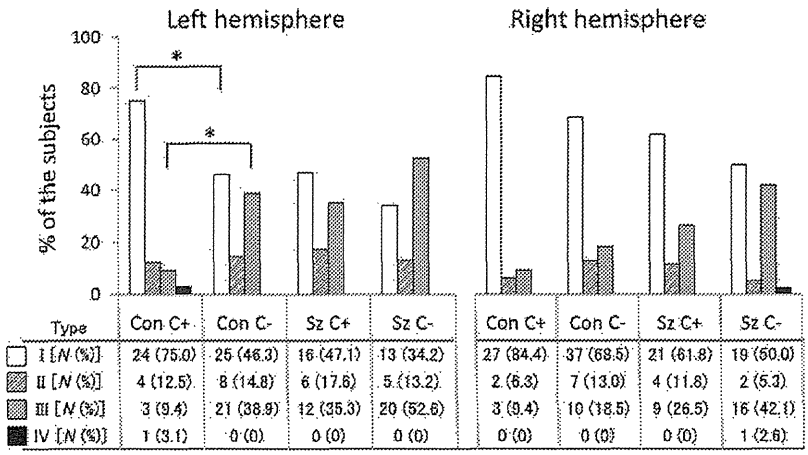

Type	Con C+	Con C-	Sz C+	Sz C-	Con C+	Con C-	Sz C+	Sz C-
I [N (%)]	24 (75.0)	25 (46.3)	16 (47.1)	13 (34.2)	27 (84.4)	37 (68.5)	21 (61.8)	19 (50.0)
II [N (%)]	4 (12.5)	8 (14.8)	6 (17.6)	5 (13.2)	2 (6.3)	7 (13.0)	4 (11.8)	2 (5.3)
III [N (%)]	3 (9.4)	21 (38.9)	12 (35.3)	20 (52.6)	3 (9.4)	10 (18.5)	9 (26.5)	16 (42.1)
IV [N (%)]	1 (3.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.6)

Fig. 2. Distribution of the orbitofrontal sulcogyral pattern in each diagnostic group. C+, subjects with C allele; C−, subjects without C allele; Con, controls; Sz, schizophrenia. *$p < 0.01$.

illness duration of approximately 5 years in this study. Illness chronicity (Haijma et al., 2013) and medication with antipsychotics (Andreasen et al., 2013; Lieberman et al., 2005; Moncrieff and Leo, 2010) can significantly affect brain morphology. Although there was no difference in these variables between the patients with and without the C allele (Table 1) and gross cortical folding patterns remain rather stable throughout life in healthy subjects (Armstrong et al., 1995; Magnotta et al., 1999), the present findings should be replicated using patients at early illness stages and in un-medicated patients.

5. Conclusion

The present study replicated an altered sulcogyral pattern of the OFC in schizophrenia and further suggested that genotype variation in *YWHAE* may be related to the development of cortical folding patterns in the orbitofrontal region. Although we did not observe a genotype effect of *YWHAE* on the OFC pattern specific to schizophrenia, our findings support the possible role of the OFC sulcogyral pattern as an endophenotype for future genetic studies of schizophrenia.

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Altered depth of the olfactory sulcus in ultra high-risk individuals and patients with psychotic disorders

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ABSTRACT

A shallow olfactory sulcus has been reported in schizophrenia, possibly reflecting abnormal forebrain development during early gestation. However, it remains unclear whether this anomaly exists prior to the onset of psychosis and/or differs according to illness stage. In the current study, magnetic resonance imaging was used to investigate the length and depth of the olfactory sulcus in 135 ultra high-risk (UHR) individuals [of whom 52 later developed psychosis (UHR-P) and 83 did not (UHR-NP)], 162 patients with first-episode psychosis (FEP), 89 patients with chronic schizophrenia, and 87 healthy controls. While there was no group difference in the length of the sulcus, UHR-P subjects had significantly shallower olfactory sulcus at baseline as compared with UHR-NP and control subjects. The depth of this sulcus became increasingly more superficial as one moved from UHR-P subjects to FEP patients to chronic schizophrenia patients. Finally, the depth of the olfactory sulcus in the UHR-P subjects was negatively correlated with the severity of negative symptoms. These findings suggest that the altered depth of the olfactory sulcus, which exists before psychosis onset, could be predictive of transition to psychosis, but also suggest ongoing changes of the sulcus morphology during the course of the illness.

1. Introduction

The olfactory sulcus appears during fetal development at around 16 weeks of gestation (Chi et al., 1977) and its depth is considered to relate to olfactory function in healthy subjects (Hummel et al., 2003). Given the evidence that schizophrenia patients exhibit olfactory dysfunction as a possible vulnerability marker (Brewer et al., 2001, 2003; Turetsky et al., 2009b; Kamath et al., in press), as well as the fetal stage of the sulcus formation at which neurodevelopmental disruption could increase the risk for schizophrenia (Fatemi and Folsom, 2009), olfactory sulcus morphology might be a potential early neurodevelopmental marker of schizophrenia. However, magnetic resonance imaging (MRI) studies of the olfactory sulcus in schizophrenia have yielded inconsistent results. We demonstrated an abnormally shallow olfactory sulcus in first-episode psychosis patients (Takahashi et al., 2013a), while both normal (Nguyen et al., 2011) and shallow (Turetsky et al., 2009a) sulcus depths were reported in chronic patients. This inconsistency may be partly due to methodological issues such as different sample characteristics (e.g., illness stage, medication) and tracing methodologies. Although a recent MRI study found no progressive changes in the sulcus depth in first-episode schizophrenia (Takahashi et al., 2013a), the nature of the sulcus morphology in the course of the illness remains unclear. In addition, to our knowledge, no MRI studies have investigated whether the olfactory sulcus abnormalities in schizophrenia are diagnostically specific or common to various psychotic disorders (e.g., affective psychosis).

Our previous MRI studies in ultra high-risk (UHR) individuals (Yung et al., 2004a), 35% of whom made the transition to psychosis according to their long-term outcome (Nelson et al., 2013), revealed abnormalities in sulcus/gyral folding in the anterior cingulate cortex (ACC) (Yücel et al., 2003) or in the size of the adhesio interthalamica (AI) (Takahashi et al., 2008a) regardless of later transition status, which could represent pre-existing vulnerability to psychopathology as a

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consequence of early neurodevelopmental insult (Pantelis et al., 2005). On the other hand, we found no abnormality in the cavum septum pellucidum (CSP) that is also related to fetal neurodevelopment (Rakic and Yakovlev, 1968) in UHR individuals (Takahashi et al., 2008b), suggesting different biological processes responsible for these gross brain abnormalities. A recent MRI study demonstrated decreased olfactory sulcus depth in a Japanese high-risk sample (Takahashi et al., 2013b), supporting the notion that olfactory impairment appears to be a promising vulnerability marker of the psychosis risk status especially for those who subsequently develop schizophrenia (Brewer et al., 2003; Turetsky et al., 2012). However, that preliminary MRI study could not take account of sample outcome (e.g., with and without later transition) due to small sample size and needs replication in a larger well-defined high-risk cohort.

The present study aimed to investigate the olfactory sulcus morphology in a large sample of patients at various stages of psychotic illness and with various diagnoses [first-episode psychosis (FEP), chronic schizophrenia, and ultra high-risk individuals who did (UHR-P) and did not (UHR-NP) develop psychosis] compared with healthy controls. On the basis of a possible role of the olfactory sulcus depth as an early neurodevelopmental marker, as well as previous MRI (Turetsky et al., 2009a; Takahashi et al., 2013a,b) and olfactory ability (Brewer et al., 2001, 2003; Turetsky et al., 2009b, 2012) findings, we predicted that the UHR-P subjects, FEP patients, and chronic schizophrenia patients would have a shallower olfactory sulcus to a similar degree as compared with controls. We also investigated the association between the olfactory sulcus morphology and clinical features (clinical variables and diagnosis) as well as other brain structures potentially related to early neurodevelopment (i.e., ACC folding, AI length, and CSP length).

2. Methods

2.1. Subjects

Eighty-nine patients with chronic schizophrenia, 162 patients with first-episode psychosis (FEP), 135 individuals at ultra high-risk (UHR) for developing psychosis, and 87 healthy comparisons participated in this study (Table 1). Inclusion criteria and demographic characteristics of the study participants have been described in detail elsewhere (Velakoulis et al., 1999; Garner et al., 2005; Velakoulis et al., 2006).

Briefly, the patients with chronic schizophrenia were recruited from the Adult Mental Health Rehabilitation services of the North Western Mental Health Program, Melbourne. The FEP patients were recruited from the Early Psychosis Prevention and Intervention Centre (EPPIC), were aged 16–30 years, and were currently psychotic as reflected by the presence of at least one positive symptom (delusions, hallucinations, disorder of thinking or speech other than simple acceleration or retardation, or disorganized, bizarre, or markedly inappropriate behavior). DSM-III-R diagnoses (American Psychiatric Association, 1990) of patients with chronic schizophrenia and FEP were based on chart review in addition to either the Structured Clinical Interview for DSM-III-R (SCID; Spitzer et al., 1990) or the Royal Park Multidiagnostic Instrument for Psychosis (RPMIP; McGorry et al., 1989). Based on these assessments administered during the initial treatment episode (median illness duration = 27.0 days), the FEP patients were further divided into four sub-groups: schizophrenia ($n = 46$), schizophreniform psychosis ($n = 57$), affective psychosis ($n = 34$), and other psychosis (e.g., psychosis not otherwise specified, brief psychosis, delusional disorder) ($n = 25$) (Velakoulis et al., 2006). All FEP patients were neuroleptic-naïve prior to admission but 150 had received neuroleptic medication for a short period prior to scanning.

The UHR subjects were recruited from admissions to the Personal Assessment and Crisis Evaluation (PACE) Clinic, a specialized service for UHR subjects in Melbourne, Australia. Criteria for identification of the UHR cohort and the rationale for these criteria have been fully described elsewhere (Yung et al., 2003, 2004a). The UHR subjects were assessed with the Brief Psychiatric Rating Scale (BPRS; Rhoades and Overall, 1988), the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1983), and the Comprehensive Assessment of At Risk Mental States (CAARMS; Yung et al., 2004b). All UHR subjects were aged 14–30 years and had not experienced a previous psychotic episode. Individuals were included in the study if they had been followed up for at least 12 months. After baseline scanning, they were monitored regularly for the onset of full psychotic symptoms

Table 1
Sample characteristics and olfactory sulcus measures of the participants.

