Table 1
Demographic and clinical characteristics 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)	20.6 (3.6)	19.0 (3.5)	21.5 (3.4)	34.9 (9.6)	$F(4, 468)=82.69$, $p<0.001$; Sz>controls>UHR-P, UHR-NP, and FEP
M/F	55/32	54/42	24/15	108/54	76/13	Chi-square=19.74, $p<0.001$; M>F in Sz compared with all other groups
Handedness (right/mixed/left)[a]	80/2/5	81/3/10	34/0/4	139/4/17	74/5/6	$p=0.625$, Fisher's exact test
Height (cm)[a]	175.3 (9.7)	170.8 (9.0)	171.9 (9.0)	172.8 (9.4)	174.3 (7.9)	$F(4, 457)=3.25$, $p=0.012$; controls>UHR-NP
Premorbid IQ[a,b]	102.3 (10.5)	96.1 (13.9)	94.8 (12.5)	93.9 (13.6)	95.6 (15.1)	$F(4, 368)=5.08$, $p=0.001$; controls>Sz, FEP, and UHR-NP
BPRS score at intake[a]	–	17.8 (7.0)	18.8 (7.1)	–	–	$F(1, 108)=0.92$, $p=0.586$
SANS score at intake[a]	–	20.9 (14.4)	29.1 (15.5)	–	–	$F(1, 108)=1.16$, $p=0.283$
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)	1414 (147)	1464 (143)	1422 (133)	1441 (130)	$F(4, 467)=1.52$, $p=0.194$

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.

ventricle and the intensity threshold was adjusted to grow the seed so that it filled the ventricle as much as possible. Further seeds were placed in other parts of the ventricle to fill the entire ventricle. The resulting binary image was reconstructed three-dimensionally by ANALYZE software and the volume estimated by volume rendering. Inter-and intra-rater ICCs in a subset of 10 randomly selected brains were over 0.96.

2.5. Statistical analysis

Clinical and demographic differences between groups were examined with one-way analysis of variance (ANOVA) or chi-square test.

The AI length was analyzed using the analysis of covariance (ANCOVA) with ICV and age as covariates, with diagnosis (healthy controls, UHR-NP, UHR-P, FEP, and chronic schizophrenia) and gender as between-subject factors. Chi-square tests, or Fisher's exact tests when expected cell sizes were less than five, were used for assessing the frequency of the AI. Since there were significant group differences in age, gender, and height (Table 1), the healthy controls were then divided into two subgroups: older controls [28 males and 9 females, mean (SD)=35.5 (9.7) years, matched to chronic schizophrenia for age ($F=0.09$, $df=1, 124$, $p=0.765$), gender (chi-square=1.71, $p=0.191$), and height ($F=0.86$, $df=1, 120$, $p=0.355$)] 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, $p=0.104$; height, $F=1.58$, $df=1, 210$, $p=0.210$) and both UHR groups (age, $F=2.98$, $df=2, 182$, $p=0.053$; gender, chi-square=0.53, $p=0.768$; height, $F=2.36$, $df=2, 180$, $p=0.097$)]. The statistical conclusions reported here (the prevalence and length of the AI) did not change when we separately analyzed the younger groups (younger controls, FEP patients, and UHR subjects) and older groups (older controls and chronic schizophrenia patients).

To explore the relation of the AI with ventricular enlargement, the volumes of the lateral ventricles were analyzed using ANCOVA with age and ICV as covariates, and the AI (presence versus absence) as a between-subject factor. The volumes of the lateral ventricles were log-transformed because of their skewed distribution. Each diagnostic group was not separately treated for this analysis because of small number of subjects without AI especially for the UHR ($N=2$) and healthy ($N=2$) subjects. Post hoc Tukey honestly significant difference (HSD) test was employed. The correlation between the length of the AI and the volumes of the lateral ventricles (log) was examined for each diagnostic group using Pearson's partial correlation controlling for age and ICV.

The relationship between the AI length and age was examined using Spearman's rank correlation coefficients. For the patients with FEP and chronic schizophrenia, the correlation between the AI length and illness duration or daily medication dosage was also analyzed. Statistical significance was defined as $p<0.05$ (two-tailed).

