Table 2
Prevalence of the PS-R rank among PS-R+ samples.

Rank	Definition	All PS-R+ (n=281) n (%)	Clinical PS-R+ (n=199) n (%)	Age-matched Clinical PS-R+ (n=75) n (%)	Community PS-R+ (n=82) n (%)
10	Selected three or more "definitely agree" responses with durations of more than one year	47 (17)	31 (16)	10 (13)	16 (20)
9	Selected two "definitely agree" responses with durations of more than one year and one or more "somewhat agree" response with a duration of more than one year	32 (11)	24 (12)	8 (11)	8 (9.8)
8	Selected two "definitely agree" responses with durations of more than one year or selected two or more "definitely agree" responses without regard to the duration and one or more "somewhat agree" response with a duration of more than one year	23 (8.2)	18 (9.1)	7 (9.3)	5 (6.1)
7	Selected one "definitely agree" response with a duration of more than one year and one or more "somewhat agree" response with a duration of more than one year	36 (13)	25 (13)	9 (12)	11 (13)
6	Selected two or more "definitely agree" responses without regard to the duration or selected three or more "somewhat agree" responses with durations of more than one year	58 (21)	47 (24)	16 (23)	11 (13)
5	Selected one "definitely agree" response with a duration of more than one year or selected two "somewhat agree" response with durations of more than one year	82 (29)	53 (27)	24 (32)	29 (35)
4	Have a total PS-R score of 39 or over	3 (1.1)	1 (0.5)	1 (1.3)	2 (2.4)

apparent help-seeking behaviors (Addington et al., 2002; O'Callaghan et al., 2010). Our findings may partly support this outcome, since the results showed that the PLEs in the non-help-seekers were no less severe than those in help-seekers.

Another clinical implication is that our results suggest that some psychosis-like symptoms may underlie the appearance of depressive symptoms; these experiences might easily be hidden and therefore often cannot be identified, even in subjects with help-seeking behavior. Moreover, subjects experiencing PLEs may not necessarily recognize the 'real' nature of their attenuated psychotic symptoms. For example, a female college student with a persecutory idea reports that she is always being watched by someone, but simultaneously does not consider this experience to be a 'symptom'. Though she may be aware of distress, anxiety or depressive symptoms, she may be unaware of the psychosis-like nature of these symptoms. Given that psychosis-like symptoms confer an increasing risk of the onset of psychosis, especially when comorbid with depressive symptoms, greater clinical effort should be made to detect these attenuated symptoms and to inform subjects of their significance.

Our findings regarding the prevalence of subjects with psychosis-like symptoms in a community mental health clinic may also provide valuable information for primary mental health services. Whereas numerous studies have examined the prevalence of PLEs in general populations, only a few studies have reported the prevalence of psychosis-risk subjects among clinical populations. Our results indicating that over 20% of the clinical help-seekers endorsed some psychosis-risk symptoms may be somewhat higher than expected, since a recent review on the subclinical psychotic experience revealed a prevalence in general populations of around 5% (van Os et al., 2009). The pathways to care of patients with early psychosis may differ depending on the first contact (Anderson et al., 2010), suggesting that a cautious first contact may lead to a successful early intervention. Thus, it is of great significance that these potential risk symptoms be assessed accurately by community mental health services.

The present study had some limitations. First, the reliability of the self-reported symptoms remains somewhat uncertain. In addition, almost all the information was obtained from the patients themselves. We should consider the possibility that young participants may often misunderstand the questions or interpret them in unintended ways. Secondly, we have little detailed information on the help-seeking behavior of the subjects. We have no data on the degree to which the subjects needed help or whether the subjects or their family members sought help. Although help-seeking behavior cannot be easily quantified or objectified (Gladstone et al., 2007), we should consider this limitation as a methodological weakness. Thirdly, no information was available regarding whether the community sample had any history of visits to psychiatric services. In particular, if the students with more severe PLEs had sought help from professionals, the results would be changed. However, more subjects in the community PS-R-positive group responded negatively to the item regarding 'insight into illness' ("I have been concerned that I might be 'going crazy'") than in the clinical PS-R-positive group (Table 1), suggesting that only a small percentage of the community PS-R-positive subjects, if any, had sought care from professionals. Lastly, as mentioned above,

Table 3
Logistic regression analysis examining association between PS-R item score and help-seeking behavior.

	All PS-R+ (n=281)				Age-matched PS-R+ (n=157)			
	Unadjusted		Adjusted[a]		Unadjusted		Adjusted[a]	
PS-R item	OR	(95% C.I.)	OR	(95% C.I.)	OR	(95% C.I.)	OR	(95% C.I.)
Delusional mood	1.16*	(1.03–1.31)	1.06	(0.91–1.22)	1.12	(0.96–1.30)	1.00	(0.83–1.21)
Overvalued belief	0.96	(0.84–1.10)	1.06	(0.89–1.26)	0.93	(0.79–1.10)	1.06	(0.85–1.32)
Ideas of passivity	1.17*	(1.04–1.32)	1.01	(0.86–1.19)	1.20*	(1.01–1.41)	1.04	(0.84–1.29)
Magical thinking	0.95	(0.84–1.08)	0.86	(0.73–1.00)	0.93	(0.80–1.08)	0.87	(0.72–1.06)
Derealization	1.15*	(1.02–1.29)	0.87	(0.74–1.02)	1.17*	(1.01–1.36)	0.90	(0.74–1.10)
Telepathy-like experiences	0.85*	(0.73–0.99)	0.86	(0.72–1.03)	0.78**	(0.65–0.93)	0.87	(0.72–1.03)
Ideas of reference	1.20**	(1.06–1.35)	0.95	(0.82–1.11)	1.17*	(1.01–1.35)	0.89	(0.73–1.09)
Increased self-esteem	0.93	(0.82–1.04)	1.05	(0.90–1.22)	0.91	(0.79–1.05)	1.00	(0.83–1.20)
Perceptual distortions	1.21**	(1.08–1.36)	1.00	(0.87–1.16)	1.24**	(1.07–1.43)	1.04	(0.87–1.24)
Any auditory hallucinations	1.09	(0.97–1.22)	0.98	(0.85–1.12)	1.16*	(1.01–1.33)	1.04	(0.88–1.24)
Thought hearing	1.14*	(1.00–1.29)	0.99	(0.84–1.15)	1.20*	(1.03–1.40)	1.04	(0.85–1.26)
Insight into illness	1.31**	(1.11–1.52)	1.00	(0.82–1.22)	1.36**	(1.11–1.67)	1.04	(0.81–1.33)

Note: PS-R: the PRIME Screen-Revised, ZSDS: the Zung Self-rating Depression Scale.
[a] Adjusted for ZSDS total score.
* $p<0.05$.
** $p<0.01$.

the present study did not assess the personal/common barriers for help-seeking behavior. If such data were available, our hypothesis regarding the attenuated psychotic symptoms and help-seeking behavior would be more robust.

In spite of these limitations, our findings shed new light on community-based interventions for subjects at risk for the onset of psychosis. Now that attenuated psychotic symptoms or PLEs appear to not be associated with help-seeking behavior, we should reconsider these psychosis-risk-positive subjects as a heterogeneous sample. A recent systematic review on the pathways to care underlined the complexity of the issue of help-seeking behaviors among subjects with early psychosis (Anderson et al., 2010). Further longitudinal studies, including studies examining the phase after the onset of psychosis, are required to clarify the relationship among attenuated psychotic symptoms, depressive symptoms, and help-seeking behaviors.

