.6±9.1	21.6±3.5	32.7±7.6	ANOVA: $F(2, 57)=8.95$, $p<0.001$
Male/female	15/11	16/7	10/1	Chi-square=3.97, $p=0.14$
Handedness (right/mixed/left)	24/1/1	18/0/5 [a]	10/1/0	Chi-square=7.44, $p=0.11$
Height (cm) [b]	174.9±11.6	171.3±7.8	174.5±7.5	ANOVA: $F(2, 51)=0.86$, $p=0.428$
Premorbid IQ [b]	101.2±9.7	92.8±15.0	101.4±10.0	ANOVA: $F(2, 44)=2.77$, $p=0.074$
Inter-scan interval (years)	2.16±0.91 (range, 0.88–4.18)	2.02±0.76 (range, 0.80–4.18)	2.41±0.97 (range, 1.03–4.21)	ANOVA: $F(2, 57)=0.75$, $p=0.476$
Age of onset (years)	–	21.4±3.6	20.7±3.7	ANOVA: $F(1, 32)=0.29$, $p=0.595$
Duration of illness (years)	–	0.18±0.28	12.00±6.96	ANOVA: $F(1, 32)=68.47$, $p<0.001$
Medication at baseline (mg/day) [b, c]	–	161.8±102.2	492.5±380.4	ANOVA: $F(1, 27)=12.98$, $p=0.001$
Medication at follow-up (mg/day) [b, c]	–	193.5±198.9	626.0±560.7	ANOVA: $F(1, 29)=10.49$, $p=0.003$
PANSS positive at baseline [d]	–	22.1±7.1	19.9±5.1	ANOVA: $F(1, 16)=0.58$, $p=0.458$
PANSS negative at baseline [d]	–	20.9±6.6	16.7±6.1	ANOVA: $F(1, 16)=1.99$, $p=0.177$
PANSS general at baseline [d]	–	41.7±6.7	39.6±10.8	ANOVA: $F(1, 16)=0.25$, $p=0.625$
PANSS positive at follow-up [e]	–	20.6±7.8	15.6±6.9	ANOVA: $F(1, 24)=1.75$, $p=0.199$
PANSS negative at follow-up [e]	–	18.7±7.9	15.2±3.0	ANOVA: $F(1, 24)=0.94$, $p=0.342$
PANSS general at follow-up [e]	–	40.7±10.3	33.8±12.9	ANOVA: $F(1, 24)=1.63$, $p=0.213$
Intracranial volume (cm^3)	1407.3±141.8	1402.0±137.4	1446.1±130.9	ANCOVA [f]: $F(2, 56)=0.20$, $p=0.822$

Data are presented as mean±SD, except where noted. FEP, first-episode psychosis; PANSS, Positive and Negative Syndrome Scale; Sz, schizophrenia.

[a] Effect of handedness on the laterality of whole insular cortex volume in FEP patients (baseline) was tested using a laterality index [2×(left−right/left+right)]. ANCOVA with age and intracranial volume as covariates revealed a non-significant trend for a handedness effect [F (1, 19)=3.53, p=0.076], with left-handed patients having smaller laterality index (mean=0.013, SD=0.081) than right-handed patients (mean=0.082, SD=0.071).

[b] Data missing for some participants.

[c] Chlorpromazine equivalent dose.

[d] Data were available for 9 FEP and 9 chronic Sz patients.

[e] Data were available for 21 FEP and 5 chronic Sz patients.

[f] Age was used as a covariate.

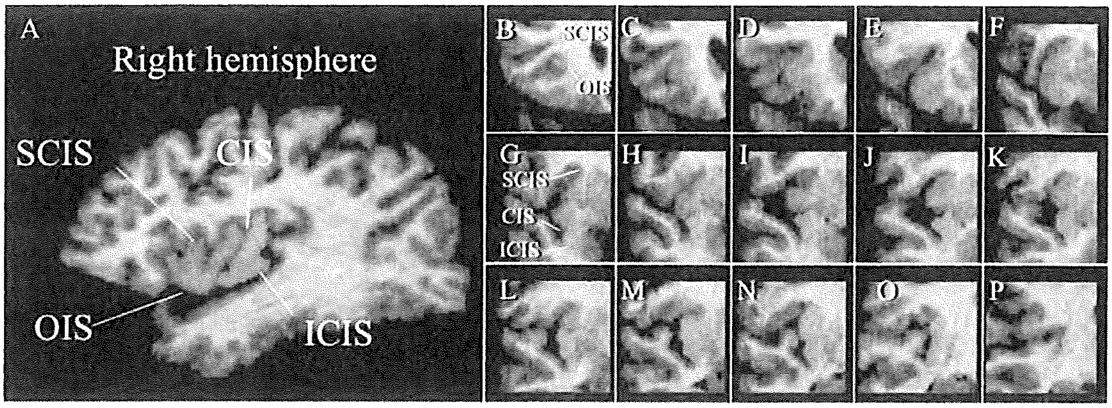

Fig. 1. Sagittal view (A) and sample coronal slices (B–P) of the short (blue) and long (red) insular cortices manually traced in this study. Abbreviations: CIS = central insular sulcus; ICIS = inferior circular insular sulcus; OIS = orbitoinsular sulcus; SCIS = superior circular insular sulcus. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