3. Results

3.1. Demographic characteristics

Comparison of the groups revealed significant group differences in age, gender, height, and premorbid IQ (Table 1). Males were taller [$F(1, 460)=306.27$, $p<0.001$] and older [$F(1, 471)=5.85$, $p=0.016$] than females, and premorbid IQ was higher in females than in males [$F(1, 371)=5.43$, $p=0.020$]. There was no gender difference in handedness. 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. Length and prevalence of the AI

ANCOVA of AI length revealed significant main effects for diagnosis [$F(4, 461)=19.96$, $p<0.001$] and gender [$F(1, 461)=12.27$, $p=0.001$].

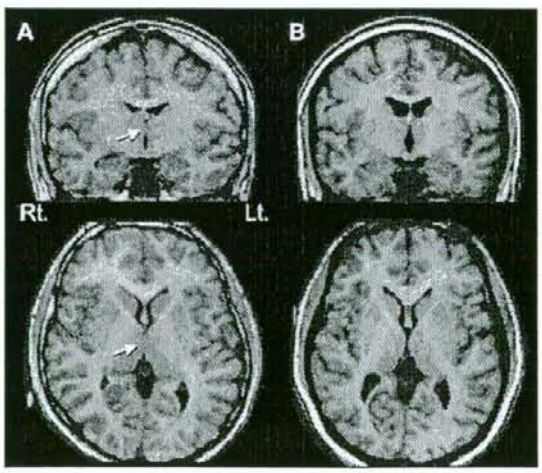

Fig. 1. Coronal (upper) and axial (lower) views of the T1-weighted MR images (0.9375-mm slice thickness) in subjects with (A) and without (B) the adhesio interthalamica (AI). Arrows indicate the position of the AI.

Table 2
Prevalence and length of the adhesion interthalamica (AI)

	AI absent [a]	AI length (mm) [b]
	N(%)	mean (Sd)
Controls (N=87)	2 (2.3)	13.8 (3.7) [c]
Male (N=55)	2 (3.6)	13.1 (4.0)
Female (N=32)	0 (0)	15.1 (2.5)
UHR without psychosis (N=96)	2 (2.1)	11.4 (2.8)
Male (N=54)	2 (3.7)	11.0 (3.1)
Female (N=42)	0 (0)	12.0 (2.3)
UHR with psychosis (N=39)	0 (0)	12.1 (3.1)
Male (N=24)	0 (0)	12.0 (3.2)
Female (N=15)	0 (0)	12.3 (3.0)
First-episode psychosis (N=162)	10 (6.2)	11.1 (3.5)
Male (N=108)	8 (7.4)	10.7 (3.7)
Female (N=54)	2 (3.7)	11.9 (3.1)
Chronic schizophrenia (N=89)	19 (21.3) [d]	7.4 (4.3) [e]
Male (N=76)	17 (22.4)	7.0 (4.2)
Female (N=13)	2 (15.4)	9.3 (4.0)

UHR, ultra high-risk group.
[a] Significantly more common in males than in females.
[b] Significantly longer in females than in males.
[c] Significantly longer than all other groups.
[d] Significantly more common than all other groups.
[e] Significantly shorter than all other groups.

Post hoc tests indicated that the chronic schizophrenia patients had a shorter AI than all other groups ($p<0.001$), and that both UHR groups (UHR-NP, $p<0.001$; UHR-P, $p=0.026$) and FEP patients ($p<0.001$) had a shorter AI than controls. The AI length did not differ among four subgroups of the FEP patients [$F(3, 152)=0.58$, $p=0.630$]. Males had a shorter AI than females ($p<0.001$), but there was no gender-by-diagnosis interaction [$F(4, 461)=1.12$, $p=0.347$].

There was a significant difference in the prevalence of the AI between the groups ($P<0.001$, Fisher's exact test); its absence was significantly more common in the patients with chronic schizophrenia than in the FEP patients, both UHR groups, and controls (Table 2). The chronic schizophrenia patients without an AI ($N=19$) were receiving significantly larger amounts of antipsychotic at the scanning [$F(1, 87)=4.07$, $p=0.047$] and tended to have longer illness duration [$F(1, 86)=3.53$, $p=0.063$] as compared with the patients with an AI ($N=70$). The prevalence of an absent AI did not differ among the subgroups of FEP patients [8.7% (4/46) in schizophrenia, 3.5% (2/57) in schizophreniform psychosis, 5.9% (2/34) in affective psychosis, and 8% (2/25) in other psychoses] ($p=0.717$, Fisher's exact test). The AI was absent in 9.5% (29/305) of males and 2.8% (4/142) of females, showing a significant gender difference ($p=0.012$, Fisher's exact test).