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Contributors

Hiroyuki Kobayashi and Masafumi Mizuno designed the study and wrote the protocol. Takahiro Nemoto and Haruo Kashima were involved at the conceptualization level of the project. Masaaki Murakami and Hiroyuki Kobayashi collected the data. Hiroyuki Kobayashi analyzed and interpreted the data and wrote the first draft of this manuscript. Masafumi Mizuno contributed to the writing, editing and revision of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

All authors declare that they have no conflicts of interest.

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Short Communication

Cerebral blood flow changes in very-late-onset schizophrenia-like psychosis with catatonia before and after successful treatment

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The purpose of the present study was to investigate regional cerebral blood flow (rCBF) changes in a patient with very-late-onset schizophrenia-like psychosis (VLOS) with catatonia. A 64-year-old woman developed catatonia after experiencing persecutory delusions. The patient's rCBF was examined using single photon emission computed tomography (SPECT) with easy Z-score imaging system. Before treatment, hypoperfusion was observed in the striatum and the thalamus, whereas hyperperfusion was observed in the left lateral frontal cortex and the left temporal cortex. After treatment, the disproportions in rCBF disappeared, and hyperperfusion was observed in the motor cortex. Sequential SPECT findings suggest that rCBF abnormalities may be correlated with the symptomatology of catatonia in patients with VLOS.

Key words: catatonia, delusion, easy Z-score imaging system, SPECT, very-late-onset schizophrenia-like psychosis.

CATATONIA IS A psychomotor syndrome that can be characterized by stupor, immobility, mutism, and echophenomena. Catatonia is observed in several psychiatric disorders such as mood disorders, schizophrenia, and organic brain diseases. Catatonia is also known to occur in patients with late-onset schizophrenia (LOS) and very-late-onset schizophrenia-like psychosis (VLOS).[1] Clinical differentiation of the underlying causes of catatonia is frequently difficult, however, and the neuropsychological and pathophysiological mechanisms of catatonia remain unknown.

Recent advances in neuroimaging technology seem to be helpful in clarifying the mechanisms of catatonia. Functional brain imaging techniques, such as single photon emission computed tomography (SPECT), can demonstrate dynamic changes in neuroactivities during catatonia. We report a VLOS patient with catatonia who underwent sequential ^{99m}Tc-ethyl cysteinate dimer single photon emission computed tomography (^{99m}Tc-ECD SPECT) with the easy Z-score imaging system (eZIS).[2]

CASE REPORT

The patient was a 64-year-old Japanese woman who was right-handed. She had no history of psychiatric episodes. She was not active, and her spontaneity had been declining since around the age of 63 years. At the age of 64 years she began to insist that someone was watching her, that she was stripped naked, and that someone with a handsaw was pursuing her. The patient subsequently complained of these delusional ideas and often remained in bed. She was referred to the Toho University Omori Medical Center in Tokyo after she developed catatonia (mutism, waxy

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flexibilities, immobility, and posturing). She was admitted to the psychiatric ward. She met both the recent consensus criteria for VLOS[1] and the DSM-IV-TR criteria for schizophrenia.[3] On electroencephalography the main background activity consisted of a 9-Hz bioccipital rhythm, and paroxysmal waves were not observed. No abnormal laboratory findings were obtained.

Pharmacotherapy with haloperidol (5 mg/day) given i.v. was initiated. Within 5 days the patient

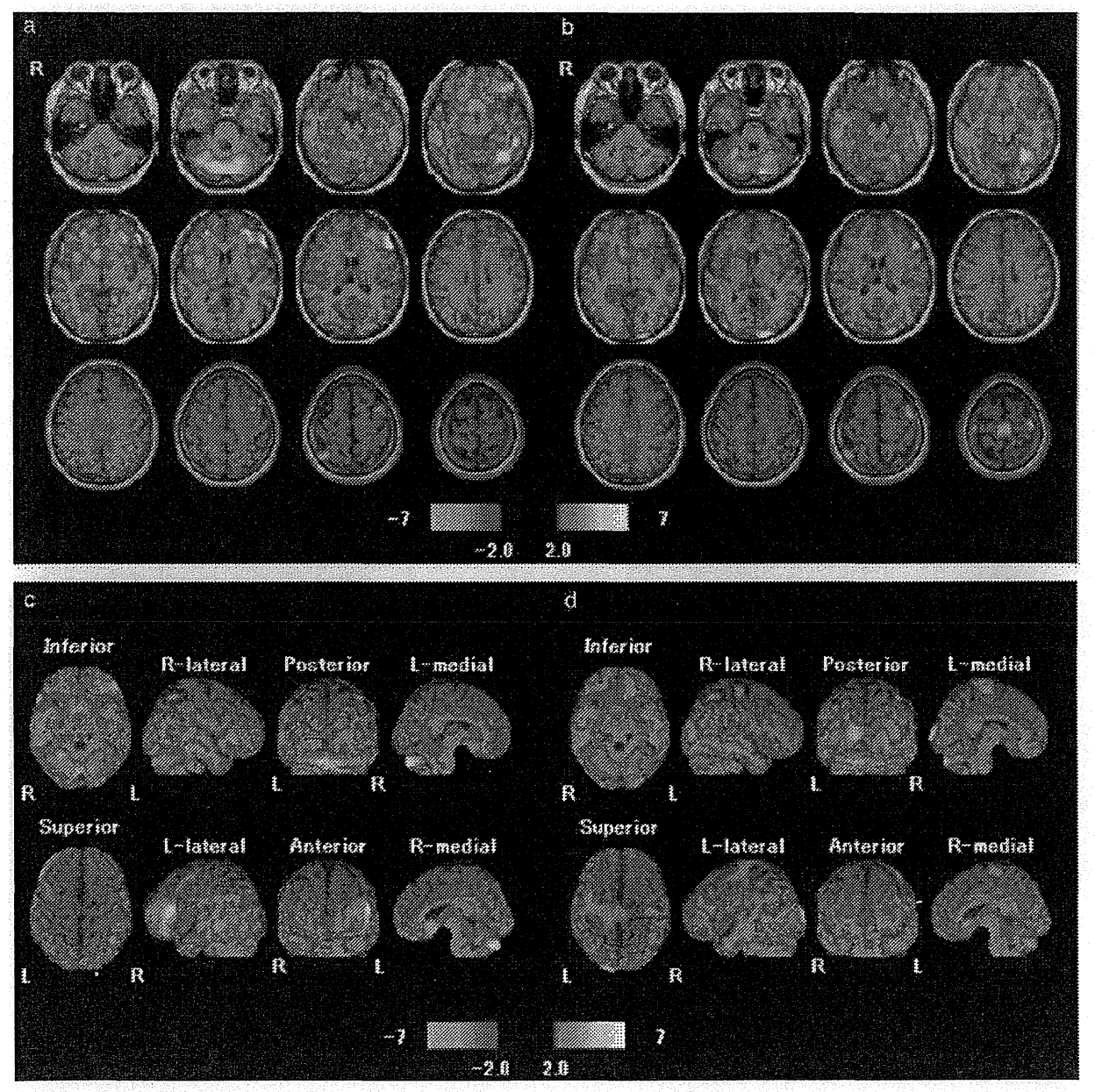

Figure 1. 99mTc-ECD SPECT images with easy Z-score imaging system of the patient (a,c) before and (b,d) after treatment. Color-coding represents the statistical significance (Z-score) of the increase (red) and the decrease (blue) in cerebral blood flow compared to normal.

gradually recovered from the catatonia and began to take oral medicine. Aripiprazole (6 mg/day) and lorazepam (1 mg/day) were initiated on day 10 of hospital admission. After the dosage of aripiprazole was increased to 12 mg/day on day 19, her complaints were alleviated. The patient made satisfactory improvement and was discharged from hospital on day 65.