absolute volume at baseline] as the dependent variable. A repeated measures ANCOVA with inter-scan interval (year), age at first scan, gender, and ICV as covariates, diagnosis as a between-subject factor, and side and subregion as within-subject variables was performed. The percent volume changes for insular cortex subregions were normally distributed (Kolmogorov–Smirnov test). Post hoc Tukey tests were used to follow up the significant main effects or interactions yielded by these analyses. The statistical conclusions reported here remained the same when we included only 16 first-episode schizophrenia patients among the FEP patients or when we investigated the gray matter loss over time by using ANCOVA with side, subregion, and time of scan (baseline, second scan) as within-subject variables.

Since the extent of progressive brain changes during the initial periods of psychosis might reflect the subsequent clinical course (Cahn et al., 2002; Ho et al., 2003; Nakamura et al., 2007; van Haren et al., 2008), the association of gray matter loss of the insular cortex (% volume change between scans) in the FEP patients to the PANSS subscale scores (positive, negative, and general) at follow-up was examined using Pearson's partial correlation coefficients controlling for inter-scan interval and ICV. The PANSS scores and inter-scan interval were normally distributed in the FEP group (Kolmogorov–Smirnov test). Correlations between the insular cortex volume changes over time and dosage of antipsychotic medication (baseline, follow-up) and premorbid IQ were also evaluated. Statistical significance was defined as $p<0.05$ (two-tailed).

3. Results

3.1. Sample characteristics

There was no significant group difference in gender, handedness, height, IQ, and inter-scan interval, but the chronic schizophrenia patients were older than other groups (Table 1). The FEP patients took smaller amounts of antipsychotics than did chronic patients.

3.2. Cross-sectional comparison

ANCOVA results are summarized in Table 2. At baseline, the FEP and chronic schizophrenia patients had a significantly smaller short insular cortex than did controls (post hoc test, $p<0.001$ for both patient groups), while there was no difference between the FEP and chronic schizophrenia groups (post hoc test, $p=0.306$). The insular cortex was larger in the left than in the right hemisphere for all groups (post hoc test, $p<0.001$). The results at second scan were similar to those at baseline; the short insular cortex was significantly smaller in both patient groups compared with controls (post hoc test, $p<0.001$) and the insular cortex had a leftward asymmetry (post hoc test, $p=0.016$). These cross-sectional results did not change even when we used relative insular volume [100 × absolute volume/whole brain volume at each time point] in ANCOVA with only age and gender as covariates.

3.3. Longitudinal comparison

ANCOVA revealed a significant main effect for diagnosis [$F\ (2, 53)=3.67$, $p=0.032$] without a significant subregional effect [$F\ (1, 57)=3.21$, $p=0.079$] or a diagnosis-by-subregion interaction [$F\ (2, 57)=1.32$, $p=0.275$]. There was no effect involving side. Post hoc analyses demonstrated that the FEP patients (mean = −4.3%) had a greater gray matter reduction of the insular cortex over time compared with controls (mean = 0.3%) ($p=0.019$), but there was no difference between the patients with chronic schizophrenia (mean = − 1.7%) and FEP patients ($p=0.446$) or healthy comparison subjects ($p=0.608$) (Fig. 2). Even when we used relative insular volume over the whole brain volume to calculate the percent volume change, separate analysis of the left total insular volume revealed a significant diagnosis effect [ANCOVA, $F\ (2, 54)=3.34$, $p=0.043$; post hoc test, $p=0.009$ (FEP > controls)].

3.4. Correlational analysis

For the FEP patients whose PANSS score at follow-up were available ($n=21$), the greater total gray matter loss of the left insular cortex was correlated with higher scores for positive ($r=0.609$, $p=0.006$), negative ($r=0.652$, $p=0.002$), and general ($r=0.589$, $p=0.008$) symptoms on the PANSS subscales. The gray matter loss of the right insular cortex correlated with negative symptoms ($r=0.464$, $p=0.045$), but this correlation was not significant after Bonferroni correction [$p<0.0083$ (0.05/6)].

Table 2
Absolute volume and volume change over time of the whole brain and insular cortex

Brain region	Control subjects (15 males, 11 females)						FEP patients (16 males, 7 females)							Chronic Sz patients (10 males, 1 female)						
	Baseline		Second scan		% Change[a]		Baseline		Second scan		% Change[a]			Baseline		Second scan		% Change[a]		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Effect size (Cohen *d*)	Mean	SD	Mean	SD	Mean	SD	Effect size (Cohen *d*)
Whole brain (cm^3)[b]	1128	125	1128	134	−0.1	2.1	1118	108	1102	115	−1.5	3.1	0.53	1099	128	1076[c]	137	−2.2	3.3	0.76
Short insular cortex (mm^3)[d]																				
Left	5315	914	5329	974	0.2	6.0	4681[c]	613	4387[c]	504	−5.9[c]	7.0	0.94	4365[c]	541	4247[c]	600	−2.9	3.9	0.61
Right	5235	828	5253	874	0.4	7.9	4551[c]	871	4361[c]	866	−3.8[c]	8.3	0.52	4190[c]	607	4137[c]	668	−1.5	3.0	0.32
Long insular cortex (mm^3)[d]																				
Left	3107	667	3099	650	0.2	7.1	3049	668	2881	561	−4.8[c]	7.1	0.70	2683	343	2649	354	−1.3	1.9	0.29
Right	2996	528	2998	530	0.3	7.1	2687	651	2610	641	−2.6[c]	8.1	0.38	2721	398	2691	403	−1.1	2.6	0.26