When only schizophrenia patients (46 first-episode and 89 chronic patients) were included in the analyses, there was no group difference in the length of the AI between first-episode [mean=10.7 mm (SD=3.7)] and chronic [mean=7.4 mm (SD=4.3)] patients [$F(1, 129)=0.70$, $p=0.403$]. However, the chronic patients had a trend towards a higher prevalence of the absent AI compared with first-episode patients ($p=0.064$, Fisher's exact test).

The comparison of the ventricular volumes between the subjects with ($N=440$) and without ($N=33$) an AI showed a significant main effect of AI [$F(1, 469)=35.69$, $P<0.001$], with the subjects missing an AI having larger lateral ventricles than the subjects with an AI (Tukey HSD test, $P<0.001$).

3.3. Correlational analysis

There was a negative correlation between AI length and age for patients with chronic schizophrenia ($rho=-0.341$, $p=0.001$), FEP

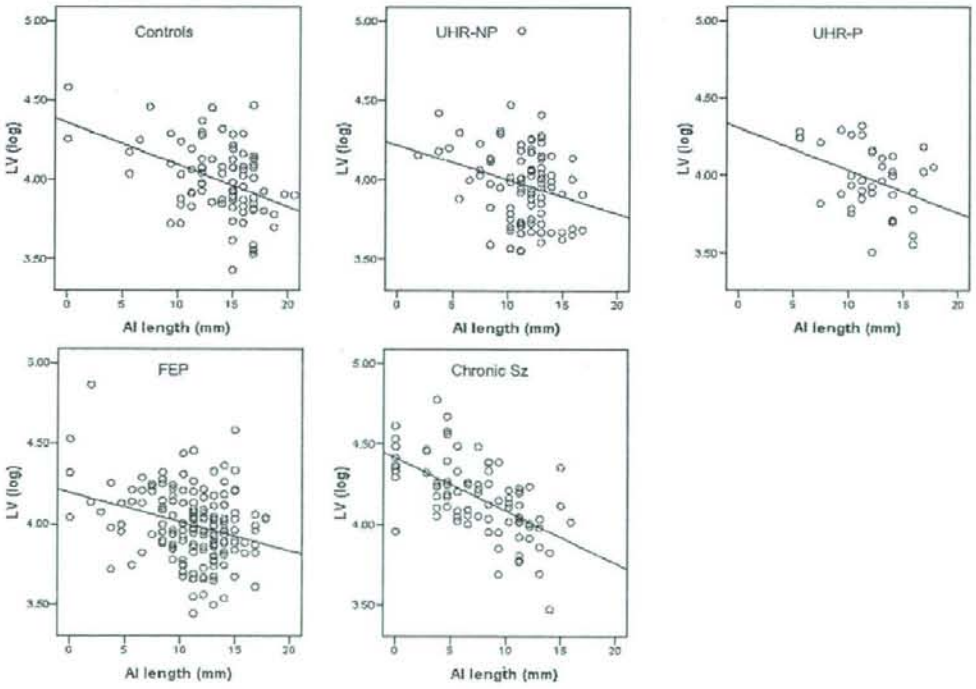

Fig. 2. Scatter plots for the length of the adhesio interthalamica (AI) and lateral ventricular (LV) volume. Abbreviations: FEP=first-episode psychosis; Sz=schizophrenia; UHR-P=ultra high-risk individuals who developed psychosis; UHR-NP=ultra high-risk individuals who did not develop psychosis.

(*rho*=−0.194, p=0.013), and healthy controls (*rho*=−0.337, p=0.001). For the patient groups, the AI length was negatively correlated with illness duration (chronic schizophrenia, *rho*=−0.282, p=0.008) and daily medication dosage (chronic schizophrenia, *rho*=−0.254, p=0.034; FEP, *rho*=−0.208, p=0.009).