	Controls		UHR-NP		UHR-P		FEP		Chronic Sz		Group comparisons
	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	
Age (years)	26.9	(10.1)	20.4	(3.6)	19.6	(3.5)	21.5	(3.4)	34.9	(9.6)	$F(4, 468) = 82.32$, $p < 0.001$; Sz > controls > UHR-P, UHR-NP, and FEP
M/F	55/32		48/35		30/22		108/54		76/13		Chi-square = 19.39, $p < 0.001$; M > F in Sz compared with all other groups
Handedness (right/mixed/left)[a]	80/2/5		69/3/10		46/0/4		139/4/17		74/5/6		$p = 0.488$, Fisher's exact test
Height (cm)[a]	175.3	(9.7)	170.8	(9.1)	171.6	(8.8)	172.8	(9.4)	174.3	(7.9)	$F(4, 457) = 3.22$, $p = 0.013$; controls > UHR-NP
Premorbid IQ[a,b]	102.3	(10.5)	96.6	(13.7)	94.3	(13.2)	93.9	(13.6)	95.6	(15.1)	$F(4, 368) = 5.19$, $p < 0.001$; controls > FEP
BPRS total at intake[a]	–		43.7	(8.3)	44.6	(8.3)	–		–		$F(1, 132) = 0.38$, $p = 0.538$
BPRS psychotic subscale at intake[a]	–		8.1	(2.5)	8.8	(2.8)	–		–		$F(1, 132) = 1.96$, $p = 0.164$
SANS total at intake	–		17.3	(12.7)	21.5	(12.4)	–		–		$F(1, 133) = 3.52$, $p = 0.063$
Duration of illness (days)[a]							54	(87)	4673	(3613)	$F(1, 245) = 260.44$, $p < 0.001$; Sz > FEP
Drug (mg/day, CP equivalent)[c]							154.7	(118.2)	842.9	(715.8)	$F(1, 224) = 136.66$, $p < 0.001$; Sz > FEP
Intracranial volume (ml)	1450	(143)	1424	(148)	1435	(146)	1422	(133)	1441	(130)	$F(4, 467) = 0.68$, $p = 0.609$
Whole brain volume (ml)	1361	(140)	1315	(137)	1324	(135)	1305	(123)	1325	(119)	$F(4, 467) = 3.27$, $p = 0.011$; C > FEP
Olfactory sulcus length (mm)											$F(4, 461) = 1.04$, $p = 0.385$
Left	44.9	(3.9)	44.1	(5.2)	44.9	(4.8)	44.6	(4.8)	43.3	(5.1)	
Right	45.6	(4.0)	45.3	(4.9)	45.7	(4.9)	45.7	(5.0)	44.3	(5.2)	
Olfactory sulcus depth (mm)											$F(4, 461) = 95.50$, $p < 0.001$; controls and UHR-NP > UHR-P > FEP > Sz
Left	11.5	(1.3)	11.4	(1.2)	10.5	(1.1)	9.6	(1.0)	9.2	(1.0)	
Right	12.6	(1.3)	12.5	(1.2)	11.4	(1.2)	10.5	(0.9)	10.1	(1.1)	

BPRS, Brief Psychiatric Rating Scale; CP, chlorpromazine; F, female; FEP, first episode psychosis; M, male; SANS, Scale for Assessment of Negative Symptoms; Sz, schizophrenia; UHR-NP, ultra high-risk group without psychosis; UHR-P, ultra high-risk group with psychosis.

[a] Data missing for some participants.

[b] Estimated using the National Adult Reading Test (NART).

[c] 25 patients (19 with chronic Sz and 6 with FEP) had incomplete medication data.

based on operationalized criteria (Yung et al., 2004a) and were then divided into subgroups according to their long-term outcome [2–14 years later (Nelson et al., 2013)]. 52 UHR subjects (38.5%) developed psychosis (UHR-P) and 83 (61.4%) did not (UHR-NP). DSM diagnoses were available for 34 patients in the psychosis group. The predominant diagnosis was schizophrenia spectrum ($n = 20$), but there were also diagnoses of affective psychosis ($n = 7$), and other psychoses ($n = 7$). All UHR subjects were neuroleptic naïve at the time of the brain scan. After the brain scan, 21 subjects started low-dose risperidone therapy and cognitive behavior therapy as part of a double-blind randomized study examining a 6-month therapeutic intervention to reduce the risk of progression to psychosis (McGorry et al., 2002). Most of the remaining UHR participants received case management and supportive therapy for at least six months.

Healthy volunteers were recruited from similar socio-demographic areas as the patients by approaching ancillary hospital staff and through advertisements. These controls did not have any personal or family history of psychiatric illness.

All subjects were physically healthy, and none had a lifetime history of serious head trauma, neurological illness, serious medical or surgical illness, steroid or substance abuse. The sizes of the AI and CSP of the participants in this study have been examined previously (Takahashi et al., 2008a,b). ACC folding pattern data (Yücel et al., 2002, 2003) were available for 354 of 473 subjects in this study (111 FEP, 71 chronic schizophrenia, 97 UHR, and 75 control subjects). This study was approved by the regional ethics committee while written informed consent was obtained from all subjects prior to study participation.

2.2. Magnetic resonance imaging procedures

MRI scans were acquired with a 1.5-T GE Signa scanner (General Electric Medical Systems, Milwaukee, Wisconsin). A 3D volumetric spoiled gradient recalled echo in the steady state sequence generated 124 contiguous 1.5 mm coronal slices (TR = 14.3 ms, TE = 3.3 ms, flip = 30°, FOV = 24 × 24 cm, matrix = 256 × 256, voxel dimension = 0.938 × 0.938 × 1.5 mm). The intracranial volume (ICV) and whole brain volume were measured to correct for differences in head size as previously described (Velakoulis et al., 2006); the five groups (healthy controls, UHR-NP, UHR-P, FEP, and chronic schizophrenia) did not differ significantly in their ICV volumes but the controls had a larger whole brain volume than FEP patients (Table 1).

2.3. Olfactory sulcus measurements

For the assessment of the olfactory sulcus, the images were processed on a Linux PC (Fujitsu Limited, Tokyo, Japan) using 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 anterior commissure–posterior commissure line. As described in detail elsewhere (Takahashi et al., 2013a), one rater (TT), who was blind to the subjects' identity, measured the depth of the olfactory sulcus in all coronal slices where the sulcus was clearly seen (Fig. 1). On each coronal slice, the olfactory sulcus was traced beginning with the deepest point of the sulcus and ending inferiorly with a tangent line connecting the top surfaces of the gyrus rectus and medial orbital gyrus (Rombaux et al., 2009). The length of the sulcus in the anterior–posterior direction (mm) was determined by the multiplication of the number of these coronal slices by 0.938. Intra- and inter-rater (TT and YN) reliabilities of the sulcus measurements were assessed using intraclass correlation coefficients (ICCs) in 10 randomly selected brains. Intra-rater ICCs were 0.91 (left depth), 0.94 (left length), 0.91 (right depth), and 0.98 (right length). Inter-rater ICCs were 0.92 (left depth), 0.92 (left length), 0.83 (right depth), and 0.93 (right length).

2.4. Statistical analysis

Clinical and demographic differences between groups were examined with one-way analysis of variance (ANOVA) or chi-square test. The average depth (sum of the depth in all slices containing the sulcus/slice number) and length of the olfactory sulcus were analyzed using the repeated measures analysis of covariance (ANCOVA), with age and ICV as covariates, diagnosis (healthy controls, UHR-NP, UHR-P, FEP, and chronic schizophrenia) and gender as between-subject factors, and hemisphere as a within-subject variable. Post-hoc Scheffé's tests were used to follow-up these analyses.

Since there were significant group differences in age and gender (Table 1), the healthy controls were also divided into two subgroups; older controls [28 males and 9 females, mean (SD) = 35.5 (9.7) years, matched to chronic schizophrenia for age ($F = 0.09$, $df = 1, 124$, $p = 0.765$) and gender (chi-square = 1.71, $p = 0.191$)] and younger controls [27 males and 23 females, mean (SD) = 20.5 (3.2) years, matched to FEP (age, $F = 3.39$, $df = 1, 210$, $p = 0.067$; gender, chi-square = 2.65, $p = 0.104$) and both UHR groups (age, $F = 1.18$, $df = 2, 182$, $p = 0.309$; gender, chi-square = 0.21, $p = 0.899$)]. The relationships between the olfactory sulcus measures and clinical variables as well as the length of AI/CSP were examined by Pearson's partial correlation coefficients controlling for ICV. The length of the CSP was log-transformed because of their skewed distribution (Takahashi et al., 2008b). In order to examine the relationship between the olfactory sulcus measures and ACC folding pattern, the olfactory sulcus length and depth were analyzed by ANCOVAs with age and ICV as covariates, with diagnosis and ACC sulcal pattern for each hemisphere (prominent, present, and absent) as between-subject factors. The relationship between the olfactory sulcus measures and paracingulate asymmetry index (leftward, symmetric, and rightward) was also analyzed using the same model. Statistical significance was defined as $p < 0.05$ (two-tailed).

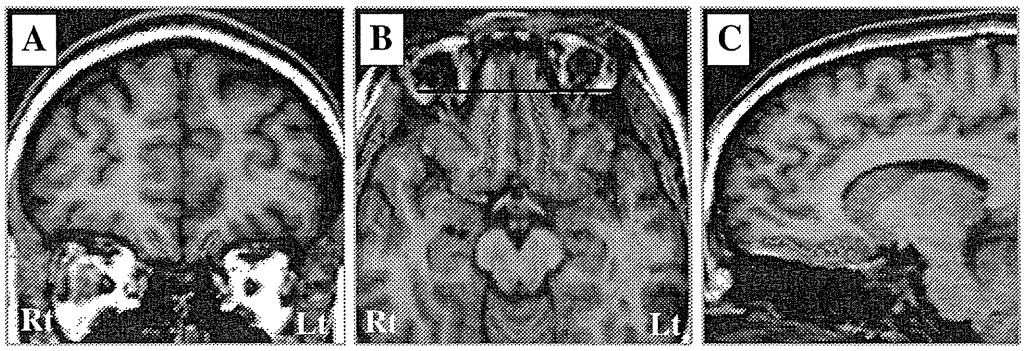

Fig. 1. Olfactory sulci on coronal (A), axial (B), and sagittal (C, right hemisphere) views, which were colored on 0.938-mm consecutive coronal slices. Panel A and the dotted line on panel B show the plane of the posterior tangent through the eyeballs (PPTE).

The findings presented here, including those of correlational analyses, remained essentially the same even when we used UHR diagnoses according to the outcome at 12 months after intake (rather than the longer term follow up data) as in our early studies (Yücel et al., 2003; Takahashi et al., 2008a,b). There was a group difference in the whole brain volume (controls > FEP; Table 1), but the present results of the olfactory sulcus did not change even when we used the whole brain volume instead of ICV as a covariate for the ANCOVAs.

3. Results

3.1. Demographic characteristics

Comparison of the groups revealed no difference in handedness and ICV, but there were significant group differences in age, gender, height, and premorbid IQ (Table 1). The two UHR groups (UHR-P versus -NP) did not differ with respect to global psychopathological state according to the BPRS or negative symptoms according to the SANS.