We assessed the patient's psychotic symptoms using the Positive and Negative Syndrome Scale (PANSS)[4] and the Clinical Global Impression Scale (CGI).[5] The PANSS and CGI scores were 77 and 7, respectively before treatment. After treatment, the PANSS and CGI scores were 41 and 3, and we considered that her psychotic symptom had improved.

At the time of initial presentation brain magnetic resonance imaging (MRI) showed mild frontal and parietal atrophy and septum pellucidum. ^{99m}Tc-ECD SPECT with eZIS was performed before and after treatment. Written informed consent for these procedures was obtained from the patient and her family.

Before treatment, hypoperfusion was observed in the bilateral striatum and the bilateral thalamus, whereas hyperperfusion was observed in the left lateral frontal cortex and the left temporal cortex. After treatment, the hypoperfusion in the bilateral striatum almost disappeared, while only a slight hypoperfusion was observed in the bilateral thalamus. The hyperperfusion in the left frontal and temporal cortex disappeared, while hyperperfusion was observed in the motor cortex (Fig. 1).

DISCUSSION

This report is the first in sequential SPECT with eZIS findings on VLOS with catatonia. To our knowledge, only a few studies have investigated rCBF using SPECT in patients with catatonia. The present results show an asymmetrical change in the rCBF in the frontal and temporal lobes of a patient with catatonia. Other studies have also demonstrated an asymmetry in rCBF in patients with catatonia.[6–8] The locations of asymmetrical rCBF, however, were inconsistent among the studies. These inconsistent results may have arisen from differences in the techniques used or from differences in the clinical manifestations of catatonic types between the primary diseases. Further studies are needed to clarify the relationship between asymmetrical rCBF in the frontal and temporal lobes and catatonia.

Hyperperfusion in the left frontal and temporal cortex may be more closely related to psychotic symptoms, such as delusion, rather than catatonia. The present patient exhibited persecutory delusions prior to developing catatonia. The 'lateralization defect' hypothesis for schizophrenia has been reported in several studies.[9] This hypothesis states that schizophrenia patients have an abnormal left hemisphere function. Catafau *et al.* reported that schizophrenia patients had significant interhemispheric differences in prefrontal and posterior temporal index values at rest (left hyperfrontality and left hypotemporality).[9]

Hypoperfusion in the striatum and the thalamus may be closely related to catatonic motor symptoms. Because both the striatum and the thalamus clearly participate in the regulation of voluntary movements, this hypothesis seems to be valid. In addition, hyperperfusion in the motor cortex after treatment is of particular interest. It is suggested that the removal of the suppression caused by the catatonic symptoms after treatment may have activated the motor area.

Although further studies are needed to clarify a more precise relationship, the present sequential SPECT findings suggest that rCBF abnormalities may be correlated with the symptomatology of catatonia in patients with VLOS.

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

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Abstract

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

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

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

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

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Introduction

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

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

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

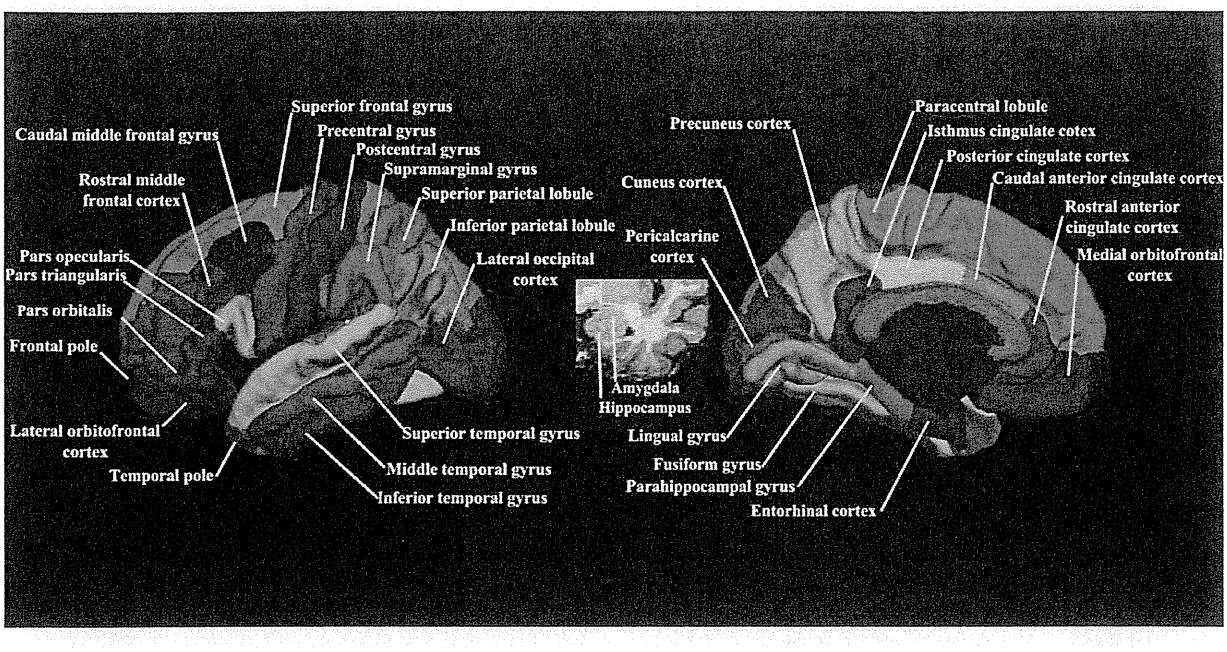

Figure 1. Representations of ROIs examined in this study on the left hemisphere. Cortical ROIs are shown in lateral view (left) and medial view (right). Two subcortical ROIs (i.e., amygdala and hippocampus) are visible in coronal view (middle).
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Table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

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

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

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

Materials and Methods

Subjects

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

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

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

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

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

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

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

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

MRI data acquisition

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

Automated MRI data processing

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

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

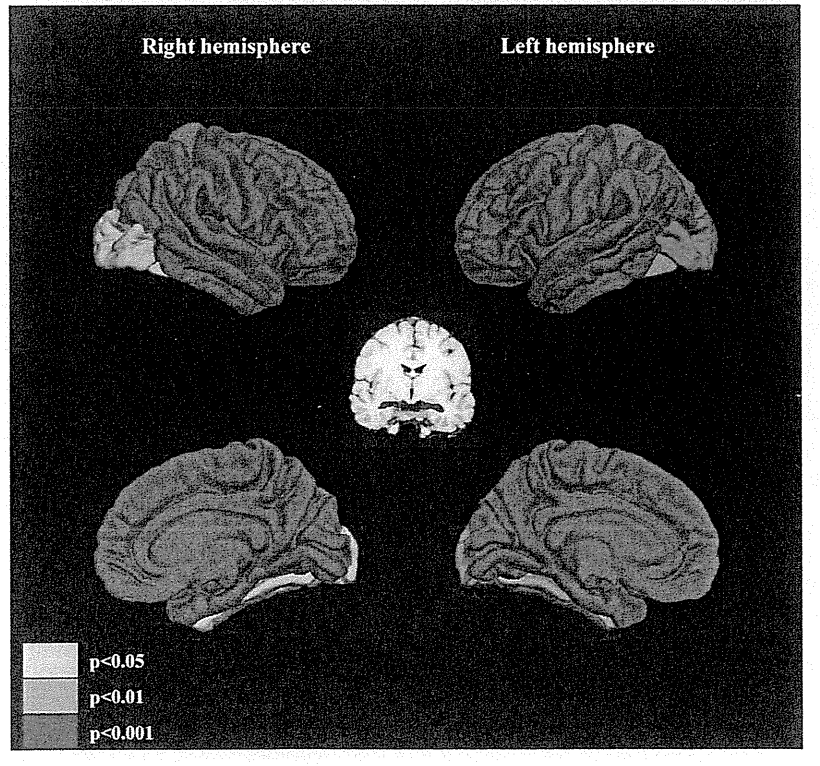

Figure 2. ROIs for which the volumes were significantly reduced in schizophrenia patients compared with those of healthy subjects. ROIs were differentially colored according to the p values of the post hoc tests.
doi:10.1371/journal.pone.0021047.g002