FEP, first-episode psychosis; Sz, schizophrenia.
[a] Calculated as follows: 100×[(absolute volume at second scan−absolute volume at baseline)/absolute volume at baseline]. Negative value indicates decrease in volume.
[b] ANCOVA with ICV, gender, and age as covariates at baseline revealed a significant main effect for diagnosis [F (2, 54)=5.19, p=0.09], but post hoc test did not show significant results. ANCOVA at second scan revealed a significant main effect for diagnosis [F (2, 54)=6.15, p=0.004], with chronic Sz patients having a smaller volume than controls (post hoc test, p=0.019). ANCOVA of the percent volume change with age, gender, ICV, and interscan interval as covariates revealed a significant main effect for diagnosis [F (2, 53)=3.44, p=0.040], but post hoc test did not show significant results.
[c] Significantly different from controls.
[d] ANCOVA at baseline revealed significant main effects for diagnosis [F (2, 54)=16.33, p<0.001], side [F (1, 57)=13.82, p<0.001], and subregion [F (1, 57)=456.76, p<0.001] and a diagnosis-by-subregion interaction [F (2, 57)=5.62, p=0.006]. ANCOVA at second scan revealed significant main effects for diagnosis [F (2, 54)=20.42, p<0.001], side [F (1, 57)=5.62, p=0.021], and subregion [F (1, 57)=403.45, p<0.001] and a diagnosis-by-subregion interaction [F (2, 57)=7.53, p=0.001]. ANCOVA of the percent volume change revealed a significant main effect for diagnosis [F (2, 53)=3.67, p=0.032]. For the results of post hoc tests, see text.

We did not find any significant correlation between the gray matter reduction of the insular cortex over time and daily dosage of antipsychotic medication in either the FEP or the chronic schizophrenia group. Partial correlation controlling for age and inter-scan interval did not reveal significant correlation between the insular cortex volume change and premorbid IQ in any groups after Bonferroni correction.

4. Discussion

The current cross-sectional and longitudinal ROI-based MRI study investigated gray matter changes of the insular subdivisions in both first-episode psychosis (FEP) and chronic schizophrenia patients. The chronic schizophrenia as well as the FEP patients had significantly smaller short insular cortex than did controls at both time points, indicating that morphologic changes are already present by the onset of psychosis. Compared with controls, FEP patients showed significant gray matter reduction over time bilaterally in insular cortex without prominent subregional effect. Although there was no significant difference in the baseline insular volume between the FEP and chronic schizophrenia patients possibly due to small sample size, the absolute volumes of the insular cortex in these patients at both time points (Table 2) are in line with progressive gray matter reduction in this region across the course of the illness. This progressive change occurred at a more rapid rate in FEP patients than in chronic schizophrenia patients, supporting the notion that there is a circumscribed period of intense cortical gray matter reduction in various brain regions at the time of their first psychotic episode.

The reduction rate of the insular cortex in our FEP sample (−2.2%/year) is likely to be greater than that of whole brain (−0.8%/year) (Table 2), whole temporal or frontal lobe gray matter as well as the medial temporal structures (Gur et al., 1998; Nakamura et al., 2007; Pantelis et al., 2005), but is considerably less than changes of the left superior temporal gyrus (−6.6%/year) (Kasai et al., 2003a) in first-episode schizophrenia. These findings support the growing evidence of an ongoing pathological process during the onset of psychosis affecting specific brain regions.

The anterior and posterior portions of the insular cortex have been reported to have connectional and functional differences (Augustine, 1996; Türe et al., 1999). The anterior portion (short insula) has extensive connections with the frontal lobe and is involved in emotional and language-related functions, whereas the posterior portion (long insula), which includes somatosensory and auditory processing areas, connects with the parietal and temporal lobes. Regarding the topographical specificity of the insular cortex in schizophrenia, one MRI study (Makris et al., 2006) found a volume reduction predominantly in the anterior portion as in this study, while others reported a global reduction (Kasai et al., 2003c; Saze et al., 2007; Takahashi et al., 2005). The reason for this inconsistency is unclear because these studies used a similar parcellation method, but might be due to different sample characteristics (race, first episode versus chronic patients, and diagnostic heterogeneity).