3.2. Depth and length of the olfactory sulcus

ANCOVA of the olfactory sulcus length revealed no significant effect involving diagnosis (Table 1), but that for depth showed significant main effects of diagnosis [$F(4, 461) = 95.50, p < 0.001$] and hemisphere [$F(1, 463) = 531.51, p < 0.001$] and an interaction between these factors [$F(4, 463) = 2.60, p = 0.036$]. Post-hoc analyses showed that the olfactory sulcus depth was shallower in the UHR-P subjects ($p < 0.001$ for both hemispheres), but not in UHR-NP subjects ($p = 1.000$), as compared with healthy controls and that the patients with later illness stages had increasingly shallower depth of the olfactory sulcus (i.e., controls and UHR-NP > UHR-P > FEP > chronic schizophrenia; all $p < 0.001$ for both hemispheres) (Table 1, Fig. 2). The olfactory sulcus depth was significantly deeper in the right hemisphere for all groups ($p < 0.001$). The sulcus depth did not differ among four FEP subgroups (schizophrenia, schizophreniform psychosis, affective psychosis, and other psychosis patients) [$F(3, 152) = 0.52, p = 0.672$] or three UHR-P subgroups (subjects who later developed schizophrenia spectrum, affective psychosis, and other psychoses) [$F(2, 26) = 0.17, p = 0.846$]. There was no significant effect involving gender in any of these analyses.

The present results of the sulcus depth did not change even when we separately analyzed the older groups (older controls and chronic schizophrenia patients) and younger groups (younger controls, FEP, and UHR subjects). Briefly, the olfactory sulcus was significantly deeper in the older controls than in chronic schizophrenia patients [ANCOVA, $F(1, 120) = 73.65, p < 0.001$; post-hoc tests, $p < 0.001$ for both hemispheres] and the sulcus depth became increasingly more superficial at later illness stages [ANCOVA, $F(3, 337) = 101.20, p < 0.001$; younger controls and UHR-NP > UHR-P > FEP (post hoc tests, all $p < 0.001$ for both hemispheres)].

3.3. Correlational analysis

There was a negative correlation between the olfactory sulcus depth and age only for the controls (left, $r = -0.376, p < 0.001$; right, $r = -0.399, p < 0.001$). For the FEP and chronic schizophrenia patients, the olfactory sulcus length and depth did not correlate with illness duration or daily medication dosage. Total SANS score in the UHR-P subjects was negatively correlated with the sulcus depth in the right hemisphere ($r = -0.426, p = 0.002$), but no correlations were found between the sulcus measures and clinical variables in the UHR-NP subjects.

3.4. Relationship between the olfactory sulcus measures and other structures

The olfactory sulcus depth correlated with whole brain volume only for the controls (right, $r = 0.330, p = 0.002$). However, the sulcus length and depth did not significantly correlate with morphologic changes in the AI and CSP in either diagnostic group. For the relationship between the olfactory sulcus measures (depth and length) and ACC folding pattern [sulcal pattern (left, right) and asymmetry index], ANCOVAs revealed no main effects of ACC sulcal features or diagnosis-by-ACC interactions.

4. Discussion

To our knowledge, this is the first MRI study to report morphologic changes of the olfactory sulcus across various illness stages including those of a sample at clinical high-risk of psychosis that was followed-up longitudinally. The UHR subjects who developed psychosis (UHR-P) had a significantly shallower olfactory sulcus as compared with both UHR who did not develop psychosis (UHR-NP) and control subjects, suggesting that such anomaly already exists prior to the onset as a possible risk marker of transition to psychosis. On the other hand, although this cross-sectional study cannot directly address progressive brain changes, the sulcus depth in various stages of psychosis

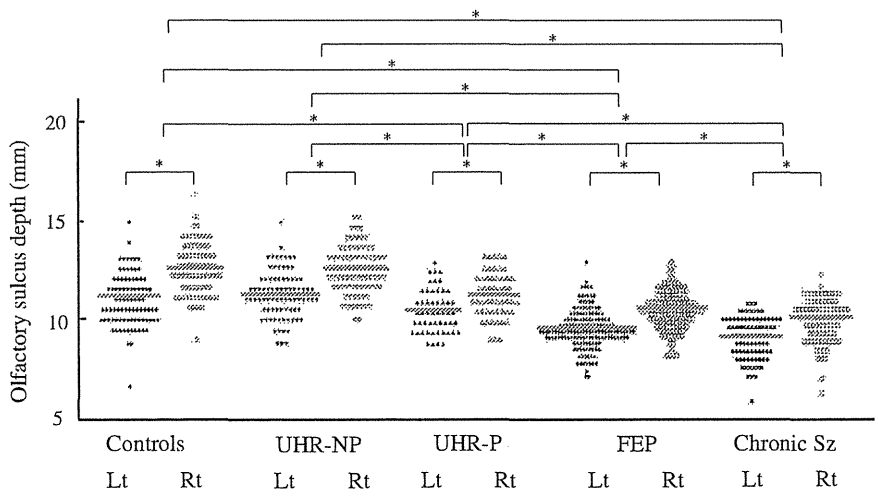

Fig. 2. Scatterplots of olfactory sulcus depth in healthy controls, ultra high-risk nonpsychotic (UHR-NP) subjects, ultra high-risk psychotic (UHR-P) subjects, patients with first episode psychosis (FEP), and patients with chronic schizophrenia (Sz). Horizontal bars indicate means of each group. *$p < 0.001$.

(UHR-P > FEP > chronic schizophrenia) is an indication that these patients may also manifest progressive changes in the sulcus morphology during the course of the illness.

The present study replicated previous findings in patients with first-episode (Takahashi et al., 2013a) and chronic (Turetsky et al., 2009a) schizophrenia as well as in a small sample of clinical high-risk individuals (Takahashi et al., 2013b) in showing that patients with psychotic disorders had abnormally shallow olfactory sulci before psychosis onset. Our findings also demonstrated that altered depth of the olfactory sulcus, which could be due to an embryonic disruption of the olfactory system (Abolmaali et al., 2002; Hummel et al., 2003), might be a neurobiological predictor of future transition to psychosis. Medication with antipsychotics might affect brain morphology in schizophrenia (Lieberman et al., 2005; Andreasen et al., 2013), but we found no significant relationship between the sulcus morphology and dosage of antipsychotic medication in our FEP and chronic schizophrenia patients. In addition, we also found altered depth of the olfactory sulcus in antipsychotic-naïve UHR-P subjects. A negative finding of olfactory sulcus in chronic schizophrenia by Nguyen et al. (2011) might partly be due to technical issues, as they measured the sulcus depth using a single slice based on external landmarks [i.e., the plane of the posterior tangent through the eyeballs (PPTE)], whereas our results and those of Turetsky et al. (2009a) were based on the measurement of the entire structure. These MRI findings are consistent with the notion that olfactory dysfunction, which exists in the first-episode or prodromal phase of schizophrenia (Brewer et al., 2001, 2003) as well as in the patients' first-degree relatives (Kamath et al., in press), may be a sensitive indicator of schizophrenia pathology and may even serve as an early warning sign of disease vulnerability or onset (Turetsky et al., 2009b).

A series of our MRI studies of possible neurodevelopmental markers in various illness stages may provide a clue to the timing of neurodevelopmental abnormalities underlying psychosis. Our group has shown that the UHR cohort shares abnormalities in the olfactory sulcus depth and ACC folding in patients with florid psychosis (Yücel et al., 2003), suggesting neurodevelopmental disturbance by the third trimester of gestation, as these sulco-gyral patterns develop around 16 to 25 weeks' gestation (Chi et al., 1977; Garel et al., 2001). In the same UHR and FEP subjects as in this study, we also found abnormally small AI (Takahashi et al., 2008a), which suggested an abnormal neurodevelopment around 13 to 14 weeks of gestation (Rosales et al., 1968). However, these patients had a CSP with a normal size (Takahashi et al., 2008b), which is related to fusion of the septum pellucidi within 3–6 months of birth (Shaw and Alvord, 1969), supporting the idea that psychotic disorders are more closely related to aberrant neurodevelopment early in gestation. Interestingly, only olfactory sulcus depth among these possible neurodevelopmental markers was predictive of future transition into psychosis, suggesting different biological processes responsible for these gross brain abnormalities. Discrepant findings such as increased prevalence of a large CSP have been also reported in a clinical high-risk sample (Choi et al., 2008), although 37% (11/30) of them were receiving antipsychotics at the time of scanning. Since our findings suggested a mild relation between the olfactory sulcus depth and prodromal symptomatology, it seems worthwhile to further evaluate the relation between these potential neurodevelopmental markers and clinical features of high-risk subjects (e.g., medication status, future transition, and symptom severity).

On the other hand, the current results of an increasingly more superficial sulcus in subjects with later stages of psychosis (UHR-P > FEP > chronic schizophrenia) imply that the olfactory sulcus abnormalities in psychosis cannot be fully explained by abnormal neurodevelopment. Illness duration in the current FEP and chronic schizophrenia patients did not correlate with the olfactory sulcus measures, but our results in healthy subjects raise the possibility that the sulcal depth changes with age. Childhood maltreatment, which has been shown to elevate the risk of psychiatric disorders, could also affect subsequent brain development including the orbitofrontal cortex (Kelly et al., 2013). Interestingly, a shallow olfactory sulcus (Wang et al., 2011) and olfactory dysfunction (Mesholam et al., 1998) have also been reported in neurodegenerative diseases such as Parkinson's disease, although the pathological mechanism is unknown. Thus, our findings of the olfactory sulcus in psychosis may also reflect ongoing changes possibly due to the illness itself and/or other factors (e.g., effect of antipsychotics), and may be associated with or even be consequent on other progressive brain structural changes. Indeed, dynamic brain changes, including excessive cortical thinning (Sun et al., 2009a,b; van Haren et al., 2011) or gray matter reduction (Mané et al., 2009) over time in the frontal area, may occur during or after the onset of schizophrenia (Pantelis et al., 2007). Previous longitudinal analyses demonstrated that the olfactory sulcus depth remained stable over time in first-episode schizophrenia with mean inter-scan interval of 2.7 years (Takahashi et al., 2013a), but further longitudinal follow-up of first-episode and additional prodromal/chronic patients would be required to examine the nature of the olfactory sulcus changes associated with psychosis.

Consistent with the results of olfactory identification ability in neuroleptic-naïve FEP patients (Brewer et al., 2001), which demonstrated that olfactory identification deficits were not specific to schizophrenia among various psychotic conditions, the current study did not identify any difference in the olfactory sulcus measures between the FEP subgroups, suggesting that olfactory sulcus malformation is present in a rather diverse population with psychotic symptoms, such as affective psychosis or other psychoses. We also found no difference between UHR-P subgroups, although this comparison was limited by small sample size especially for the prodromal state of affective and other psychoses. Given that olfactory deficits might be specific to high-risk subjects of schizophrenia spectrum (Brewer et al., 2003) and there have been only a few MRI studies of brain abnormalities predating the onset of affective psychoses (Bechdolf et al., 2012; Dazzan et al., 2012), disease specificity of the olfactory sulcus abnormalities before psychosis onset should be further tested in a larger sample.