Statistical analysis-1 Group comparison

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

Statistical analysis-2 Classification by brain measures

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

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

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

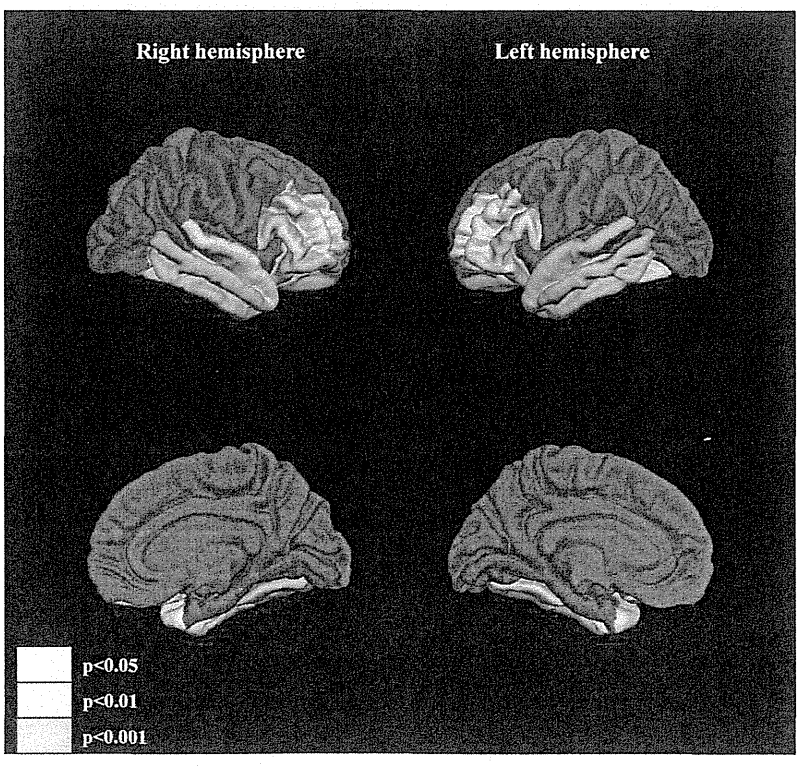

Figure 3. Significant cortical thinning of ROIs in schizophrenia patients compared with that of healthy subjects observed in this study. ROIs were differentially colored according to the p values of the post hoc tests.
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solely from the first group, the classification of the second group was achieved independently of subjects' diagnosis of the second group. Sensitivity, specificity, accuracy, positive predictive value (PPV), negative predictive value (NPV), and false positive rate (FPR) of the classifier were calculated. Detailed descriptions of discriminant function analysis and stepwise variable selection can be found at the Statsoft website (http://www.statsoft.com/textbook/).

All statistical analyses were performed using the STATISTICA 06J software package (Statsoft, Tulsa, OK).

Results

Demographic and clinical characteristics

Tables 1 and 2 present the results of group comparison of the demographic and clinical measures of male subjects and female subjects, respectively. When all subjects were combined, there were significant main effects of diagnosis on SES ($F = 41.77$, $df = 1,87$, $p<0.001$) and estimated IQ ($F = 6.90$, $df = 1,85$, $p = 0.01$). Post hoc tests showed that schizophrenia patients had lower SES ($p<0.001$) and lower estimated IQ ($p = 0.01$) than controls.

Comparison of the brain measures

Tables S1 and S2 show the comparisons of the volumes and the mean cortical thicknesses of ROIs among diagnostic groups, respectively. Below, we describe the significant results of post hoc tests.

Comparison of the ROI volumes. Post hoc tests demonstrated significant gray matter volume reductions of the bilateral hippocampus ($p<0.001$ for both hemispheres), the bilateral fusiform gyri ($p = 0.002$ for left, $p = 0.024$ for right), and the bilateral lateral occipital cortices ($p = 0.001$ for left, $p = 0.014$ for right) in schizophrenia patients compared with those of healthy subjects (Figure 2). Gender differences of ROI volumes were seen in the bilateral amygdala (male>female, $p<0.001$ for both hemispheres).

Comparison of the mean thickness of ROIs. Significant cortical thinning in schizophrenia patients compared with controls was observed in the bilateral rostral middle frontal gyri ($p = 0.007$ for left, $p = 0.007$ for right), the bilateral pars opecularis ($p = 0.002$ for left, $p<0.001$ for right), the bilateral pars triangularis ($p<0.001$ for left, $p = 0.009$ for right), the bilateral pars orbitalis ($p = 0.002$ for left, $p<0.001$ for right), the bilateral lateral orbitofrontal cortices ($p<0.001$ for both hemispheres), the bilateral superior temporal gyri ($p<0.001$ for left, $p = 0.001$ for right), the bilateral middle temporal gyri ($p<0.001$ for both hemispheres), the bilateral inferior temporal gyri ($p<0.001$ for both hemispheres), the bilateral fusiform gyri ($p = 0.005$ for left, $p<0.001$ for right), and the bilateral temporal pole ($p = 0.004$ for left, $p = 0.04$ for right) (Figure 3).

Classification of schizophrenia patients and healthy subjects by brain measures

Among male subjects, the following 2 measures were entered in a stepwise manner: the left lateral occipital cortex volume and right lateral orbitofrontal cortex thickness (Figure 4). Accuracy, sensitivity, specificity, PPV, NPV and FPV of the obtained classifier were 86.1%, 80.0%, 93.8%, 94.1%, 78.9%, and 5.9%, respectively in the first male cohort. In the second cohort, the