The present and previous cross-sectional MRI findings in first-episode schizophrenia (Crespo-Facorro et al., 2000; Kasai et al., 2003c; Kim et al., 2003) and recent findings of

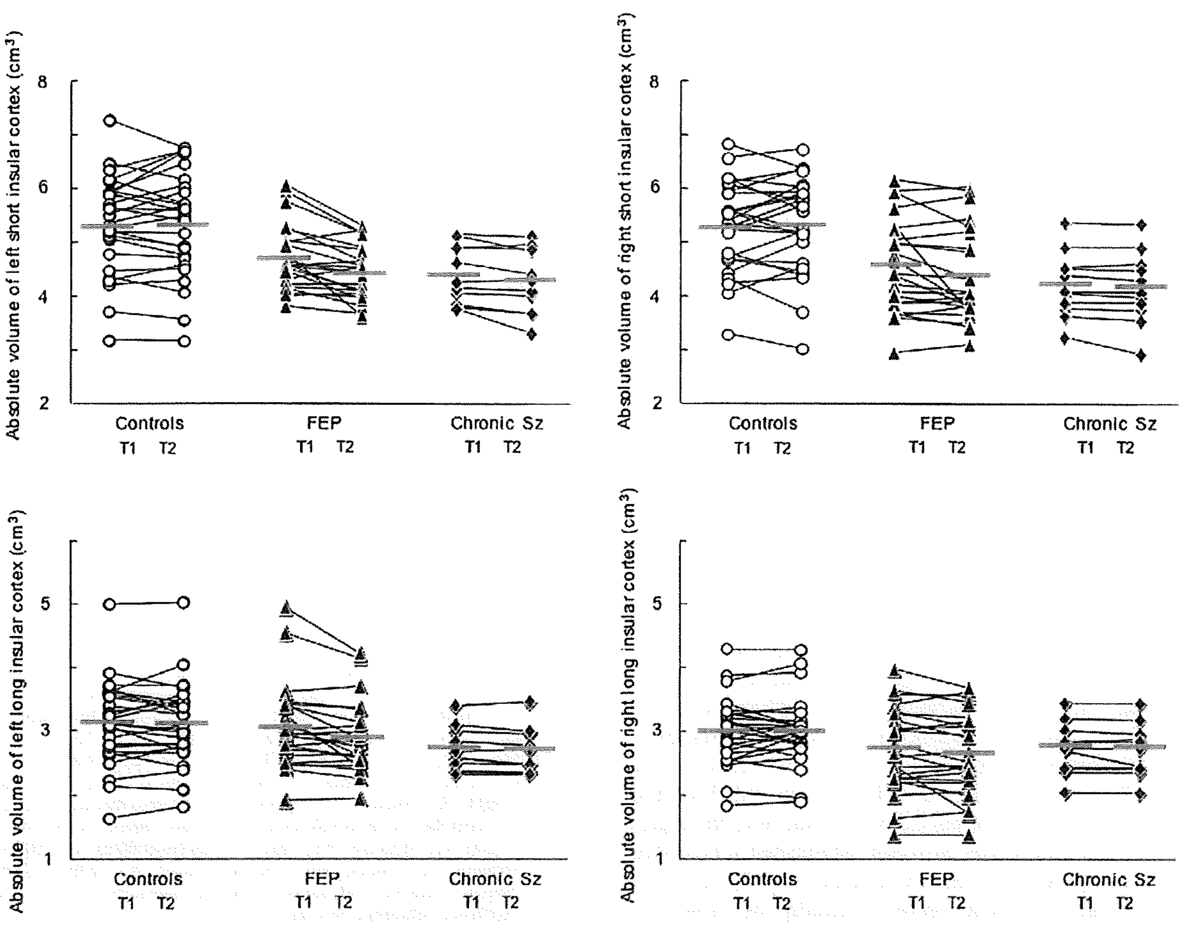

Fig. 2. Scatter plots of absolute volumes of short and long insular cortices in healthy controls, patients with first-episode psychosis (FEP), and patients with chronic schizophrenia (Sz). Values of baseline (T1) and follow-up scan (T2) in each subject are connected with a straight line. Horizontal bars indicate means of each group.

smaller insular gray matter in clinical high-risk subjects of developing psychosis (Borgwardt et al., 2007; Meisenzahl et al., 2008; Pantelis et al., 2003) indicate that the insular cortex abnormalities are present at the earliest stages of psychosis, consistent with the notion of a neurodevelopmental pathology (Weinberger, 1987). However, as suggested by our finding of the progressive gray matter loss in the early years of psychosis as well as the inverse correlation between the duration of the prodromal phase and left insular gray matter volume in first-episode psychosis (Lappin et al., 2007), these cross-sectional findings are more likely due to an onset-related pathological process that predates the first expression of frank psychosis. Although previous longitudinal VBM studies in high-risk subjects did not find progressive atrophy of the insular cortex during the transition to psychosis (Borgwardt et al., 2008; Job et al., 2005; Pantelis et al., 2003), further examination using detailed ROI methods will be needed.