Several limitations of the current study should be taken into account. First, although our findings of altered depth of the olfactory sulcus may at least partly reflect embryonic disruption of the olfactory system, we did not assess olfactory function or other olfactory structures. Reduced olfactory bulb volume in schizophrenia patients (Turetsky et al., 2000; Nguyen et al., 2011) and in first-degree relatives (Turetsky et al., 2003) suggests its significant role in the neurodevelopmental pathology of schizophrenia. The olfactory bulb can be well identified on T2-weighted MR images (Rombaux et al., 2009; Duprez and Rombaux, 2010), but our T1-weighted images did not allow reliable measurement of the bulb. Second, the participants in this study were not matched for age and gender between the groups. The olfactory sulcus morphology has been implicated in early neurodevelopment, but age may affect its depth as demonstrated in this study. However, statistical conclusions of the present study remained the same when we separately analyzed the older groups (older controls and chronic schizophrenia patients) and younger groups (younger controls, FEP, and UHR subjects) using two age- and gender-matched control subgroups. Moreover, there was no significant effect involving gender in any of the analyses of this study. Third, detailed clinical data of the patients with FEP and chronic schizophrenia such as the symptomatology at the time of scanning were not available. Given that impairment of olfactory identification has been associated with negative symptoms in schizophrenia (Brewer et al., 1996, 2001), the possible relation between the olfactory sulcus morphology and clinical features of psychotic disorders is worthy of further examination. Finally, as olfactory deficits are also reported in other psychiatric disorders such as major depression (Burón and Bulbena, 2013) and reduced global sulcation appears to be a feature of schizophrenia (Penttilä et al., 2008), the disease and regional specificities of our findings should be further examined.

In conclusion, we found a shallow olfactory sulcus in high-risk individuals prior to the onset of psychosis, implicating that such morphological anomalies could be an early neurodevelopmental marker related to future transition to psychosis. However, current results of prominent sulcus changes in patients with later illness stages suggest that olfactory sulcus abnormalities in psychotic disorders may also reflect progressive brain changes during and after the onset of illness. Additional longitudinal studies would be required for the understanding of the nature of olfactory sulcus changes in the course of psychosis.

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Contributors

In this study, Drs. Suzuki, Pantelis, and Brewer conceived the idea and methodology of the study. Dr. Takahashi conducted the statistical analyses and wrote the manuscript. Drs. McGorry, Yung, Brewer, Nelson, Lin, Phillips, and Proffitt recruited subjects, and were involved in clinical and diagnostic assessments. Drs. Takahashi and Nakamura analyzed the MRI data. Drs. Suzuki, Pantelis, Velakoulis, Wood, and Yücel contributed to writing and editing 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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The association between cognitive deficits and depressive symptoms in at-risk mental state: A comparison with first-episode psychosis

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ABSTRACT

Cognitive deficits and a high prevalence of depressive symptoms have been reported in at-risk mental state (ARMS) for psychosis, but the relationships between these variables remain unclear. The Brief Assessment of Cognition in Schizophrenia (BACS) was administered to 50 individuals with ARMS, 50 with first-episode psychosis (FEP), and 30 healthy controls (HC). Clinical symptoms were assessed by the Positive and Negative Syndrome Scale (PANSS) and the Beck Depression Inventory-2nd edition (BDI-II). Composite z-scores in BACS were compared between the three groups. Pearson correlations between composite z-scores on the BACS and indices of clinical symptoms were compared in the ARMS and FEP groups. The mean composite z-scores on the BACS for the ARMS (−2.82) and FEP (−2.85) groups were significantly lower than the HC group ($P < 0.001$); no differences between the ARMS and FEP groups emerged ($P = 0.995$). Cognitive deficits and depressive symptoms were significantly correlated in the ARMS group (PANSS depression: $r = -0.36$, $P = 0.010$; BDI-II: $r = -0.34$, $P = 0.02$), while the correlation between cognitive deficits and negative symptoms was significant in the FEP group ($r = -0.46$, $P = 0.001$) and approached significance in the ARMS group ($r = -0.25$, $P = 0.08$). The correlation between cognitive deficits and depressive symptoms significantly differed between the ARMS and FEP groups (PANSS depression: $Z = 2.50$, $P = 0.012$; BDI-II: $Z = 1.96$, $P = 0.0499$). Thus, a relationship between cognitive deficits and depression appears to be specific to ARMS compared to FEP.

1. Introduction

Cognitive impairment has been known to be present in individuals with at-risk mental state (ARMS) for psychosis (Fusar-Poli et al., 2012a). Specifically, significant neurocognitive deficits in ARMS have been recorded in general intelligence, attention, executive function, verbal fluency, working memory, verbal memory, and visual memory, but not processing speed domains.

However, high clinical heterogeneity is inherent in the ARMS population, with only a subgroup of this population transitioning to psychosis (Fusar-Poli et al., 2013a). Therefore, Fusar-Poli et al. (2012b) suggested that some attenuated psychotic symptoms exhibited by ARMS participants may reflect the emergence of an underlying "core" psychotic process, while some symptoms may be "clinical noise" or epiphenomena associated with a non-psychotic clinical condition; and some symptoms may be normal variations among the general population.

The research is mixed regarding the magnitude of cognitive disturbance in ARMS participants, with some reports of significant differences compared to controls and others reporting no differences (Brewer et al., 2006; Fusar-Poli et al., 2012a). Moreover, the profile of neurocognitive impairments has varied across studies. These findings suggest that heterogeneity in ARMS participants is observed in both psychopathology and cognition.

Cognitive impairment in individuals with ARMS has largely been investigated in comparison to patients with schizophrenia (Brewer et al., 2006), and some studies report relationships between cognitive deficits and positive (Frommann et al., 2011) and/or negative symptoms (Frommann et al., 2011; Meyer et al., 2014). Others report no association with positive (Niendam et al., 2006; Meyer et al., 2014) or negative

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symptoms (Niendam et al., 2006). Moreover, little attention has focused on the relationship between cognitive deficits and processes other than psychotic or negative symptoms in ARMS.

ARMS can be comorbid with depression. In previous research (Fusar-Poli et al., 2012b), 40% of ARMS participants had a depressive disorder, and a comorbid diagnosis was associated with impaired global functioning. Additionally, significant cognitive disturbances have been reported, and correlations between those deficits and depression have been shown in young adults with major depressive disorder (Egeland et al., 2003; Lee et al., 2012; Merriam et al., 1999; Trivedi and Greer, 2014). These findings suggest the possibility that cognitive deficits observed in ARMS participants can be associated with participants' depressive symptoms. Moreover, affective dysregulation has an assumed association with reality distortion and the formation of psychotic experiences (van Rossum et al., 2011). It also appears that only one study has investigated the association between cognition and depression in ARMS, and no association was found (Frommann et al., 2011). Therefore, it seems important to clarify the relationship between cognitive deficits and depressive symptoms in ARMS participants.

In the current study, we compared cognitive performance in ARMS and first-episode psychosis (FEP); we also examined if cognitive deficits were associated with clinical symptoms. We hypothesized that cognitive deficits and depressive symptoms would be correlated in ARMS participants, while negative symptoms associated with biological processes in schizophrenia (Baare et al., 1999; Sanfilipo et al., 2000; Roth et al., 2004) would be correlated with FEP participants' cognitive deficits.

2. Methods

2.1. Participants

Participants included 50 individuals with ARMS, 50 patients with FEP, and 30 healthy control (HC) participants who were Japanese-speaking and between 14 and 35 years of age. The exclusion criteria were as follows: (i) serious risk of suicide or violence due to a personality disorder, (ii) current substance dependence, (iii) intellectual disability (IQ < 70), or (iv) neurological disorder, head injury, or any other significant medical conditions associated with psychiatric symptoms.

Participants in the ARMS and FEP groups were recruited from the Sendai At-Risk Mental State and First Episode (SAFE) clinic at Tohoku University Hospital, which is a specialized clinic for early psychosis (Mizuno et al., 2009; Katsura et al., 2014). They were referred to the SAFE clinic by health providers or self-referral. Trained psychiatrists and psychologists assessed them with the clinical and cognitive measures described below.

Participants who met the criteria for ARMS or FEP were evaluated during a baseline examination for future comparative studies examining the clinical follow-up of patients. The data reported herein are baseline data from the ARMS or FEP participants who consented to participation.

The ARMS group was assessed using the Japanese version of the Comprehensive Assessment of At-Risk Mental States (CAARMS-J; Miyakoshi et al., 2009), and diagnosis was confirmed by the clinical team. Participants had no history of DSM-IV psychotic disorders and met one or more of the following criteria for ARMS developed by the Personal Assessment and Crisis Evaluation (PACE) Clinic in Melbourne, Australia (Yung et al., 2004). This procedure has been widely used as standard criteria of ARMS (Fusar-Poli et al., 2012c) and includes the following: (i) attenuated psychotic symptoms (APS), (ii) brief limited intermittent psychotic symptoms (BLIPS; a psychotic episode that resolves within 1 week), and (iii) state and trait risk factors (e.g., a recent decline in functioning, plus either a first-degree relative with psychosis or a schizotypal personality disorder). The distribution of the fulfilled criteria in the ARMS group and their comorbid diagnoses for DSM-IV Axis I are summarized in Table 2. Nine of the ARMS participants made a transition during the follow-up period and were included in the analyses. The mean duration of follow-up was 39.4 months (SD = 18.1, median 40.3).

Participants included in the FEP group met the CAARMS-J criteria for psychosis and had a Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) score of 4 or more on the items for delusion, hallucinatory behavior, grandiosity, suspiciousness, or unusual thought content for more than 1 week. Although participants were experiencing their first episode and had not fully remitted at the time of the neuropsychological examination, they were all sufficiently stable to undergo neuropsychological examination. The distribution of baseline diagnosis in the FEP group is summarized in Table 2.

The HC participants were recruited from a local university. All participants reported that they had never been diagnosed with a psychiatric disorder.

The study was conducted with the authorization of the Ethics Committee of Tohoku University Graduate School of Medicine and Tohoku University Hospital. Written informed consent was obtained from participants 18 years of age or older and from the parents of participants under 18, with written assent from the participants.

2.2. Measures

2.2.1. Clinical assessments

Psychopathology (positive symptoms, negative symptoms, depression, and anxiety) was assessed with the PANSS. Subjective severity of depression was assessed with the Beck Depression Inventory-2nd edition (BDI-II, Beck et al., 1996). Global functioning was assessed with the Global Assessment of Functioning (GAF, American Psychiatric Association, 1994). Social functioning was assessed with the Japanese version of the Social Functioning Scale (SFS, Birchwood et al., 1990; the Japanese version of SFS, Nemoto et al., 2008). Estimated premorbid IQ was assessed using the Japanese version of the National Adult Reading Test (NART, Nelson, 1982; JART, Matsuoka et al., 2006).