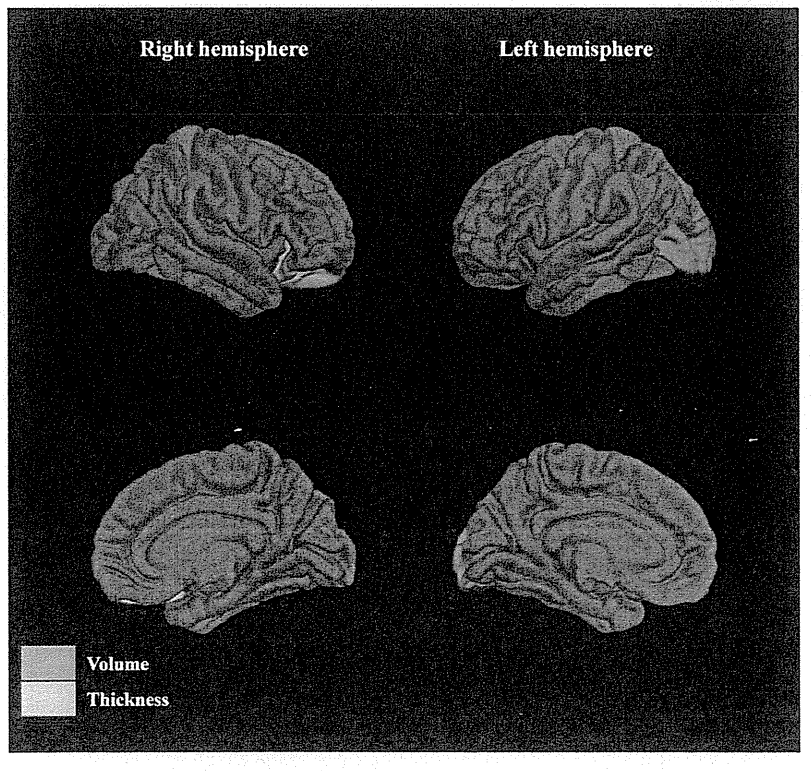

Figure 4. Discriminative pattern for male subjects. Selected regions were differentially colored when volume (blue) or thickness (yellow) of those regions were entered into the model.
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classifier correctly assigned 86.7% of the subjects. Accuracy, sensitivity, specificity, PPV, NPV and FPV for second cohort were 86.7%, 88.9%, 83.3%, 88.9%, 83.3%, and 11.1%, respectively (Table 3).

During the stepwise procedure, the following 5 measures were selected as variables in female subjects: the left temporal pole volume, the right medial orbitofrontal cortex volume, the right pars triangularis volume, the left pars orbitalis thickness, and the left superior temporal gyrus thickness (Figure 5). Accuracy, sensitivity, specificity, PPV, NPV and FPV of the classifier were 96.7%, 94.1%, 100%, 100%, 92.9%, and 0%, respectively in the first female cohort. Obtained classifier correctly classified 81.2% of the subjects of the second cohort. Accuracy, sensitivity, specificity, PPV, NPV and FPV for the second cohort were 81.2%, 66.7%, 100%, 100%, 71.4%, and 0%, respectively (Table 3).

Discussion

Classification performance

To the best of our knowledge, this is the first MRI study to reliably classify first-episode patients with schizophrenia and healthy subjects using fully automated MRI-based discriminant analysis based on both brain regional volumes and regional cortical thicknesses. Our results were comparable to those of previous MRI-based classification studies in chronic [14–16,18] and first-episode [13,17] schizophrenia patients. Our results suggest that the combination of automated brain measures is a candidate for an objective biological marker of early schizophrenia adjunct to clinical diagnosis.

In the present study, the fronto-temporolimbic regions as well as the occipital cortex exhibited the discriminative patterns among the diagnostic groups. These patterns appear to be somewhat different from those of previous classification studies between schizophrenia patients and healthy controls using whole brain analysis by VBM [16] or cortical pattern matching [17], which highlighted the fronto-temporal regions as contributing to between-group differentiation. Interestingly, we replicated recent findings by Rimol et al. [47] in showing robust cortical thinning of posterior cortices in first-episode schizophrenia. Our results might thus suggest that combination of cortical thickness (including occipital regions) and gray matter volume contributed to high classification accuracies reported in this study.

Several studies have attempted to distinguish between persons with psychiatric conditions and healthy controls using neuropsychological tests [48], a combination of structural brain measures and neuropsychological tests [49], and functional MRI [50]. Although these previous studies also reported high classification accuracy, neuropsychological and functional measures are considered more susceptible to the subjects' condition (i.e., state-dependent). In contrast, brain morphologic changes in schizophrenia are considered to be more static and already exist at the first episode of the illness [5] or even before/during the onset of overt psychosis [51–53] Our findings that MRI measures alone could reliably differentiate healthy controls and schizophrenia patients might thus suggest a role of brain structural measures in the earlier detection of psychosis. In fact, a recent VBM-based classification study demonstrated successful discrimination of individuals with at risk mental state (ARMS) who later developed psychosis from those without transition to psychosis [54].

Table 3. Classification performance.

A. First group	Male (n = 36)		Female (n = 30)	
	Predicted diagnosis		Predicted diagnosis	
	HC	SZ	HC	SZ
Clinical diagnosis				
HC	15	1	13	0
SZ	4	16	1	16
Accuracy (%)	86.1		96.7	
Sensitivity (%)	80.0		94.1	
Specificity (%)	93.8		100.0	
PPV (%)	94.1		100.0	
NPV (%)	78.9		92.9	
FPR (%)	5.9		0.0	
B. Second group	**Male (n = 15)**		**Female (n = 11)**	
	Predicted diagnosis		Predicted diagnosis	
	HC	SZ	HC	SZ
Clinical diagnosis				
HC	5	1	5	0
SZ	1	8	2	4
Accuracy (%)	86.7		81.2	
Sensitivity (%)	88.9		66.7	
Specificity (%)	83.3		100.0	
PPV (%)	88.9		100.0	
NPV (%)	83.3		71.4	
FPR (%)	11.1		0.0	

FPR, false positive rate; HC, healthy control; NPV, negative predictive value; PPV, Positive predictive value; SZ, schizophrenia.

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Volume reductions and cortical thinning of ROIs in patients

This study demonstrated significant gray matter volume reductions of temporal, limbic, and occipital regions in schizophrenia patients compared with those of controls. In schizophrenia patients, significant cortical thinning was more widely observed, relative to volume reductions, in prefrontal and temporal regions. These results are consistent with previous studies that reported fronto-temporolimbic gray matter volume reductions [5–11] and cortical thinning of prefrontal/temporal regions [20–25] in schizophrenia patients. Prefrontal and temporolimbic regions are considered to be involved in cognitive function, auditory/visual processing, speech, emotional processing, executive function, and decision-making, all of which are often impaired in schizophrenia patients [55–57]. Onitsuka et al. [58] demonstrated volume reductions of the bilateral occipital sub-region (the visual association areas), which largely includes the lateral occipital cortex where the schizophrenia patients had a decreased volume in this study. In general, the present study has replicated the brain structural abnormalities in schizophrenia patients demonstrated in previous MRI-based studies.

Gender difference was seen in the bilateral amygdala volume (male>female) in accordance with previous studies [44]. In order to exclude such gender effect which potentially confounds classification analyses, we divided the subjects into male and female cohorts in this study.

Limitations

A few limitations in this study should be taken into account. First, this study was partly limited by the lack of inclusion of other