Both positive and negative symptoms in FEP patients at follow-up were correlated with gray matter reduction of the left insular cortex over time, consistent with previous structural (Crespo-Facorro et al., 2000; Shapleske et al., 2002; Takahashi et al., 2004) and functional (Crespo-Facorro et al., 2001a; Shergill et al., 2000) neuroimaging findings. These observations support the role of the anterior insular cortex in the neural substrate of emotion as 'interoceptive cortex' (Craig, 2005) as well as the notion that abnormalities in sensory and memory functions of the insular cortex (Augustine, 1996) may lead to perceptual disturbances that can account for psychotic symptoms in schizophrenia (Crespo-Facorro et al., 2000). Our findings further emphasize the clinical relevance of the severity of ongoing pathological processes during the initial periods of psychosis, which could reflect the subsequent course of the illness (Cahn et al., 2002; Ho et al., 2003; Nakamura et al., 2007; van Haren et al., 2008).

The neurobiological basis for insular cortex gray matter reduction in psychotic disorders is unknown. Poorly developed layers II and III in the dorsal insular cortex in schizophrenic brains (Jakob and Beckmann, 1986) suggest a cell migration disturbance, but this post-mortem finding has not been replicated. This MRI study cannot address the underlying pathological mechanism of the observed progressive atrophy of the insular cortex, but anomalies of synaptic plasticity, abnormal brain maturation as well as stress or other environmental factors may be relevant (Pantelis et al., 2005). Glutamatergic excess due to hypofunction of the *N*-methyl-D-aspartate (NMDA) receptors on corticolimbic gamma-aminobutyric acid (GABA)-ergic interneurons may also lead to adverse neurotoxic effects in the early stages of psychosis (Coyle et al., 2003; Stone et al., 2007).

Several limitations of this study need to be addressed. First, some patients withdrew from their medication or failed to make outpatient consultations during the follow-up so that the sample size was small and their entire clinical data (e.g., cumulative dose of antipsychotics between scans, symptomatology, or clinical course) were not available. A relationship between gray matter reduction and antipsychotics has been reported in schizophrenia (Cahn et al., 2002; Lieberman et al., 2005), while mood stabilizers may increase gray matter volume (Moore et al., 2000; Nakamura et al., 2007). Thus, it is possible that the longitudinal gray matter changes of the FEP patients in this study were related to neuroleptic medication. Given the similar medication status in our patient groups, however, the effects of medication alone could not explain the marked progressive gray matter reduction only in FEP patients. In addition, the gray matter changes of the insular cortex over the follow-up interval in both patient groups were not correlated with the dosage of antipsychotics taken at the time of the scans. Secondly, although not statistically significant, lower IQ and relatively large number of left-handed subjects [21.7% (5/23)] in the FEP group might have biased our results. In fact, left-handed FEP patients tended to have less leftward asymmetry of the insular cortex volume than right-handed patients (Table 1). However, no difference was found between the left- and right-handed patients in longitudinal insular volume changes [effect of handedness for ANCOVA, $F(1, 18)=1.22$, $p=0.284$], and the gray matter loss of the insular cortex over time did not correlate with premorbid IQ in the FEP group. Finally, our FEP group included a rather diverse population with psychotic symptoms. Neurobiological similarities and differences between established schizophrenia and other psychoses remain controversial (Maier et al., 2006). Although the results were essentially the same even when we included only 16 first-episode schizophrenia patients among the FEP patients, recent study of early-onset FEP patients reported that smaller gray matter volume of the insula was not associated with a follow-up diagnosis of schizophrenia or bipolar disorder (Janssen et al., 2008). Thus, the diagnostic specificity of insular cortex abnormalities in psychotic disorders remains to be further elucidated.

In conclusion, our findings indicate that patients with psychotic disorders such as schizophrenia exhibit a progressive gray matter reduction of the insular cortex especially during the early phase after the onset, the rate of which is likely to reflect the severity of both positive and negative symptoms. Our findings also demonstrate that morphologic abnormalities of the insular cortex (especially its anterior portion) are already present by the onset of psychosis, implicating a regional progressive pathological process before first expression of frank psychosis.

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Contributors

Drs. Suzuki, Velakoulis, and Pantelis conceived the idea and methodology of the study. Dr. Takahashi conducted the statistical analyses and wrote the manuscript. Drs. Wood, McGorry, Velakoulis, and Pantelis recruited subjects, were involved in clinical and diagnostic assessments and for MRI scanning. Drs. Takahashi and Tanino analyzed magnetic resonance imaging. Ms. Soulsby provided technical support (data processing). Drs. Wood, McGorry, Suzuki, Velakoulis, and Pantelis contributed in writing of the manuscript. All authors contributed to and have approved the final manuscript.