The AI length was negatively correlated with ventricular enlargement in all the diagnostic groups (controls, *rho*=−0.351, p<0.001; UHR-NP, *rho*=−0.250, p=0.015; UHR-P, *rho*=−0.412, p=0.011; FEP, *rho*=−0.313, p<0.001; and chronic schizophrenia, *rho*=−0.552, p<0.001) (Fig. 2), while our previous study of the lateral ventricular volume in the same sample (Pantelis et al., 2008) indicated significant group difference [$F(3, 473)=7.17$, $p<0.001$]; compared with the controls, ventricular enlargement was 43.9% greater in chronic schizophrenia, 11.9% larger in FEP and 3.3% larger in UHR subjects.

4. Discussion

To our knowledge, this is the first MRI study to report AI changes in UHR subjects. The main findings were: (i) AI length was commonly shorter in patients with psychotic disorders and UHR individuals as compared with controls; (ii) the AI findings did not differ between the UHR subjects who did and did not later develop psychosis; (iii) the AI changes were more prominent in chronic schizophrenia patients compared with FEP patients; and (iv) there was a negative correlation between the AI length and lateral ventricular enlargement in all the diagnostic groups.

4.1. Methodological issues

The prevalence of an absent AI in this study [17.0% (23/135) in the first-episode and chronic schizophrenia patients and 2.3% (2/87) in the controls] was comparable with or rather lower than that in previous MRI studies [4.7–34.6% in the patients and 5.9–22.3% in the controls (de Souza Crippa et al., 2006; Erbagci et al., 2002; Meisenzahl et al., 2000, 2002; Nopoulos et al., 2001; Shimizu et al., 2008; Snyder et al., 1998; Takahashi et al., 2008, in press)]. This wide variance in the prevalence of AI missing may be partly due to differences among previous studies in imaging techniques, criteria used to define the AI as absent/present, and sample sizes or characteristics (e.g., race, gender distribution, first-episode or chronic patients). For example, several studies defined the AI as present if it could be identified in at least two coronal slices (de Souza Crippa et al., 2006; Erbagci et al., 2002; Nopoulos et al., 2001; Snyder et al., 1998), but differences in slice thickness might lead to conflicting results. In fact, two MRI studies with relatively thick slices (3 mm), which could potentially miss a small AI, reported a higher prevalence of the absent AI (Erbagci et al., 2002; Snyder et al., 1998). This study is strengthened by the larger sample size and the use of thinner MRI slices, compared with those in some previous studies. Nevertheless, the rate of AI absence in the healthy controls in this study was even lower than that in recent high-resolution MRI study [3/51 controls (Shimizu et al., 2008)], which could detect smaller AIs compared to previous studies. Thus, our result of unexpectedly low prevalence of AI missing in healthy controls would require further replication.

4.2. AI changes in psychotic disorders

Although the length of the AI seems to be related to age or gender also in healthy comparisons, we replicated that the patients with psychotic disorders exhibit a shorter AI and higher prevalence of AI missing (Erbagci et al., 2002; Nopoulos et al., 2001; Shimizu et al., 2008; Snyder et al., 1998; Takahashi et al., 2008), consistent with the notion that improper development in midline neural circuits may explain the diverse symptoms of schizophrenia (Andreasen et al., 1994). This notion is also supported by the relationship between AI absence or shorter length and clinical symptomatology in schizophrenia (Meisenzahl et al., 2000, 2002; Takahashi et al., 2008). The midline nuclei of the thalamus including the AI have efferent connections with the amygdaloid nuclei (Graff-Radford, 1997) and are involved in the regulation of the dopamine release of the basal ganglia (Romo et al., 1984). Low thalamic D2/D3 receptor binding (Buchsbaum et al., 2006) as well as thalamic volume reduction (Andreasen et al., 1994; Ettinger et al., 2001) implicates deficits of the thalamic dopaminergic system (Sanchez-Gonzalez et al., 2005) in schizophrenia. Our findings further suggest that the AI malformation itself is present in a rather diverse population with psychotic symptoms, such as affective psychosis or other psychoses. This possibility should be further confirmed on a larger and well-characterized sample of patients.