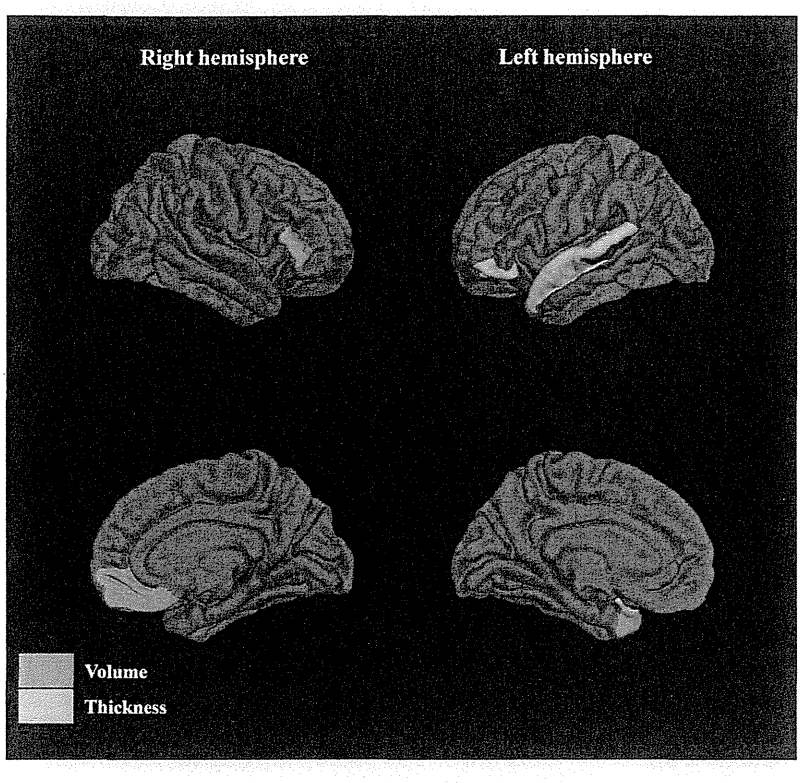

Figure 5. Discriminative pattern for female subjects. Selected regions were differentially colored when volume (blue) or thickness (yellow) of those regions were entered into the model.
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psychiatric disorders such as bipolar affective disorder (BD). Our preliminary classification analysis using the current sample as well as 15 BD patients [8 males (mean age, 33.5 years) and 7 females (mean age, 33.7 years)] correctly assigned 81.4% of male subjects and 87.5% of female subjects, respectively (unpublished data). However, larger number of BD patients will be needed to delineate the conclusion that such technique may possibly attribute to the clinical diagnosis of different psychiatric conditions. Second, the higher socio-economic status of control group compared to schizophrenia patients might have confounded the analyses, although parental socio-economic status was not different between groups. Third, the results may have been influenced by antipsychotic medication that all patients in this study had received prior to scanning [59–61]. Finally, as the sample size of this study is modest (51 males and 41 females), we needed to assign more subjects to the training cohort than to the validation cohort in order to obtain more reliable classifiers. A larger number of subjects should be tested for validation in future study.

Conclusion

In conclusion, our results showed that combinations of fully automated brain measures successfully classified diagnostic groups (i.e., schizophrenia patients and controls), and suggest that such neuroimaging approaches may provide objective biological information adjunct to clinical diagnosis of early schizophrenia.

Supporting Information

Table S1 The results of comparison of the ROI volumes between schizophrenia patients and healthy controls.
(XLSX)

Table S2 The results of comparison of the mean thickness of the ROIs between schizophrenia patients and healthy controls.
(XLSX)

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Author Contributions

Conceived and designed the experiments: YT MS MK. Performed the experiments: YT LO YM YS. Analyzed the data: YT MS TT YK KN. Wrote the paper: YT MS TT HY KK. Supervised the overall research project: MI YO.

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Gray matter changes in subjects at high risk for developing psychosis and first-episode schizophrenia: a voxel-based structural MRI study

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Objectives: The aim of the present study was to use a voxel-based magnetic resonance imaging method to investigate the neuroanatomical characteristics in subjects at high risk of developing psychosis compared with those of healthy controls and first-episode schizophrenia patients.

Methods: This study included 14 subjects with at-risk mental state (ARMS), 34 patients with first-episode schizophrenia, and 51 healthy controls. We used voxel-based morphometry with the Diffeomorphic Anatomical Registration through Exponentiated Lie Algebra tools to investigate the whole-brain difference in gray matter volume among the three groups.

Results: Compared with the healthy controls, the schizophrenia patients showed significant gray matter reduction in the left anterior cingulate gyrus. There was no significant difference in the gray matter volume between the ARMS and other groups.

Conclusion: The present study suggests that alteration of the anterior cingulate gyrus may be associated with development of frank psychosis. Further studies with a larger ARMS subjects would be required to examine the potential role of neuroimaging methods in the prediction of future transition into psychosis.

Keywords: schizophrenia, psychosis, high risk, MRI, cingulate gyrus

INTRODUCTION

Neuroimaging studies have demonstrated subtle but widespread brain structural alterations, such as volume reduction of fronto-temporo-limbic regions as well as enlarged lateral and third ventricles, in first-episode schizophrenia (Steen et al., 2006; Vita et al., 2006; Ellison-Wright et al., 2008), which are not due to illness chronicity and antipsychotic medication. Recent prospective longitudinal magnetic resonance imaging (MRI) studies, including our own data showing progressive gray matter reduction of the temporal region (approximately 2–3% per year) (Takahashi et al., 2010, 2011), further revealed progressive brain structural change and its relationship to clinical course or outcome in first-episode schizophrenia (Andreasen et al., 2011). These longitudinal findings might be consistent with the clinical observation that a long duration of untreated psychosis (DUP), which could lead to severe brain pathological changes during the early illness stage (Lappin et al., 2006; Takahashi et al., 2007), is related to poor outcome of schizophrenia patients (Marshall et al., 2005; Perkins et al., 2005). Examining potential neurobiological markers that predate the onset of psychosis might lead to appropriate early intervention and thus prevent deterioration of social function and the progression of structural brain alterations.

It is not yet clear at which illness stage brain abnormalities occur in schizophrenia. Subjects with at-risk mental state (ARMS), who exhibit prodromal-like symptoms and have an increased risk of developing psychosis (Yung et al., 2003), might share disease vulnerability as well as brain morphological changes with patients with overt schizophrenia. Subjects with ARMS are heterogeneous on the basis of their outcome, as only about 36% of them develop psychosis during 3-year follow-up (Fusar-Poli et al., 2012). Previous MRI studies using voxel-based morphometry (VBM), which allows automated whole-brain analysis, revealed more severe gray matter reduction predominantly in the fronto-temporo-limbic regions in ARMS subjects with later transition than in those without (Pantelis et al., 2003; Borgwardt et al., 2007; Fusar-Poli et al., 2011). More specifically, Fornito et al. (2008) revealed that baseline differences in the anterior cingulate cortical thickness distinguished between ARMS with and without later transition, but they did not directly compare ARMS subjects and patients with overt psychosis.

This voxel-based MRI study aimed to investigate the nature of neuroanatomical abnormalities in high-risk subjects compared with both healthy controls and first-episode schizophrenia patients. On the basis of previous neuroimaging findings, we predicted that both first-episode schizophrenia and ARMS subjects, especially those with later transition, would show brain morphological changes in fronto-temporo-limbic regions compared with healthy subjects.

MATERIALS AND METHODS

PARTICIPANTS

Fourteen individuals (10 males and 4 females) defined as ARMS for psychosis were recruited from the Consultation Support Service in Toyama (CAST), which was launched in 2006 as a specialized clinical setting to study and treat young persons (aged 15–30 years) at risk of developing psychosis (Mizuno et al., 2009). The subjects with ARMS were diagnosed according to the Comprehensive Assessment of ARMS (CAARMS) (Yung et al., 2004); they were characterized by one or more of the following: (1) attenuated psychotic symptoms; (2) brief, limited intermittent psychotic symptoms with spontaneous resolution; or (3) family history of psychosis in first-degree relatives or a personal history of schizotypal personality disorder accompanied by a decline in general functioning. Their clinical symptoms were assessed using the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983) and the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984) at the time of scanning. Eleven ARMS subjects were neuroleptic-naïve at scanning, but two subjects were treated with atypical neuroleptics and one was receiving sulpiride. Their duration of medication use was shorter than 2 weeks for atypical neuroleptics and shorter than 6 months for sulpiride. They were also receiving benzodiazepines ($N = 2$), antidepressants ($N = 1$), and tandospirone ($N = 3$).