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

Yoichiro Takayanagi [a,b,f], Yasuhiro Kawasaki [a], Kazue Nakamura [a], Tsutomu Takahashi [a], Lina Orikabe [b,c], Ema Toyoda [b,c,f], Yuriko Mozue [d], Yoko Sato [e], Masanari Itokawa [b,f], Hidenori Yamasue [c], Kiyoto Kasai [c], Masayoshi Kurachi [g], Yuji Okazaki [b], Masaaki Matsushita [b,f], Michio Suzuki [a,*]

[a] Department of Neuropsychiatry, University of Toyama Graduate School of Medicine and Pharmaceutical Sciences, 2630 Sugitani, Toyama 930-0194, Japan
[b] Department of Psychiatry, Tokyo Metropolitan Matsuzawa Hospital 2-1-1 Kamikitazawa, Setagaya, Tokyo 156-0057, Japan
[c] Department of Neuropsychiatry, Graduate School of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo, Tokyo 113-8655, Japan
[d] Tosa Hospital, 2-10-24 Shinhonmachi, Kochi 780-0062, Japan
[e] Department of Radiology, Tokyo Metropolitan Matsuzawa Hospital 2-1-1 Kamikitazawa, Setagaya, Tokyo 156-0057, Japan
[f] Tokyo Institute of Psychiatry, 2-1-8, Kamikitazawa, Setagaya, Tokyo 156-8585, Japan
[g] Department of Psychiatric Early Intervention, University of Toyama, 2630 Sugitani, Toyama 930-0194, Japan

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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.

* Corresponding author. Tel.: +81 76 434 7323; fax: +81 76 434 5030.
E-mail address: suzukim@med.u-toyama.ac.jp (M. Suzuki).

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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

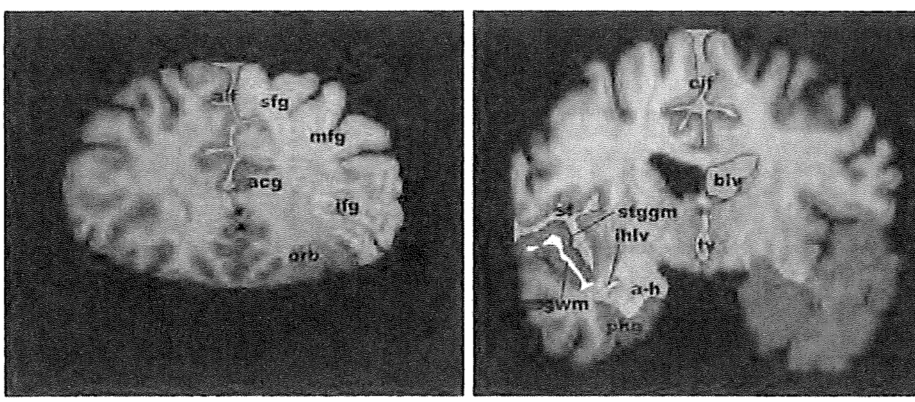

Fig. 1. Examples of the prefrontal regions of interest (left) and central regions of interest (right) traced manually in this study. acg: anterior cingulate gyrus; a–h: amygdala-hippocampal complex; aif: anterior interhemispheric fissure; blv: body of the lateral ventricle; cif: central interhemispheric 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).

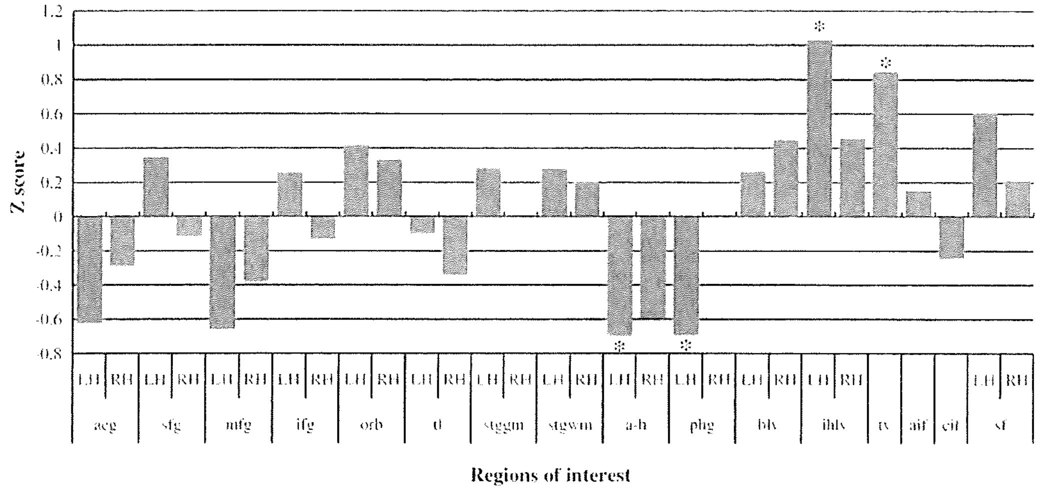

Fig. 2. Standardized z scores for each ROI of male patients with schizophrenia. For the control subjects, the expected mean z score was 0. LH: left hemisphere; RH: right hemisphere; acg: anterior cingulate gyrus; a–h: amygdala–hippocampal complex; aif: anterior interhemispheric fissure; blv: body of 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