2.2.2. Cognitive assessments

The Japanese version of the Brief Assessment of Cognition in Schizophrenia (BACS) was used in the current study (Kaneda et al., 2007). The BACS (Keefe et al., 2004) consists of six subtests of verbal memory, working memory, motor speed, verbal fluency, attention/processing speed, and executive function. All study participants were administered the BACS and raw subtest scores were standardized by creating z-scores. The HC group's means and standard deviations were set to 0 and 1 respectively (Keefe et al., 2004). A composite z-score was calculated by averaging the z-scores from all six subtests and then dividing

Table 1
Demographic data.

	ARMS (n = 50)	FEP (n = 50)	HC (n = 30)	Statistic value	P
Number of males (%)	18 (36.0)	15 (30.0)	13 (43.3)	Exact test	0.49
Age in years at testing, M (SD)	20.1 (4.3)	23.2 (5.9)	21.3 (1.0)	F = 5.83	0.004
Years of education, M (SD)	12.0 (2.1)	12.7 (2.1)	14.4 (0.8)	H = 27.2	<0.001
Premorbid IQ, M (SD)	100.1 (10.5)	99.2 (7.9)	111.9 (6.6) [a]	F = 22.0	<0.001

ARMS: At-Risk Mental State; FEP: First-Episode Psychosis; HC: Healthy Control; premorbid IQ was measured by the Japanese version of the National Adult Reading Test (JART).
[a] Data missing for 1 participant.

Table 2
Distribution of DSM-IV axis I diagnosis and fulfilled ARMS criteria.

ARMS ($n = 50$)		FEP ($n = 50$)	
Diagnosis for DSM-IV axis I			
Mood disorder	38%	Schizophrenia	60%
Major depressive disorder	16%	Schizophreniform disorder	8%
Depressive disorder NOS	16%	Brief psychotic disorder	4%
Bipolar II disorder	2%	Delusional disorder	2%
Mood disorder NOS	4%	Bipolar disorder with	
Anxiety disorder	60%	Psychotic features	4%
Somatoform disorder	8%	Psychotic disorder NOS	22%
Dissociative disorder	4%		
Eating disorder	4%		
Adjustment disorder	4%		
Pervasive developmental disorder NOS	4%		
No axis I diagnosis	2%		
Fulfilled ARMS criteria			
APS	80%		
BLIPS	2%		
State and trait factors	2%		
APS plus state and trait factors	14%		
APS plus BLIPS	2%		

ARMS: At-Risk Mental State; FEP: First-Episode Psychosis; NOS: Not Otherwise Specified; APS: attenuated psychotic symptoms; BLIPS: brief limited intermittent psychotic symptoms.

Table 3
Clinical variables and medication status.

	ARMS ($n = 50$)	FEP ($n = 50$)	Statistic value	P
Clinical variables				
PANSS positive, M (SD)	13.1 (3.3)	18.1 (5.4)	$t = -5.61$	<0.001
PANSS negative, M (SD)	13.0 (5.0)	16.9 (7.0)	$t = -3.25$	0.002
PANSS depression, M (SD)	3.4 (0.9)	2.7 (1.2)	$t = 3.04$	0.003
BDI-II, M (SD)	30.2 (12.3)	23.5 (13.4)	$t = 2.61$	0.01
GAF, M (SD)	47.3 (7.3)	38.9 (9.8)	$t = 4.82$	<0.001
SFS total, M (SD)	106.5 (21.2) [a]	109.0 (24.4) [b]	$t = -0.54$	0.59
Medications				
Antipsychotics, n (%)	13 (26.0%)	44 (88.0%)	Exact test	<0.001
Atypical antipsychotics, n (%)	12 (24.0%)	42 (84.0%)	Exact test	<0.001
Mean dose (CP eq.) (mg) (SD) range (mg)[c]	223.2 (104.9) 75–475 ($n = 13$)	346.7 (227.0) 75–976 ($n = 44$)	$t = -2.75$	0.009
Antidepressants, n (%)	13 (26.0%)	2 (4.0%)	Exact test	0.004
Benzodiazepines, n (%)	25 (50.0%)	30 (60.0%)	Exact test	0.42
Mood stabilizers, n (%)	5 (10.0%)	5 (10.0%)	Exact test	1.00
Anticholinergics, n (%)	5 (10.0%)	8 (16.0%)	Exact test	0.55

ARMS: At-Risk Mental State; FEP: First-Episode Psychosis; PANSS: Positive and Negative Syndrome Scale; BDI-II: Beck Depression Inventory-2nd edition; GAF: Global Assessment of Functioning; SFS: Social Functioning Scale; CP: chlorpromazine; SD: standard deviation
[a] Data missing for 3 participants.
[b] Data missing for 5 participants.
[c] Not including data for those who did not receive antipsychotics.

them by the standard deviation in the HC groups; higher scores reflected higher cognitive performance.

2.3. Statistical analysis

One-way ANOVAs were used to compare the ARMS, FEP, and HC groups for the demographic variables (i.e., age at testing, years of education, estimated premorbid IQ) and BACS scores. Tukey post-hoc tests were used to determine specific group differences.

T-tests were performed to compare the ARMS and FEP groups on PANSS, BDI-II, GAF, and SFS scores, and dose of medicated antipsychotics. Fisher's exact tests were performed to compare the ratio of gender in the three groups, and psychotropic medication in the ARMS and FEP groups. Pearson correlations were calculated to examine the relationships between the indices of cognition and symptomatology in the ARMS and FEP groups. Additionally, we compared correlation coefficients between the two groups using a test for the equality of correlation coefficients.

Statistical analyses were conducted using the statistical package SPSS for Windows (version 17.0). Testing was two-tailed at a 5% significance level.

3. Results

3.1. Demographic data

Table 1 summarizes the demographic data. Age at testing differed significantly among the three groups, and the FEP group was significantly older than the ARMS group ($P = 0.004$). More females than males were included in each group, which was due to the high proportion of female clients in the SAFE clinic. Moreover, the groups differed significantly in years of education and premorbid IQ. The HC group had a higher mean education level and estimated premorbid IQ compared with the ARMS and FEP groups.

3.2. Clinical variables and medication status

Clinical characteristics and medication status in the ARMS and FEP groups are summarized in Table 3. The ARMS participants had significantly more depressive symptoms. In contrast, the FEP samples had significantly more positive and negative symptoms. Moreover, the GAF score in the FEP group was significantly lower than in the ARMS group, whereas no significant difference in the SFS total score was found between the two groups.

Thirteen participants (26%) in the ARMS group were medicated with antipsychotics at testing; this proportion was lower than in the FEP group (44 participants, 88%) but similar to proportions observed in other previous studies (Cannon et al., 2008; Ruhrmann et al., 2010; Fusar-Poli et al., 2013b). Most of the participants in the ARMS and FEP groups were prescribed atypical antipsychotics, with the mean daily dose for those in the ARMS group (n = 13) significantly lower than the dose in the FEP group (n = 44). However, the rate of antidepressant medication in the ARMS group was significantly higher than in the FEP group. There were no significant differences in other medications.

3.3. Cognitive profiles

The results of the BACS are summarized in Table 4. The composite z-scores on the BACS were −2.82 ($SD = 1.88$) in the ARMS group and −2.85 ($SD = 1.43$) in the FEP group. A significant difference in the BACS composite z-scores was observed among the ARMS, FEP, and HC groups ($F = 39.23$, $df = 2, 127$, $P < 0.001$). Follow-up Tukey's tests indicated that the ARMS and FEP groups significantly differed from the HC group ($Ps < 0.001$), while no differences between the ARMS and FEP groups were evident ($P = 0.995$). Moreover, these differences remained significant when age at examination, years of education, dose of antipsychotics, and JART score were controlled. Similarly, on all six subtests, significant differences were found among the three groups. The scores of five of the six subtests (verbal memory, working memory, verbal fluency, attention and processing speed, and executive function) in the ARMS and FEP groups were significantly lower than those of the HC group; no significant differences were found between the ARMS and FEP groups. The score of the motor speed test in the ARMS group was significantly lower than the score in the HC group; no significant differences were found between the ARMS and FEP groups or between the FEP and HC groups.

3.4. Correlations between cognitive profiles and clinical symptoms

The correlations between the cognitive profiles and clinical variables, as well as a comparison of correlation coefficients between the ARMS and FEP groups are summarized in Table 5. Depressive symptoms

Table 4
Z-scores on the BACS in each group.

	ARMS	FEP	HC	F	P	Multiple comparison
BACS subtest	Mean (SD) 95% CI	Mean (SD) 95% CI	Mean (SD) 95% CI			
Verbal memory	−2.36 (2.01) −2.93 to −1.79	−2.15 (1.52) −2.59 to −1.72	0 (1) −0.37 to 0.37	22.11	<0.001	HC > ARMS HC > FEP
Working memory	−2.13 (1.96) −2.69 to −1.58	−2.39 (1.20) −2.73 to −2.05	0 (1) −0.37 to 0.37	26.41	<0.001	HC > ARMS HC > FEP
Motor speed	−0.82 (1.11) −1.14 to −0.51	−0.37 (1.16) −0.70 to −0.04	0 (1) −0.37 to 0.37	5.42	0.005	HC > ARMS
Verbal fluency	−1.26 (1.19) −1.60 to −0.93	−1.30 (0.96) −1.57 to −1.02	0 (1) −0.37 to 0.37	16.68	<0.001	HC > ARMS HC > FEP
Attention and processing speed	−1.32 (1.19) −1.65 to −0.98	−1.58 (0.92) −1.84 to −1.32	0 (1) −0.37 to 0.37	22.76	<0.001	HC > ARMS HC > FEP
Executive function	−1.02 (1.43) −1.42 to −0.61	−1.22 (1.49) −1.64 to −0.79	0 (1) −0.37 to 0.37	7.93	0.001	HC > ARMS HC > FEP
Composite score	−2.82 (1.88) −3.36 to −2.29	−2.85 (1.43) −3.26 to −2.45	0 (1) −0.37 to 0.37	39.23	<0.001	HC > ARMS HC > FEP

ARMS: At-Risk Mental State; FEP: First-Episode Psychosis; HC: Healthy Control; BACS: Brief Assessment of Cognition in Schizophrenia; CI: Confidence Interval; the BACS subtest and composite scores are shown as z-scores normalized by the mean and standard deviation of healthy control participants; Post-hoc multiple comparisons were performed using Tukey's test.