Thirty-four patients with first-episode schizophrenia (20 males and 14 females), who met the ICD-10 research criteria (World Health Organization, 1993), were recruited from the inpatient and outpatient clinics of the Department of Neuropsychiatry, Toyama University Hospital. The patients were diagnosed following structured clinical interviews by experienced psychiatrists using the Comprehensive Assessment of Symptoms and History (CASH; Andreasen et al., 1992). Their durations from manifestations of overt psychotic symptoms were shorter than 1 year. Their clinical symptoms were assessed using SANS and SAPS at the time of scanning. Thirty-three patients were receiving neuroleptic medication at the time of scanning; 2 patients were treated with typical neuroleptics, 26 were receiving atypical neuroleptics, 5 were taking both typical and atypical neuroleptics, and 1 patient was neuroleptic-free. They were also receiving anticholinergic drugs ($N = 8$), benzodiazepines ($N = 9$), antidepressants ($N = 1$), carbamazepine ($N = 1$), and lithium carbonate ($N = 3$).

Exclusion criteria for ARMS subjects and schizophrenia patients were other neurological diseases, past or present regular alcohol abuse, and/or consumption of illicit drugs as reported by the study participants and/or the patients' records, as well as past head trauma with loss of consciousness or electro-convulsive treatment.

The control subjects consisted of 51 healthy volunteers (30 males and 21 females) recruited from members of the community, hospital staff, and university students. They were given a questionnaire consisting of 15 items concerning their personal (13 items; including a history of obstetric complications, substantial head injury, seizures, neurological or psychiatric diseases, impaired thyroid function, hypertension, diabetes, and substance use) and family (2 items) histories of illness. They did not have any personal or family history of psychiatric illness in their first-degree relatives. This study was approved by the ethics committee of Toyama University. Written informed consent was obtained from all subjects prior to study participation.

MRI ACQUISITION

Magnetic resonance images were obtained by utilizing a 1.5-T Magnetom Vision (Siemens Medical System, Inc., Erlangen, Germany) with a three-dimensional gradient-echo sequence FLASH (fast low-angle shots) yielding 160–180 contiguous T1-weighted slices of 1.0-mm thickness in the sagittal plane. The imaging parameters were as follows: TR = 24 ms; TE = 5 ms; flip angle = 40°; field of view = 256 mm; and matrix size = 256 × 256 pixels. The voxel size was 1.0 mm × 1.0 mm × 1.0 mm. All scans in the patient and control groups were acquired in the same system with the same protocol.

MRI DATA PROCESSING

All T1-weighted MRI data were first converted from the Dicom format to the NIFTI format and then processed using Statistical Parametric Mapping 8 (SPM8, Wellcome Institute of Neurology, University College London, UK, http://www.fil.ion.ucl.ac.uk/spm) running under MATLAB R2008b (The MathWorks Inc., USA).

The unified segmentation model consisting of spatial normalization, bias field correction, and tissue segmentation was performed in order to improve the quality of data preprocessing (Ashburner and Friston, 2005). Tissue probability maps were registered to the subject's data, and final tissue probability maps were derived from prior maps with the use of a combination with tissue probabilities based on the voxel intensity. To make the processed data more accurate, we used the Diffeomorphic Anatomical Registration through Exponentiated Lie Algebra (DARTEL) (Ashburner, 2007; Ashburner and Friston, 2009; Klein et al., 2009) tool in SPM8. DARTEL is not integrated into the segmentation model and requires the input of gray matter tissue maps produced by unified segmentation. This algorithm records inter-subject images using diffeomorphisms, which preserve the object properties through deformations, twistings, and stretchings, and archives a more accurate inter-subject registration. Because DARTEL produces a more accurate registration, it improves the sensitivity of finding and localizing differences between groups in terms of the gray matter volume. Registered tissue maps were transformed to the stereotactic space of the Montreal Neurological Institute (MNI) and multiplied with the Jacobian determinants of the deformations in order to preserve the volume of tissue in each structure. Finally, the modulated, warped tissue maps were then written with an isotropic voxel resolution of 1.5 mm^3 and smoothed with a 10-mm Full-Width Half-Maximum (FWHM) Gaussian kernel (Salmond et al., 2002; Jones et al., 2005).

STATISTICAL ANALYSIS

Demographic data

Group differences in age, educational level, parental educational level, and intracranial volume (ICV) were examined with one-way analysis of variance (ANOVA) and *post hoc* Scheffé's test. Group differences in terms of gender were tested with Chi-square tests. The level of statistical significance was defined as $p < 0.05$ (two-tailed). Statistical analyses were performed with Statistica, version 06J for Windows (StatSoft Japan Inc., Tokyo, Japan).

Voxel-based analysis of gray matter volume

Gray matter volume differences between the ARMS subjects, schizophrenia patients, and healthy controls were analyzed using two-sample *t*-tests implemented in the general linear model approach of SPM8 with age and ICV as nuisance covariates. We used cluster level inference (the extent of contiguous clusters of individual significant voxels) for determination of statistical significance (Meisenzahl et al., 2008). Because cluster size distribution varies according to local smoothness, the cluster sizes in this study were adjusted according to the local smoothness within the framework of the Random Field Theory (RFT) (Worsley et al., 1999; Hayasaka et al., 2004). Our statistical inference was performed at the cluster level by assessing the SPM{t} images by the non-stationary cluster extent correction (Hayasaka et al., 2004), which has been reported to be robust when MRI experiments fulfill (1) degrees of freedom > 30 and (2) image smoothness (FWHM) > 3 × voxel sampling resolution (Hayasaka et al., 2004), as in this study. The cluster-defining threshold was set to $p < 0.001$. Then, a family-wise error-corrected (FWE) cluster size threshold of $p < 0.05$ was applied to account for multiple comparisons of the results (corrected cluster sizes). Finally, cluster sizes were adjusted for smoothness non-uniformity using the VBM8 toolbox (Gaser, 2009), which implements the methodology of Hayasaka et al. (2004).

Voxel coordinates are given as an indication of location in a standardized brain. Voxels were localized in MNI space and transformed into Talairach and Tournoux coordinates (Talairach and Tournoux, 1988).

RESULTS

DEMOGRAPHIC DATA

Table 1 shows demographic and clinical data of the subjects in this study. Groups were matched for gender, parental education, and ICV. However, the controls ($p < 0.001$) and schizophrenia patients ($p < 0.001$) were older than the ARMS subjects. The controls had a higher educational level than the other two groups ($p < 0.001$) and the schizophrenia patients had a higher educational level than the ARMS subjects ($p = 0.004$).

VOXEL-BASED ANALYSIS OF GRAY MATTER VOLUME

Compared with the healthy controls, the schizophrenia patients showed significant gray matter volume reduction in the left anterior cingulate gyrus (FWE-corrected $p = 0.047$) (**Figures 1** and **2**; **Table 2**). There was no difference between the ARMS subjects and the schizophrenia patients or the healthy controls.

DISCUSSION

In this study, we performed VBM analyses using the DARTEL method to investigate gray matter change in early psychosis. In comparison to the healthy controls, first-episode schizophrenia patients showed significant gray matter reduction in the left anterior cingulate gyrus, but the ARMS subjects showed no significant difference in gray matter volume. This negative finding may be partly related to the heterogeneity of the ARMS subjects, as those with later transition to psychosis had a similar distribution of the cingulate gyrus gray matter volume to that in first-episode schizophrenia patients (**Figure 2**). These preliminary results are partly consistent with previous findings by Fornito et al. (2008), who reported that baseline differences of anterior cingulate gyrus distinguish between high-risk individuals who do and do not subsequently develop overt psychosis.