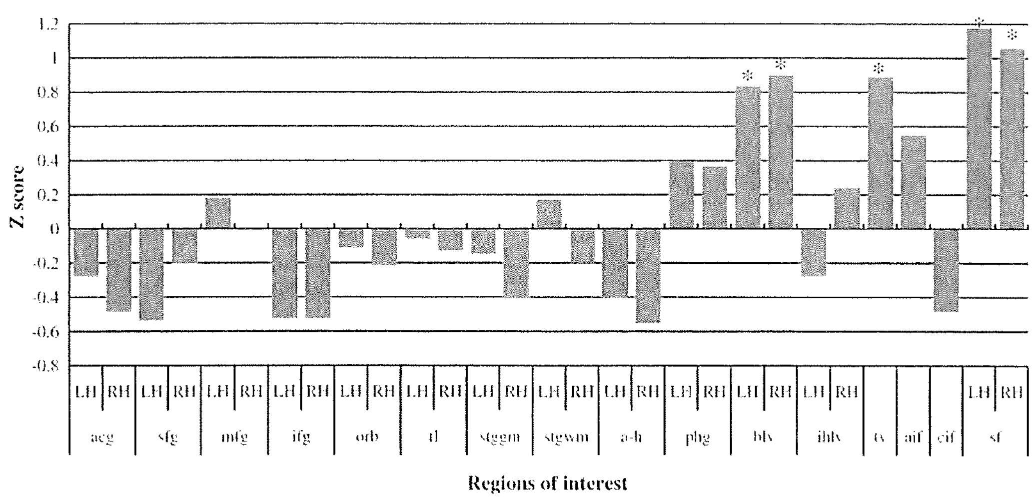

Fig. 3. Standardized z scores for each ROI of female patients with schizophrenia. For the control subjects, the expected mean z score was 0. LH: left hemisphere; RH: right hemisphere; acg: anterior cingulate gyrus; a–h: amygdala–hippocampal complex; aif: anterior interhemispheric fissure; blv: body of 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.

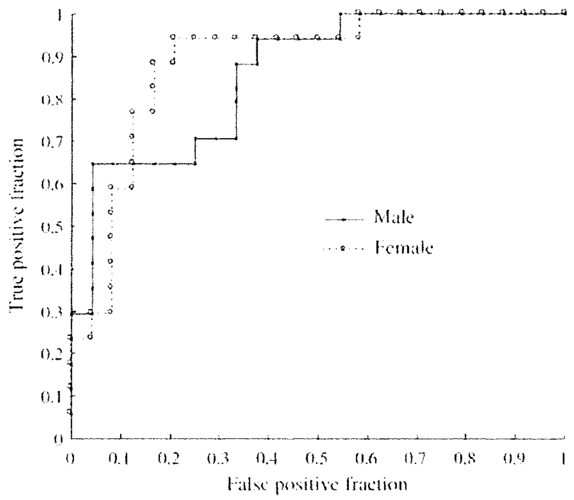

Fig. 4. Receiver operating characteristic (ROC) curves for male and female subjects. The area under the ROC curve (Az) was 0.858 for male subjects and 0.885 for female subjects. Greater Az value indicates better diagnostic performance of the classifier. True positive fraction and false positive fraction 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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臨床精神薬理　13：3-11, 2010

統合失調症の早期介入と予防：認知障害の視点

松岡洋夫[*,**]　松本和紀[**]

抄録：統合失調症の病態の中核は古くから認知障害と考えられてきた。認知障害は精神症状以上に疾患の機能的転帰に強い影響力をもっており，最近では機能的転帰に対してより特異的と思われる"社会認知"に概念が拡大し，さらに認知障害自体を治療標的と考えるようになってきた。統合失調症における認知障害の形成過程については，早期の神経発達障害に加えて，発症前の精神病への移行期前後での変化を支持する所見が増えており，さらに一部の認知機能は発症後にも変化する可能性があるとされている。こうした複数のおそらく連鎖的な病理過程が認知障害形成に関係していると推定され，認知改善のための治療"臨界期"はより早期にまで拡大して対人的，社会的機能障害の出現時点を考慮する必要があるだろう。その際，機能的転帰に特異的な認知領域に注目することと，疾患の異種性を考慮することが重要である。現時点では早期介入による認知改善の程度は限定的である。そのためより有効で安全な薬物療法の開発に加えて，精神病への発展過程を段階的に規定するモデルを構築し，機能的転帰に対する心理社会的影響因子を考慮した，しかも倫理的に十分配慮されたきめ細かい包括的治療法の開発が期待される。

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Key words : *clinical staging model, critical period, cognitive dysfunction, duration of untreated illness, early intervention, schizophrenia*

はじめに

近年，若者のメンタルヘルスの重要性が叫ばれている。この問題に積極的に取り組んでいるオーストラリアでは，若者のメンタルヘルスを促進するための拠点として国の財団が"headspace"というサービスの場を30のセンターを中心に設けている。同財団のホームページ（http://www.headspace.org.au）では，以下の7つの基本統計を挙げて若者の健康問題の中でメンタルヘルスならびにアルコール・物質使用の問題が最も重要であると指摘している：①毎年，12～17歳の14％，18～25歳の27％がこれらの問題を経験している，②メンタルヘルス問題の75％は25歳以前に発生している，③物質乱用問題の50％以上でメンタルヘルス問題が先行している，④若者での高い自殺率は，より若い時期での未治療のメンタルヘルス問題と関連している，⑤メンタルヘルス問題と物質使用障害は，15～24歳の疾病負担の60～70％に相当する，⑥メンタルヘルス問題を抱えた若者の1／4しか専門的支援を受けていない，⑦最重度のメンタルヘルス問題を抱えた若者ですら半分しか専門