(BDI-II or PANSS depression scores) were significantly related to BACS composite z-scores in the ARMS group; however, no significant correlations were observed in the FEP group. The correlation coefficients between cognitive function and depressive symptoms were significantly different between the two groups. The correlation of PANSS negative scores with the BACS composite z-score was significant in the FEP group, whereas in the ARMS group, the correlation only approached significance. The correlation coefficient between cognitive function and negative symptoms did not differ between the two groups. The BACS composite z-scores and the PANSS positive scores were not correlated in both groups, and the correlation coefficients did not differ between the two groups. Importantly, these results remained significant when partial correlation analysis was conducted with age at examination, years of education, antipsychotic medication, and estimated premorbid IQ controlled.

3.5. Additional analyses for the profiles of converters to psychosis

Baseline BACS scores did not differ for those participants who converted to psychosis and those who did not convert during follow-ups (−1.96 vs. −3.01, $t = -1.55$, $df = 48$, $P = 0.13$). In addition, there were no significant correlations between the cognitive profiles and clinical variables in the converters.

4. Discussion

Cognitive performance in both the ARMS and FEP groups was significantly lower than in the HC group, while no difference between the ARMS and FEP groups emerged. In addition, cognitive deficits were correlated with depressive symptoms in the ARMS group, and with negative symptoms in the FEP group and approached significance in the ARMS group.

The neurocognitive performance in both the ARMS and FEP groups was significantly lower than in the HC group; no significant differences were observed between the ARMS and FEP groups. These findings were confirmed in five of six subdomains; in the motor speed subdomain, there was a difference between the ARMS and HC groups, while there was no difference between the FEP and HC groups. Our finding replicates findings of disturbed motor function in those with ARMS (Niendam et al., 2006; Carrión et al., 2011; Frommann et al., 2011; Ziermans et al., 2014) but not in those with FEP (Mohamed et al., 1999; Addington et al., 2003; Brickman et al., 2004; Addington and Addington, 2008). The reason why no significant difference was found in motor speed between the FEP and HC groups in the current study is unclear; however, previous research investigating motor skill in patients with FEP seems relatively sparse, and the effect sizes in terms of impairment in this subdomain seem diverse among the studies (Aas et al., 2014). Therefore, more research is needed.

The current findings indicated that the cognitive deficits in the ARMS participants were comparable to those in the FEP participants. This is inconsistent with previous studies in which ARMS participants exhibited cognitive deficits between the levels of FEP and healthy participants (Keefe et al., 2006; Eastvold et al., 2007; Jahshan et al., 2010; Kim et al., 2011). The severe cognitive deficits exhibited in the ARMS participants may be partially explained by the correlation analysis interpreted below.

In the ARMS participants, moderate-to-severe depressive symptoms were observed and were correlated with neurocognitive deficits. This is consistent with research indicating that cognitive performance in those with major depressive disorder is significantly deteriorated when compared to healthy controls, and that cognitive deficits in depressed patients are significantly correlated with the severity of their depressive symptoms (Egeland et al., 2003; Lee et al., 2012; McDermott and Ebmeier, 2009; Merriam et al., 1999).

While cognitive performance in ARMS and FEP has been previously compared (Keefe et al., 2006; Eastvold et al., 2007; Simon et al., 2007, 2012; Ozgurdal et al., 2009; Jahshan et al., 2010; Kim et al., 2011; Üçok et al., 2013), the severity of depressive symptoms in ARMS and FEP participants has not been reported. In addition, few studies have examined the relationship between depressive symptoms and cognitive deficits in ARMS participants. Indeed, a single study reported that depressive symptoms in ARMS were not correlated with cognitive functioning (Frommann et al., 2011). Although differences in measurement make it difficult to compare the magnitude of depressive symptoms in the current sample to previous samples, the ARMS group demonstrated severe depressive symptoms, which may have affected the correlation between cognitive deficits and depressive symptoms reported herein.

Table 5
Correlations between the scores of the BACS composite z-score and the clinical variables and comparison of correlation coefficients between the ARMS and FEP groups.

	ARMS		FEP		Test for the equality of correlation coefficients	
	Pearson's r	P	Pearson's r	P	Z	P
PANSS						
Positive	−0.13	0.38	−0.23	0.11	0.52	0.61
Negative	−0.25	0.08	−0.46	0.001**	1.15	0.25
Depression	−0.36	0.010**	0.14	0.35	2.50	0.012*
BDI-II	−0.34	0.02*	0.05	0.75	1.96	0.0499*

ARMS: At-Risk Mental State; FEP: First-Episode Psychosis; PANSS: Positive and Negative Syndrome Scale; BDI-II: Beck Depression Inventory-2nd edition; asterisks indicate significant P-values.
* $P < 0.05$.
** $P < 0.01$.

In contrast, no significant relationship between depressive symptoms and neurocognitive deficits was observed in the FEP group. FEP participants' depressive symptoms were less severe than those in the ARMS group, which may have had less of an effect on cognitive deficits in the FEP group. The relationship between depression severity and cognitive disturbance in psychosis seems more inconsistent than that seen in depressive disorder. A systematic review by Dominguez Mde et al. (2009) demonstrated that depressive dimensions of psychopathology in psychosis were not consistently associated with the neurocognitive measures used. Although the dynamic course and nature of depression in the early phase of psychosis are unclear, there is a possibility that the role and/or cause of depression may differ somewhat at the pre- and post-onset phases of psychosis. As was shown in the current study, ARMS could include more severe depressive symptoms (Pruessner et al., 2011) and be more sensitive to everyday stressors (Palmier-Claus et al., 2012) than FEP, and therefore affective dysregulation may be more prevalent or prominent in ARMS individuals and may compromise cognitive functioning. These characteristics may explain why cognitive–behavioral therapy (van der Gaag et al., 2013) and antidepressants (Cornblatt, et al., 2007) can be effective in this population. In line with this argument, a recent neurodevelopmental model of psychosis posits different neural mechanisms which would be involved at the pre- and post-onset phases of psychosis (Holtzman et al., 2013).

Negative symptoms were significantly correlated with cognitive deficits in the FEP group, which is consistent with previous studies (Bilder et al., 2000; Heydebrand et al., 2004; Rund et al., 2004; Lindsberg et al., 2009). Negative symptoms and cognitive deficits in psychosis have a strong relationship to pathological alterations in the brain (e.g., Baare et al., 1999; Sanfilipo et al., 2000; Roth et al., 2004), and current evidence demonstrates that brain alteration in FEP is more severe than that in ARMS (Takahashi et al., 2009). Therefore, the relationship between negative symptoms and cognitive deficits in the current FEP group may reflect an underlying biological pathology.

We also observed a trend toward an association between cognitive deficits and negative symptoms in ARMS participants. Although previous research in this area is mixed (Niendam et al., 2006; Frommann et al., 2011; Meyer et al., 2014), neurocognitive deficits in ARMS could impact functioning prior to the onset of psychosis (Niendam et al., 2006; Carrión et al., 2011; Meyer et al., 2014) and may predict future psychosis (Bora et al., 2014) or poor functioning (Carrión et al., 2011). At the post-onset phase of psychosis, FEP individuals might present pre-existing developmental and/or illness-acquired cognitive dysfunctions, which might be closely related to the "core" psychotic process (Fusar-Poli et al., 2012a) and negative symptoms. However, since ARMS is heterogeneous in its presentation, longitudinal course, and putative pathophysiology (Fusar-Poli et al., 2013c), and approximately two thirds of those with ARMS do not develop psychosis (Fusar-Poli, et al., 2012c), the proportion of individuals who have a "core" psychotic process would be less in individuals with ARMS than in those with FEP. Thus, it could be assumed that this population is composed of both individuals whose cognitive deficits are more related to negative symptoms and those whose cognitive deficits are more related to depressive symptoms. Accordingly, the clinical characteristics of the present ARMS population (relatively mild negative and moderate-to-severe depressive symptoms) may explain the pattern of cognitive function with depressive and negative symptoms.

In terms of the relationship between cognition and depression in psychosis, most of the evidence so far has been obtained from patients with chronic schizophrenia, and evidence is scarce in early psychosis. Therefore, further studies are needed to elucidate the role and cause of depression at the pre- and post-onset phases of psychosis.

Positive symptoms were not correlated with cognitive deficits in ARMS and FEP participants. Few studies have examined the relationship between positive symptoms and cognitive deficits in ARMS participants. One study demonstrated a relationship between positive symptoms and memory disturbance (Frommann et al., 2011), whereas other studies have not (Niendam et al., 2006; Meyer et al., 2014); the latter was consistent with our results. Similarly, few studies have reported a relationship between positive symptoms and cognitive deficits in FEP participants. The studies that have been conducted in FEP participants are mixed, with some indicating a relationship between positive symptoms and memory disturbance (Heydebrand et al., 2004) or motor speed (Rund et al., 2004), and others failing to demonstrate an association (Bilder et al., 2000; Lindsberg et al., 2009), which was consistent with our results.

This study had several limitations. First, the small sample size in the present study was due to major logistical constraints. With a moderate effect size (0.30), the statistical power for this study is 0.59, which indicates that the current study was underpowered. Therefore, the results of the present study should be considered to be preliminary, and future multicenter studies are needed, involving more patients with ARMS and FEP, to replicate the present findings.

Second, there was a higher ratio of females in the clinical groups. However, previous findings on cognitive performance in ARMS indicate increases in female performance only at the trend-level (Fusar-Poli et al., 2012a), with equivocal findings in schizophrenia or FEP (Rubin et al., 2008).

Third, there was also the possibility of confounding factors caused by the correlational design and possibility of a sampling bias.

Fourth, medications that affect cognitive performance and severity of clinical symptoms may have also influenced the results.

Fifth, since the estimated premorbid IQ in the HC group was higher than that of the general population, the magnitude of the cognitive disturbance in the ARMS and FEP groups may be overestimated. However, the ANCOVA results indicated that these significant differences remained when years of education or JART were controlled, and the pattern of results did not change if we used standardized BACS values from a healthy Japanese sample (Kaneda, 2013).

Finally, the longitudinal courses of ARMS and FEP are heterogeneous; some individuals with FEP fully remit, but others develop chronic psychosis after an acute psychotic episode. Similarly, many individuals with ARMS will not develop FEP. Future work should examine the longitudinal associations between cognitive functioning and clinical symptoms in ARMS and FEP.

Overall, the findings provide clarification for the characteristics of the cognitive deficits in these groups. Specifically, cognitive deficits observed in ARMS may be more heterogeneous than those in FEP. Furthermore, cognition in FEP could be compromised mainly by fundamental biological alterations corresponding to a "core psychotic process" associated with negative symptoms, whereas cognition in ARMS could be associated with two different processes: depression and psychosis. These findings indicate that different pathological processes could lead to cognitive deficits in ARMS and FEP in differing proportions. Specifically, the severity of depressive symptoms in ARMS participants should be examined when evaluating their cognitive deficits. Future criteria regarding ARMS should take into account the heterogeneous nature of the putative pathophysiology of ARMS.