Neuroimaging studies comparing schizophrenia patients to healthy controls have shown evidence of morphological change in the anterior cingulate gyrus (Ellison-Wright et al., 2008; Shepherd et al., 2012). Gray matter volume reduction (Salgado-Pineda et al., 2003; Koo et al., 2008; Meisenzahl et al., 2008; Leung et al., 2011) and reduced cortical thickness (Schultz et al., 2010) in the anterior

Table 1 | Clinical and demographic characteristics[a].

Characteristic	ARMS (*N* = 14)	Schizophrenia (*N* = 34)	Healthy control (*N* = 51)
Gender (male/female)	10/4	20/14	30/21
Age (years)[b]	18.9 (1.4)	24.7 (5.5)	23.9 (1.8)
Educational level (years)[c]	11.6 (1.4)	13.5 (2.0)	16.0 (1.7)
Parental educational level (years)	13.7 (1.4)	13.3 (1.7)	14.1 (2.2)
Age at onset (years)	N/A	23.3 (5.4)	N/A
Duration of medication (months)	0.43 (1.6)	1.7 (1.8)	N/A
Drug (mg/day, haloperidol equivalent)[d]	0.55 (1.1)	6.3 (6.5)	N/A
Intracranial volume (cm^3)	1557.8 (130.0)	1602.1 (150.7)	1573.6 (143.0)

[a] *Values given as mean (SD).*

[b] *Significant difference between groups.*

[c] *Significant difference between groups.*

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

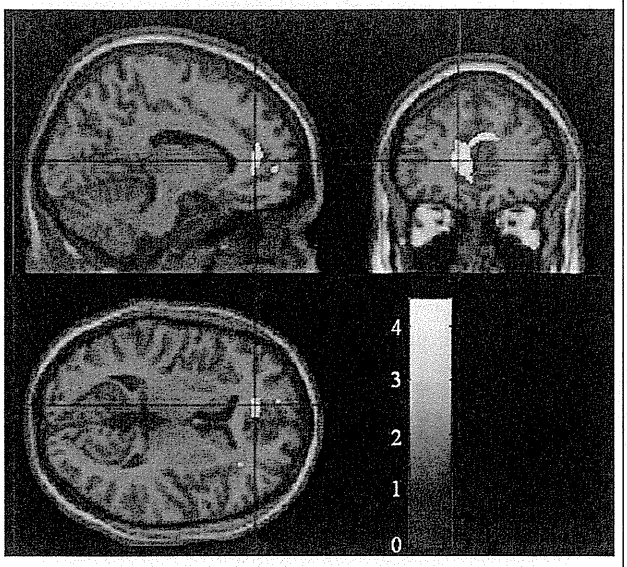

FIGURE 1 | Group difference of the gray matter between the schizophrenia patients and the healthy controls. The cluster in which the schizophrenia patients show gray matter reduction is located in the left anterior cingulate gyrus.

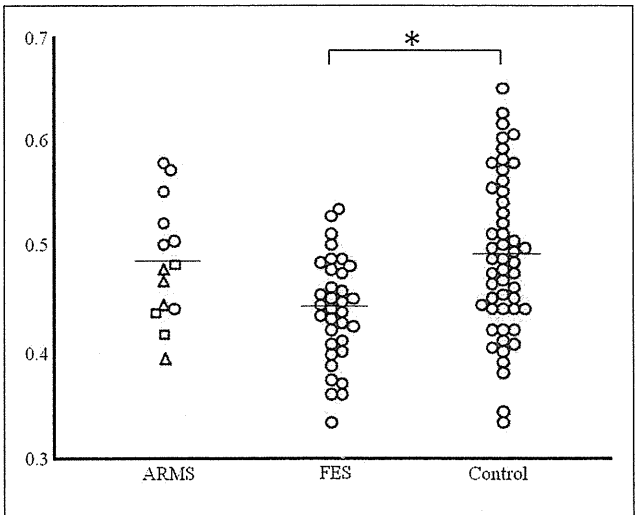

FIGURE 2 | Scatter plots of gray matter volume of the peak coordinate at the left anterior cingulate gyrus that revealed the difference between schizophrenia patients and controls. The ARMS subjects were classified into three groups according to clinical outcome (square: ARMS who developed psychosis, triangle: ARMS with unknown outcome, circle: ARMS without transition to psychosis). $*p < 0.05$.

cingulate gyrus have been revealed by MRI studies in first-episode and neuroleptic-naïve patients to minimize the influence of neuroleptic medication or chronicity of the illness. In this study, gray matter volume reduction in the left anterior cingulate gyrus in the schizophrenia patients had no relationship with any effects of medication (data not shown).

Table 2 | Talairach coordinates for regions of reduced gray matter volume in the schizophrenia patients compared to the healthy controls.

Region	Voxel	Peak coordinate			*T*	*p*
		x	*y*	*z*		
lt. anterior cingulate gyrus	631	−11	42	8	3.82	0.047

One major aim of high-risk studies for psychosis has been to identify clinical and neurobiological predictors of future transition to psychosis, which would allow specific and targeted preventive strategies (McGorry et al., 2006); indeed, previous neuroimaging studies have identified such predictive markers. The VBM study by Pantelis et al. (2003) revealed the association between later transition and gray matter reduction in temporal and frontal regions predominantly in the right hemisphere and cingulate gyrus bilaterally in clinical high-risk subjects, which was largely replicated in an independent high-risk cohort (Borgwardt et al., 2007). Recent multi-center (Mechelli et al., 2011) and meta-analytic (Smieskova et al., 2010; Fusar-Poli et al., 2011) MRI studies on large numbers of high-risk subjects generally supported the assertion that brain morphological changes in the fronto-temporolimbic regions, including the cingulate gyrus, already exist prior to the onset of psychosis. Although our data are clearly limited by the small sample size as discussed below, the distribution of the anterior cingulate gray matter volume (**Figure 2**) implies that ARMS subjects with later transition may have morphological changes of the cingulate gyrus to the same degree as those with overt schizophrenia. There has been debate about the risk-benefit ratio of antipsychotic treatment in prodromal patients (Woods et al., 2007; Weiser, 2011). However, given the hypothesized active brain pathology in the early phases of psychosis, which could affect the subsequent course of the illness (Birchwood et al., 1998), and the potential ameliorating effects of atypical antipsychotics for brain structural abnormalities (Lieberman et al., 2005; Girgis et al., 2006), intervention before the expression of frank psychosis may reduce neurobiological deterioration as well as the transition rate to psychosis (McGorry et al., 2002; McGlashan et al., 2006), especially in subjects with neurobiological risk markers.

The sample size of the current ARMS group (especially those who later developed psychosis) was small and some individuals dropped out during clinical follow-up ($N = 4$, unknown outcome group). Significant group differences in age (ARMS < schizophrenia and controls) might also have biased our results, although we used age as a controlling factor in all imaging analyses. In contrast to our prediction, we did not find significant brain morphological changes in the ARMS subjects, potentially due to the small sample size. It was also not possible to examine the relationship between brain morphology and clinical outcome (later transition) in our ARMS subjects statistically. In addition, direct comparison between the three groups using the ANOVA model with age and ICV as covariates failed to replicate significant group difference in the cingulate gyrus gray matter volume. Thus, further study with a larger well-defined