4.3. AI changes as vulnerability

Consistent with previous observations in our UHR (Yücel et al., 2003) and other clinical high-risk (Borgwardt et al., 2006) subjects, the present results suggest that the high-risk subjects share, at least partly, gross brain morphologic anomalies with patients with florid psychosis. Our results also indicate that although shorter length of the AI is present prior to the onset of psychosis, they do not identify individuals who will subsequently develop psychosis. This suggests that the AI changes are associated with an increased risk of psychosis rather than representing a predictive marker of those who will subsequently convert to psychosis. Our previous study in subjects with schizotypal personality disorder, who have a higher incidence of developing psychosis than the general population (Fenton and McGlashan, 1989), also revealed evidence of AI absence or shorter length similar to those found in established schizophrenia (Takahashi et al., in press). Interestingly, first-degree relatives of schizophrenia patients (Seidman et al., 1999) or schizotypal subjects (Byne et al., 2001) share the thalamic volume reduction with schizophrenia patients. Although not supporting the role of the AI, one recent MRI study in twins with and without schizophrenia suggested the thalamic abnormalities to be related to genetic liability for schizophrenia (Ettinger et al., 2007). Since the development of the AI occurs around 13 to 14 weeks of gestation (Rosales et al., 1968), these previous observations and results from the current study suggest that the AI findings could be a marker of disturbed neural networks including the thalamic and related regions during neurodevelopment, which might be core components of the vulnerability to psychotic disorders.

4.4. Possible non-neurodevelopmental AI changes

The present and previous findings of the association between AI and ventricular volume in healthy subjects and psychotic patients (Meisenzahl et al., 2002; Snyder et al., 1998; Takahashi et al., 2008) support the notion that the AI develops during early gestation in concert with prominent features of the ventricular system (O'Rahilly and Müller, 1990; Rosales et al., 1968). On the other hand, these findings can be interpreted as indicative of an effect of age-related ventricular enlargement on the AI, because the AI also undergoes increasing atrophy with age (Rosales et al., 1968). In fact, we found a significant effect of age on AI length in our sample. In addition to the consistent evidence for progressive ventricular enlargement in schizophrenia (reviewed by Pantelis et al., 2005), our own data have indicated that these progressive changes occur soon after the onset of psychosis and result in evident ventricular enlargement in chronic schizophrenia (Berger et al., 2007b; Pantelis et al., 2008). The current results of prominent AI changes in chronic schizophrenia patients compared with FEP patients as well as a negative correlation between the AI length and illness duration or medication dosage are likely to parallel these ventricular findings after the onset. The observation of the inverse correlation between ventricular volume and AI length may

potentially be explained by the increased loss of glial cells with the onset and progression of the disorder and is in line with a recently proposed neurobiological model of onset of psychosis (Berger et al., 2003, 2007a). Taken together, our findings indicate that the AI findings in psychosis cannot be fully explained by abnormal neurodevelopment but may also reflect ongoing atrophy of the AI after the onset of psychosis possibly due to the illness itself and/or effect of antipsychotics, and may be associated with or even be consequent on other progressive brain structural changes.

4.5. Limitations

A few possible confounding factors should be taken into account. First, the participants in this study were not matched for age and gender between the groups. The AI has been implicated in early neurodevelopment, but it also undergoes atrophy with age as mentioned above (Rosales et al., 1968). A sexual dimorphism of the AI has also been reported in healthy subjects (Allen and Gorski, 1991). We therefore used age as a control variable in all analyses involving AI length. In addition, there was no gender-by-diagnosis interaction in AI length in this study. Moreover, 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. Nevertheless, the possibility exists that the sampling issue (e.g., IQ) might have biased our results. Secondly, detailed clinical data of the patients with FEP and chronic schizophrenia such as the symptomatology at the scanning, cumulative dose of antipsychotics, or information on obstetric complications were not available, representing a limitation of this study. Finally, as mentioned above, methodological differences between this study and other studies in criteria used to define the AI as absent/present limit the comparability of the present study. However, this methodological issue did not affect our main findings based on AI length.

5. Conclusion

We found that the ultra high-risk individuals for developing psychosis share the AI shorter length with patients with florid psychosis, supporting its role as a neurodevelopmental marker related to vulnerability to psychopathology. However, the current results of prominent AI changes in chronic schizophrenia patients compared with patients with first-episode psychosis suggest that AI findings in psychotic disorders also reflect progressive brain changes related to ongoing atrophy of the AI after the onset of illness. Additional longitudinal studies would be essential for the understanding of the nature of AI changes in the course of psychotic disorders.