Early intervention and prevention for schizophrenia: a perspective of cognitive impairments.
*東北大学大学院医学系研究科精神神経学分野
〔〒980-8574　宮城県仙台市青葉区星陵町1－1〕
Hiroo Matsuoka: Department of Psychiatry, Tohoku University Graduate School of Medicine. 1-1, Seiryo-machi, Aoba-ku, Sendai, Miyagi, 980-8574, Japan.
**東北大学病院精神科
Hiroo Matsuoka, Kazunori Matsumoto: SAFE clinic, Department of Psychiatry, Tohoku University Hospital.

的支援を受けていない。

ニュージーランドのダニディンで行われた前方視的な出生コホート研究においては[27]，26歳時点で精神障害と診断されたもの（全体の23％に相当）の実に75％は11～18歳で何らかの精神障害をもっていたと報告された。ちなみに，26歳時点で精神病と診断されたものは，小児期に不安障害，気分障害，行動障害などの多様な精神障害の診断を受けていた。フィンランドで行われた出生コホート研究では[66]，24歳までに見られた男性の自殺行動が，8歳時点での情緒障害，行為障害，行動障害，心理社会的問題で予見が可能であったという。こうした例を持ち出すまでもなく，若者のメンタルヘルスがいかに重要かは多くの人々が理解しているところである。しかし，現実にはこの問題に積極的に取り組んでいる国は非常に少なく[53]，本邦も例外ではない。

精神病の早期介入に関するデータは，この15年間で急速に増え続けている。1998年には国際早期精神病協会が創立され，2005年には臨床実践の国際ガイドライン[22]が出版され，2007年には国際早期精神病協会の機関誌「Early Intervention in Psychiatry」が刊行されるに至った。しかし，精神病の早期介入に関する議論は続いており[7,19,43,54]，早期介入の妥当性，正当性，倫理性などのエビデンスが十分に確立されているとはいえない。本稿では，認知障害に焦点を当てて，統合失調症の病態論を中心に早期介入の意義と問題点について述べたい。

Ⅰ．統合失調症の病態論における認知障害の意義

認知障害は，KraepelinやBleuler以来，統合失調症の中核的病態であると考えられてきた[38]。実際，認知障害は治療の最終目標となる機能的転帰に対して精神症状以上に強い影響力をもっていることが明らかになり[17]，最近では認知障害を統合失調症の診断基準に加えようとする動きや[26]，認知障害自体を統合失調症の治療標的と位置付けて[36]，新たな認知改善薬（または認知増強薬）の開発がかなり進展している[5]。

1．病態論における認知障害の位置付け

認知障害の定義，評価方法が不十分なこともあり，病態論における位置付けは十分に確立されていない[40,41]。Reichenberg[60]は，統合失調症の病態論において，①遺伝因と環境因の影響下で精神症状と並列して認知障害を位置付ける立場，②遺伝因と環境因とは独立した病因として認知障害を位置付ける立場，③遺伝因と環境因で認知障害が形成されそれを基に精神症状が出現するという病態の中核に位置付ける立場，④認知障害を③と同様に病態の中核に位置付けるが，②のように認知障害によらない精神症状もありうるとして，②と③を組み合わせる立場，の4つの可能性を論じている。歴史的には，Zubinの脆弱性仮説，Ciompiの長期展開モデル，Klosterkötterらの層構造モデル，Andreasenの統一モデルでは，いずれも③の立場をとっている[38]。本稿でもこのモデルを踏襲するが，これが確立されるには，認知障害の症候論的，病因論的な疾患特異性に関するいくつかの問題点が明確にされねばならない[39,40,41]。

2．認知障害と脳構造変化

近年注目されている画像上の脳構造変化も病態論で重要な意義をもっており，認知障害と表裏一体の関係にある。ただし，認知障害を伴わない構造変化や，逆に構造変化を伴わない認知障害もありうることに注意する必要がある。例えば，発症直後に認知障害は安定することが多く改善を示す場合すらあるが[32,63]，脳の構造変化は発症後もある一定期間は進行することが報告されている[67]。統合失調症での脳構造変化は一般的な神経変性疾患とは異なり[63,70]，胎生期や周生期での早期神経発達過程での障害，思春期から青年期での疾患への移行期前後ならびに成人早期での神経成熟期での後期神経発達過程における限定的な進行性障害を支持する所見が増えており，複数の連鎖的な過程が存在すると考えられる[51,52]。

しかし，脳の構造変化ならびに認知障害に関する研究結果の詳細は研究者間で大きく異なり[63]，いずれも未成熟な研究領域である。特に，無用な誤解につながりかねない神経変性仮説や精神病の神経毒性仮説に関しては，現時点ではそれらに対