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Contributors

NO and KM designed the study and wrote the manuscript. KM and HM contributed to managing the project. NO, KM, MK, CO, TK, and FI recruited and clinically evaluated the participants. NO, MK, and CO managed the data. NO analyzed the data and KM, MK, CO, TK, YH, AS, KI, and FI assisted NO with analysis and interpretation of the data. They also approved the final manuscript.

Conflicts of interest

All authors declare no conflicts of interest for the work presented here.

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A naturalistic longitudinal study of at-risk mental state with a 2.4 year follow-up at a specialized clinic setting in Japan

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ABSTRACT

Objective: The notion of at-risk mental state (ARMS) is valuable for identifying individuals in a putative prodromal state of psychosis and for reducing conversion risk by pharmacological and psychological interventions. However, further systematic study is required because 1) diagnostic reliability in various clinical settings is not yet established; 2) predictive ability is insufficient; 3) optimal interventions in diversified populations are elusive; and 4) little evidence from non-Western regions exists.

Methods: A naturalistic longitudinal study was conducted at a specialized clinic for early psychosis at a university hospital in Sendai, Japan. Individuals with ARMS (n = 106) were recruited and followed up with case-by-case treatment.

Results: Two-thirds of the participants were psychiatrist referrals, and 83 were followed up for at-least 1 year (mean follow-up = 2.4 years). Fourteen developed psychosis and the estimated (by Kaplan–Meier) cumulative transition rate was 11.1% at 12, 15.4% at 24, and 17.5% at 30 months. At the end-point, about 30% of the 83 followed-up participants including 11 converters received antipsychotic medication. Compared to non-converters, converters showed more severe attenuated psychotic symptoms, including ego-boundary disturbance, formal thought disorder, and emotional disturbance.

Conclusions: The present study replicated previous major Western longitudinal studies, in terms of clinical characteristics, psychosis transition rate, and antipsychotic prescription rate. Our results emphasize the importance of phenomenological assessment of ARMS and intensive care in a clinical setting.

1. Introduction

A new diagnostic framework, at-risk mental state (ARMS), was advocated to identify a putative prodromal state of psychosis (Yung et al., 1996), which would aid in preventing, delaying, and/or ameliorating the onset of schizophrenia and other psychotic conditions. ARMS is usually defined by ultra-high risk [UHR; (Yung et al., 2003)] criteria. UHR factors include attenuated or transient psychotic symptoms, predisposition for psychosis, functional decline, help-seeking behavior, and young age. ARMS has succeeded in identifying individuals with a greater risk of conversion to psychosis, at a conversion rate of 36% after 36 months of follow-up (Fusar-Poli et al., 2012), and in reducing conversion risk by pharmacological and psychological interventions (Amminger et al., 2010; Preti and Cella, 2010; Addington et al., 2012; Fusar-Poli et al., 2012; van der Gaag et al., 2013). On the basis of evidence accumulated over 15 years, the similar concept of "attenuated psychosis syndrome" has been included as a category in the section III of the Diagnostic and Statistical Manual of Mental Disorders fifth edition (DSM-5) as a condition for further systematic study (Tsuang et al., 2013).

One fundamental concern to be addressed is whether ARMS can be reliably diagnosed in ordinary clinical settings (Tsuang et al., 2013). Diagnostic reliability is well established in academic and research settings, but remains uncertain in community and clinical settings (Yung et al., 2010; Tsuang et al., 2013). In addition, predictive validity of ARMS as an indicator for the future development of psychosis requires improvement (Yung et al., 2010). Several clinical, cognitive, and biological features can potentially improve predictive reliability, but the results for

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these features have been inconsistent across different settings. Moreover, further study is required for selecting an optimal intervention for ARMS in a population heterogeneous in presentation, longitudinal course, and treatment response, especially considering the controversies regarding use of antipsychotics (McGorry et al., 2002; McGlashan et al., 2006; Walker et al., 2009). Finally, since the characteristics of ARMS, including the conversion rate, could be affected by the nature of the population (Yung et al., 2006), more investigations in different clinical settings are necessary. Most accumulated evidence comes from longitudinal observations from Western countries including Europe, Australia, and North America (Schultze-Lutter et al., 2007; Cannon et al., 2008; Ruhrmann et al., 2010; Fusar-Poli et al., 2013b; Nelson et al., 2013). Clinically oriented observations from the rest of the world are imperative if the concept is to be generalized to various clinical settings.

In this exploratory, naturalistic longitudinal study, 106 ARMS individuals were examined and followed up for a mean of 2.4 years in a specialized clinic for early psychosis at a university hospital in Sendai, Japan. Our main purposes were to recheck the rate of conversion to psychosis in ARMS individuals in a Japanese clinical setting, and to compare converters with non-converters to find risk factors associated with the transition to psychosis. We additionally investigated baseline clinical characteristics, referral source to the specialized clinic, and treatment history.

2. Methods

2.1. Design and setting

In this prospective naturalistic study with at least one-year follow-up, we assessed baseline characteristics of consecutive ARMS subjects, offered case-by-case treatment based on clinical needs, and examined psychosis transition rate during the follow-up period. The study protocol was reviewed and authorized by the Ethics Committee of Tohoku University Graduate School of Medicine and Tohoku University Hospital. All participants provided written informed consent, or if subjects were under 18, parents provided written informed consent while the participant gave written assent.

Help-seeking participants were recruited through the Sendai ARMS and first episode (SAFE) clinic, established in 2004 as a specialized clinic for ARMS and first-episode psychosis (FEP) at the Department of Psychiatry, Tohoku University Hospital in Sendai (population 1 060 000), Miyagi Prefecture (population 2 320 000), Japan. We launched a website, produced and disseminated leaflets, and provided telephone and email counseling in order to enlighten both experts and non-experts about psychosis intervention and to promote access to the clinic.

2.2. Participants

All referrals between November 2004 and July 2012 were screened for inclusion. Subjects who met one or more of the UHR criteria were said to have ARMS. UHR is essentially composed of an attenuated psychotic symptom (APS) group, a brief limited intermittent psychotic symptom (BLIPS) group, and a trait and state-risk group (Yung et al., 2003).

APS were assessed using the Comprehensive Assessment of ARMS (CAARMS) (Yung et al., 2005), a semi-structured interview designed to evaluate comprehensive psychopathology and determine whether UHR criteria are met. We used the Japanese version validated by our group (Miyakoshi et al., 2009). Additional inclusion criteria were age of 14–35 years (Fusar-Poli et al., 2013b), which includes the age range of maximum risk of transitioning to psychosis. Exclusion criteria were 1) history of previous psychotic disorder or manic episodes that fulfilled the diagnostic criteria of bipolar I disorder specified in the DSM-IV Text Revision (DSM-IV-TR); 2) serious risk of suicide or violence due to personality disorder; 3) substance abuse or addiction within 1 year of inclusion; 4) known intellectual disability (IQ < 70); and 5) neurological disorders, head injury, or any other significant medical conditions associated with psychiatric symptoms.

2.3. Baseline assessments

The initial interview was conducted by a trained psychiatrist; then, CAARMS was administered. UHR subjects who met inclusion criteria and provided consent were subsequently assessed for their psychiatric condition and asked about their demographic background, family history, perinatal and developmental problems, present or past substance use, referral source, and medical history. All participants were clinically followed up by an experienced psychiatrist from the SAFE clinic (KM, TM, FI, NO, MK, TK, and CO), by executing diagnostic interviews, which were reviewed at a consensus meeting. Functioning and subjective depression were assessed with the Global Assessment of Functioning scale (GAF) (Hall, 1995) and the Beck Depression Inventory second edition (BDI-II) (Beck et al., 1996), respectively.

2.4. Interventions

Treatment was not standardized in this study, but was offered according to SAFE guidelines. Briefly, psychiatrists took the central role in practice, collaborating with clinical psychologists and psychiatric social workers. All subjects received the usual supportive counseling, symptom monitoring, psychosocial support, and crisis intervention. Most were offered psychiatrist- or clinical psychologist-run psychotherapy oriented to cognitive behavioral therapy, following the basic principles of Beck (Beck, 1976) and French and Morrison (French and Morrison, 2004). Usually, each session took 30–60 m during the early months of clinical care. Frequency and duration of sessions varied according to individual needs and phase of treatment. As is common in Japanese clinical settings, therapeutic sessions were continued as needed without limitation. Additional psychoeducation and family counseling were offered, where appropriate. Antipsychotics, antidepressants, mood stabilizers, and/or anxiolytics were administered, if necessary. We did not start antipsychotics unless the individuals were clinically unstable and followed the International Clinical Practice Guidelines for Early Psychosis (International Early Psychosis Association Writing Group, 2005). However, if the ARMS individuals were already taking antipsychotics prescribed by previous psychiatrists and preferred to continue them, we also prescribed these antipsychotics at least for the initial treatment phase.

2.5. Outcome measure

After an intake assessment, participants were assessed at baseline and at 6, 12, 18, 24, and 36 months thereafter, if present at the SAFE clinic. All assessments were conducted by the in-charge psychiatrist. The study outcome was the final diagnosis according to the CAARMS criteria. Transition to psychosis was monitored at each treatment session by the in-charge psychiatrist and defined by the CAARMS criteria (i.e., at least one fully positive psychotic symptom several times a week for more than one week). Telephone interviews were conducted when psychiatrists in charge could contact participants who terminated treatment at the SAFE clinic before 12 months. We also investigated end-point medication using clinical records and/or face-to-face or telephone interviews.

2.6. Data analysis

Background and psychopathological profiles of the UHR subjects required calculating mean, standard deviation, and if necessary median for continuous variables, and absolute and relative frequencies for categorical variables. Cumulative transition rates over time were estimated by the Kaplan–Meier method with transition considered as an event.

Baseline characteristics were compared between those individuals who converted to psychosis and those who did not. For numerical variables, Student's t test was applied, and for categorical variables, Fisher's exact test was used. Statistical difference was determined by two-tailed test, with a significance of $p < 0.05$. All statistical analyses were performed using IBM SPSS Statistics ver. 19.0 for Windows.

3. Results

3.1. Participants and ARMS subgroups

Out of 414 individuals referred to or voluntarily contacting the clinic, eight canceled the appointment. Of the remaining 406, 111 met the UHR and 79 met the FEP criteria. Of the 111 at UHR, 106 consenting subjects were enrolled in the study. Fig. 1 illustrates a Venn diagram showing the number of subjects corresponding to each possible combination of the three UHR criteria.

3.2. Baseline demographics

Baseline demographics are summarized in Table 1. The subjects included more women than men. Although nearly three-quarters of the subjects were attending school and 8.5% were employed, only 24.1% of them were doing so consistently. None reported present or past substance use.

The most frequent symptom fulfilling APS criteria by CAARMS was "non-bizarre ideas," and the least frequent was "disorganized speech." Average GAF scores indicated that the participants had severe difficulty with social/role functioning and psychiatric symptoms in general. The mean BDI-II score of 31.9 corresponded to severe depression.