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Prevalence of large cavum septi pellucidi in ultra high-risk individuals and patients with psychotic disorders

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Abstract

An increased prevalence of large cavum septum pellucidum (CSP), a marker of midline neurodevelopmental abnormality, has been reported in schizophrenia. However, not all studies have been able to replicate this finding and very few studies have been conducted in large samples. In the current study, magnetic resonance imaging was used to assess the presence of an abnormal CSP in 162 patients with first-episode psychosis (FEP), 89 patients with chronic schizophrenia, 135 ultra high-risk (UHR) individuals, and 87 controls. The prevalence of a large CSP (>5.6 mm) did not differ between the groups (9.3% of the FEP patients, 11.2% of the chronic schizophrenia patients, 11.1% of the UHR individuals, and 11.5% of the controls). The length of the CSP was not associated with sulcal morphology of the anterior cingulate cortex (ACC), suggesting different biological processes responsible for the CSP enlargement versus ACC folding. These findings suggest that the CSP is not a neurodevelopmental marker of psychosis and cast doubt over the notion that it plays a major role in the neurobiology of psychosis.

Keywords: Cavum septum pellucidum; Magnetic resonance imaging; Neurodevelopment; High-risk; Schizophrenia; Affective psychosis

1. Introduction

A cavum septum pellucidum (CSP) is considered to be a normal anatomical variant, but an abnormally large CSP has been implicated in disorders of fetal neurodevelopment (Rakic and Yakovlev, 1968). Several magnetic resonance imaging (MRI) studies have reported an increased prevalence of a large CSP in schizophrenia or affective psychosis (Degreef et al., 1992a,b; DeLisi et al., 1993; de Souza Crippa et al., 2006; Kasai et al., 2004; Kwon et al., 1998; Nopoulos et al., 1997). Such findings have been considered to be consistent with a neurodevelopmental pathology of psychotic disorders

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(Weinberger, 1987), but have not been consistently replicated (e.g., Hagino et al., 2001; Takahashi et al., 2007). In addition, it remains unclear if midline brain abnormalities are specific to different types of psychotic illness (Brisch et al., 2007; Jurjus et al., 1993; Kasai et al., 2004; Shioiri et al., 1996).

Our previous MRI study in ultra high-risk (UHR) individuals (Yücel et al., 2003), 30–40% of whom made the transition to psychosis within 12 months (Yung et al., 2003, 2004), as well as a study by Borgwardt et al. (2006), who used similar criteria to recruit clinical high-risk group, has shown that individuals at high-risk for developing psychosis exhibit similar brain morphologic anomalies to patients with established psychotic disorders. These findings presumably represent a vulnerability to psychopathology as a consequence of early neurodevelopmental insult (Pantelis et al., 2005). However, the few MRI studies which have focused on the CSP in clinical high-risk subjects (Choi et al., 2008; Borgwardt et al., 2007) or genetically at-risk individuals (offspring and siblings of schizophrenia patients) (Choi et al., 2008; Keshavan et al., 2002; Rajarethinam et al., 2008) have found no difference in the prevalence of a large CSP between patients with first-episode psychosis, high-risk subjects, and healthy comparison subjects (Table 1).

In summary, the current evidence suggests that individuals at risk for psychosis do not exhibit larger CSP while patients with schizophrenia do. There are several possible explanations for these findings. Firstly, it may be that a large CSP develops in the course of schizophrenia. The CSP is thought to arise in early neurodevelopment, but our data suggested that the age-related ongoing atrophy of the adhesio interthalamica (AI), another midline brain structure implicated in early neurodevelopment, is accelerated in schizophrenia (Takahashi et al., in submission). Although differences in imaging techniques or definition of abnormal CSP among the reports limit the comparability, the prevalence of the large CSP in patients with first-episode psychosis (16.2%, 12 of 74 patients) reported by Kasai et al. (2004) is lower than that in chronically medicated schizophrenia patients reported by the same group (26.7%, 4 of 15 patients) (Kwon et al., 1998). Secondly, these discrepant findings may reflect varying patient and control numbers and different study populations. Especially, high-risk groups examined in past studies might include a broad range of subjects (i.e., healthy subjects, patients with schizophrenia spectrum, and subjects who will develop psychosis). If only the high-risk subjects who subsequently develop psychosis exhibit abnormal CSP, this sample heterogeneity could partly explain the negative findings in previous studies. However, no study to date has investigated large numbers of patients across various illness stages (i.e., high-risk individuals with and without later onset, first-episode and chronic schizophrenia) compared to a control group and all scanned using the same MRI sequence.

The current study sought to address these limitations of previous studies by examining the prevalence of a large CSP in a relatively large sample of patients with first-episode psychosis, patients with chronic schizophrenia, and ultra high-risk individuals who did (UHR-P) and did not (UHR-NP) develop psychosis compared with control subjects. Based on our previous observations (Yücel et al., 2002, 2003), we also investigated the relationship between the CSP and surface morphology of the anterior cingulate cortex (ACC), another marker of early neurodevelopment.

2. Methods

2.1. Subjects

One hundred and sixty-two patients with first-episode psychosis (FEP), 89 patients with chronic schizophrenia, 135 individuals with ultra high-risk (UHR) for developing psychosis, and 87 healthy comparisons participated in this study (Table 3). Inclusion criteria and demographic characteristics of the same sample, recruited from 1994 to 2001, have been described previously (Garner et al., 2005; Velakoulis et al., 1999, 2006).

Briefly, the FEP patients were recruited from the Early Psychosis Prevention and Intervention Centre, were aged 16–30 years, and were currently psychotic as reflected by the presence of at least one symptom (delusions, hallucinations, disorder of thinking or speech other than simple acceleration or retardation, or disorganized, bizarre, or markedly inappropriate behavior). Patients with chronic schizophrenia were recruited from the Adult Mental Health Rehabilitation services of the North Western Mental Health Program, Melbourne, and healthy volunteers were recruited from similar socio-demographic areas as the patients by approaching ancillary hospital staff and through advertisements. DSM-III-R diagnoses (American Psychiatric Association, 1990) of patients with FEP and chronic schizophrenia were based on chart review and 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, the FEP patients were further divided into four subgroups: schizophrenia ($n=46$), schizophreniform psychosis ($n=57$), affective psychosis ($n=34$),

Table 1
Prevalence of large CSP in psychotic disorders and high-risk subjects demonstrated by recent high-resolution MRI[a]

Authors	Slice thickness	Criteria	Sample	Mean age	Prelavence[b]
Nopoulos et al. (1997)	1.5 mm	≥4 slices	52 Sz+3 schizoaffective disorder	29.7	10.9% (n=6)
			75 controls	27.3	1.3% (n=1)
Fukuzako and Kodama (1998)	NA	>5 mm	72 Sz	28.7	9.7% (n=7)
			41 controls	32.0	4.9% (n=2)
Kwon et al. (1998)	1.5 mm	≥4 slices	30 Sz (15 first-episode, 15 chronic)	32.5	23.3% (n=7)
			16 Aff	23.7	12.5% (n=2)
			21SPD	38.7	14.3% (n=3)
			46 controls	32.3	8.7% (n=4)
Nopoulos et al. (1998)	1.0 mm	≥6 slices	24 childhood onset Sz	14.6	12.5% (n=3)
			95 controls	11.7	1.1% (n=1)
Hagino et al. (2001)	1.0 mm	≥6 slices	86 Sz	29.3	7.0% (n=6)
			79 controls	24.0	3.8% (n=3)
Rajarethinam et al. (2001)	1.0 mm	≥6 slices	73 Sz	35.3	4.1% (n=3)
			43 controls	35.6	2.3% (n=1)
Keshavan et al. (2002)	3.0 mm	≥1 slice[c]	40 first-episode Sz	24.5	10.0% (n=4)
			19 genetic high-risk subjects	14.9	0% (n=0)
			59 controls	21.4	11.9% (n=7)
Kasai et al. (2004)	0.9375 mm	≥6 slices	33 first-episode Sz	24.7	18.2% (n=6)
			41 first-episode Aff	22.8	14.6% (n=6)
			56 controls	24.0	7.1% (n=4)
de Souza Crippa et al. (2006)	1.0 mm	≥6 slices	38 chronic Sz	29.9	21.1% (n=8)
			38 controls	29.7	2.6% (n=1)
Borgwardt et al. (2006, 2007)	3.0 mm	NA	30 first-episode psychosis	30.3	3.3% (n=1)
			37 clinical high-risk subjects	27.9	5.4% (n=2)
			26 controls	22.5	0% (n=0)
Dickey et al. (2007)	1.5 mm	≥4 slices	20 female SPD	28.8	25.0% (n=5)
			29 female controls	30.8	6.9% (n=2)
Flashman et al. (2007)	1.0 mm	≥6 slices	57 Sz+17 schizoaffective disorder+3 psychosis NOS	34.3	14.3% (n=11)
			55 controls	32.7	9.1% (n=5)
Takahashi et al. (2007)	1.0 mm	≥6 slices	154 Sz (mainly chronic)	28.0	6.5% (n=10)
			47 SPD	25.0	10.6% (n=5)
			163 controls	27.0	7.4% (n=12)
Choi et al. (2008)	0.45 mm	≥14 slices	23 genetic high-risk subjects	23.4	0% (n=0)
			30 clinical high-risk subjects	22.1	13.3% (n=4)
			34 controls	23.3	14.7% (n=5)
Rajarethinam et al. (2008)	1.0 mm	>4 mm	89 first-episode Sz	23.8	16.9% (n=15?)
			64 genetic high-risk subjects	15.2	NA
			120 controls	22.1	14.2% (n=17?)