3.3. Outcome measures

Of the 106 participants, 27 (25.4%) discontinued treatment at the SAFE clinic before 12 months. Four moved, six decided to be treated by other psychiatrists, and one opted for oriental medicine. Two dropped out after sufficient recovery from ARMS, and 14 for unknown reasons. Among the 27 discontinued participants, four underwent telephone interviews after 12 months in the outcome analysis. Thus, outcome data were obtained from 83 subjects (78.3%). Mean follow-up days of participants tracked over one year without transition to psychosis was 1167 (median, 993; range, 365–2706). The demographic and clinical variables were not significantly different between the lost 23 and 83 followed-up cases, except for BDI-II scores, which was significantly higher in the former group (37.7 ± 14.9) than the latter (30.5 ± 12.2).

Fourteen (13.2%) of 106 UHR subjects transitioned to psychosis (converters). Ten developed psychosis within the first year, three in the following year, and one developed it after 836 days. The mean interval between inclusion and transition was 263 ± 238 days (median, 196; range, 8–836). Fig. 2 plots the Kaplan–Meier survival curve reflecting the percentage of converters. Cumulative transition rate to psychosis (±SE) was 7.5 ± 2.7% at 6, 11.1 ± 3.3% at 12, 13.8 ± 3.7% at 18, 15.4 ± 4.0% at 24, and 17.5 ± 4.4% at 30 months. Of those who developed psychosis, eight, one, one, and four met DSM-IV-TR criteria for schizophrenia, schizophreniform disorder, delusional disorder, and psychotic disorder not otherwise specified, respectively. Most of the followed-up participants received CBT-oriented psychotherapy in a relatively unstructured manner by psychiatrists in charge, and 13 (15.7%) of 83 followed-up participants received structured CBT by therapists other than the psychiatrists in-charge. Among the 83 followed-up participants, 31 (37.3%) had taken antipsychotics before intake, and 22 (26.5%) of them continuously received antipsychotics at least once

Table 1
Socio-demographic and clinical characteristics of the study sample at baseline (n = 106).

Age (mean ± SD, years)	20.0 ± 4.3
Gender (male/female)	40/66
Education (mean ± SD, years)	11.9 ± 2.4
Married (%)	5 (4.7)
Living with others (%)	96 (90.1)
Place of residence (%)	
Sendai city	54 (50.9)
Miyagi prefecture excluding Sendai	48 (45.3)
Other prefectures	4 (3.8)
Occupation (%)	
Student	77 (72.6)
Employed	9 (8.5)
Housewife	4 (3.8)
Unemployed	16 (15.1)
Present and past substance use (%)	0 (0)
First-degree relative with psychotic disorder (%)	11 (10.4)
CAARMS	
Severity score (mean ± SD)	
Positive symptoms	9.9 ± 3.7
Unusual thought content	2.1 ± 1.7
Non-bizarre ideas	3.0 ± 1.3
Perceptual abnormalities	2.8 ± 1.5
Disorganized speech	1.9 ± 1.2
Over all	55.4 ± 15.3
Fulfilling APS criteria (%)	
Unusual thought content	38 (35.8)
Non-bizarre ideas	79 (74.5)
Perceptual abnormalities	59 (55.7)
Disorganized speech	10 (9.4)
GAF (mean ± SD)	
Symptom	52.1 ± 7.9
Function	49.9 ± 9.4
BDI-II (mean ± SD)	31.9 ± 13.0

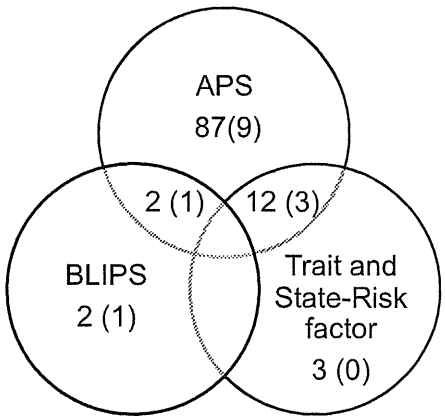

Fig. 1. Number of patients in ARMS groups (numbers in parentheses represent patients developing psychosis in the follow-up period).

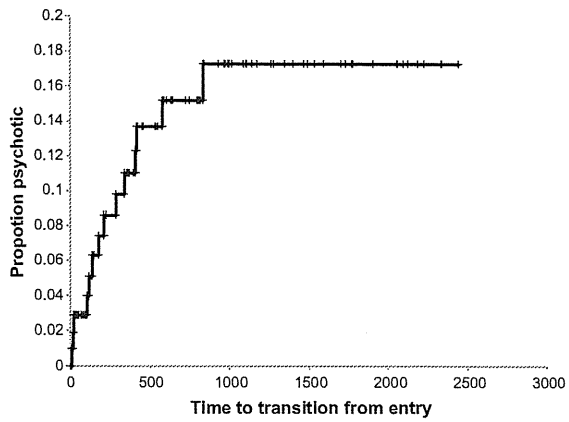

Fig. 2. Transition to psychosis. Kaplan–Meier estimates of proportion of individuals converting to psychosis over time.

during the follow-up period. Of these, six were treated with quetiapine, five with risperidone, one with aripiprazole, one with perospirone, two with olanzapine, two with blonanserin, two with sulpiride, one with zotepine, one with chlorpromazine, and one with levomepromazine. The mean maximum dose was 243 ± 208 mg chlorpromazine equivalents per day. Among the 52 antipsychotic-naïve participants, 17 (32.7%) began receiving antipsychotics at the SAFE clinic. Four were treated with quetiapine, four with aripiprazole, four with perospirone, one with olanzapine, one with blonanserin, and three with sulpiride. The mean maximum dose was 268 ± 190 mg chlorpromazine equivalents per day. At the end-point, 25 (30.1%) of the 83 followed-up participants were receiving antipsychotics, in which 11 (13.3%) of them were converters and 14 (16.8%) were non-converters. Neither therapy with structured CBT nor antipsychotic medication showed a significant difference in conversion rate (p = 1.000 and .777, respectively).

3.4. Comparison between converters and non-converters

Baseline data were compared between converters and non-converters (Table 2). No significant differences between groups were identified on any demographic variables. Regarding CAARMS-measured psychopathology, compared to non-converters, converters showed more severe symptom scores for the "unusual thought content," "disorganized speech," and "emotional disturbance" items. Similarly, converters fulfilled APS criteria more often in the "unusual thought content" and "disorganized speech" items than non-converters. The number of items fulfilling APS criteria was significantly higher in converters than non-converters. GAF-function was lower in converters than non-converters, but not statistically significantly so. Past diagnosis by a previous psychiatrist was not different between groups. Compared to converter, non-converters had received antipsychotics before the SAFE clinic more often, though the difference was not significant. Neither time from first help-seeking behavior to intake, nor time from first contact with a mental health professional to intake, was different between converters and non-converters.

3.5. Referral source and treatment history

Referral source and treatment history are summarized in Table 3. Ninety-one (85.8%) participants had seen at least one psychiatrist prior to visiting the SAFE clinic, and 72 (67.9%) were referred from psychiatrists. One third of the participants were previously diagnosed with, or suspected for, psychosis or schizophrenia; of these, five (5.5%) were previously diagnosed with schizophrenia and one (1.1%) with psychosis, 18 (19.8%) with suspected schizophrenia, and six (6.6%) with suspected psychosis. Fifteen (16.5%) participants were referred as

Table 2
Baseline characteristics of ARMS samples by clinical outcome at follow-up period (n = 83).

Characteristic	Converters (n = 14)	Non-converters (n = 69)	Test statistic[a]	p
Age (mean ± SD, years)	20.1 ± 3.6	19.9 ± 4.5	t = −.14	.889
Gender (male/female)	4/10	24/45		.764
First-degree relative with psychotic disorder (%)	1 (7.1)	8 (11.6)		1.000
Intake group (%)				
APS	13 (92.9)	66 (94.2)		1.000
BLIPS	2 (14.3)	2 (2.9)		.130
Trait and state-risk factor	3 (21.4)	10 (14.5)		.686
CAARMS				
Severity score of each category (mean ± SD)				
Positive symptoms	13.4 ± 4.1	9.3 ± 3.4	t = −3.93	<.001
Unusual thought content	3.7 ± 1.9	1.8 ± 1.4	t = −4.29	<.001
Non-bizarre ideas	3.6 ± 0.9	2.9 ± 1.3	t = −1.98	.052
Perceptual abnormalities	3.1 ± 1.4	2.8 ± 1.6	t = −.67	.504
Disorganized speech	2.9 ± 1.5	1.7 ± 1.1	t = −3.33	.001
Cognitive change concentration/attention	4.4 ± 2.4	3.5 ± 2.0	t = −1.39	.167
Emotional disturbance	5.8 ± 2.6	3.5 ± 2.4	t = −3.21	.002
Negative symptoms	6.2 ± 3.8	6.5 ± 2.9	t = .31	.758
Behavioral change	10.9 ± 4.0	10.0 ± 3.3	t = −.86	.392
Motor/physical changes	5.4 ± 3.5	4.8 ± 2.8	t = −.74	.463
General psychopathology	15.6 ± 6.8	16.8 ± 5.7	t = .71	.478
Over all	61.6 ± 18.0	54.4 ± 14.8	t = −1.61	.112
Fulfilling APS criteria (%)				
Unusual thought content	9 (64.3)	18 (26.1)		.010
Non-bizarre ideas	13 (92.9)	48 (69.6)		.099
Perceptual abnormalities	11 (78.6)	36 (52.2)		.083
Disorganized speech	5 (35.7)	5 (7.2)		.010
Number of items fulfilling APS criteria				<.001
Not fulfilling APS criteria	0	4		
One item	2	35		
Two items	1	19		
Three items	10	10		
Four items	1	1		
GAF (mean ± SD)				
Symptom	49.7 ± 8.7	52.3 ± 7.7	t = 1.15	.253
Function	46.2 ± 5.9	50.0 ± 10.2	t = 1.33	.186
BDI-II (mean ± SD)	29.0 ± 11.4	30.8 ± 11.4	t = .51	.614
Past diagnosis by psychiatrist (%)				
ARMS/suspected ARMS	1 (7.1)	11 (15.9)		.681
Psychosis/suspected psychosis	2 (14.3)	23 (33.3)		.210
Treatment with antipsychotic by previous psychiatrist, Yes/No	3/11	31/37[b]		.137
Time from first help-seeking behavior to intake (mean ± SD, days)	313.7 ± 591.8	481.9 ± 626.8	t = .92	.359
Time from first contact with a mental health professional to intake (mean ± SD, days)	310.0 ± 592.4	394.5 ± 545.6	t = .52	.604

[a] When Fisher's exact test was conducted, statistic was left blank.
[b] One was missing.