Aff, affective psychosis; NA, not available; NOS, not otherwise specified; SPD, schizotypal personality disorder; Sz, schizophrenia.
[a] For other studies using relatively thick MRI slices (>3 mm), see Nopoulos et al. (1997).
[b] Calculated as follows: 100×(number of subjects with a large CSP/number of all subjects).
[c] CSP was assessed using the grading system, but the incidence of CSP (≥1 slice) is shown here.

and other psychosis (e.g., psychosis not otherwise specifies, brief psychosis) (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. The PACE Clinic was established in 1994 to identify young people at clinical risk for developing a first psychotic episode within a short follow-up period (Yung et al., 2004). Health professionals, school welfare coordinators, teachers, other mental health service providers, and social service workers refer potential subjects to the Clinic (Phillips et al., 1999, 2002). The UHR identification criteria are outlined in Table 2, and the rationale for these criteria has been previously described (Yung et al., 2004). All UHR subjects were aged 14–30 years, had not experienced a previous psychotic episode. Individuals were included in the study if they had been followed up for at least 12 months

Table 2
Ultra high-risk intake and exit criteria

Intake criteria

Group 1: Attenuated psychotic symptoms

- Presence of ≥1 of the following symptoms: idea of reference, magical thinking, perceptual disturbance, paranoid ideation, and odd thinking and speech (score of 2–3 on unusual thought content subscale, 1–2 on hallucinations subscale, 2–3 on suspiciousness subscale, or 1–3 on conceptual disorganization subscale of BPRS)
- Held with a reasonable degree of conviction, as defined by a score of 2 on the CASH rating scale for delusions
- Frequency of symptoms is several times per week
- Change in mental state present for ≥1 week and not longer than 5 years

Group 2: Brief limited intermittent psychotic symptoms (BLIPS)

- Transient psychotic symptoms: presence of ≥1 of the following: idea of reference, magical thinking, perceptual disturbance, paranoid ideation, and odd thinking and speech [score of ≥4 on unusual thought content subscale, ≥3 on hallucinations subscale, ≥4 on suspiciousness subscale (or it is held with strong conviction, as defined by a score of ≥3 on CASH rating subscale for delusions) or ≥4 on conceptual disorganization subscale of BPRS]
- Duration of episode of <1 week
- Symptoms resolve spontaneously
- The BLIPS must have occurred within the past year

Group 3: Trait and state risk factors

- First-degree relative with a psychotic disorder or schizotypal personality disorder or individual has schizotypal personality disorder
- Significant decrease in mental state or functioning maintained for ≥1 month (reduction in GAF scale of 30 points from premorbid level)
- The decrease in functioning occurred within the past year

Exit criteria: acute psychosis

- Presence of ≥1 of the following symptoms: hallucinations (defined by a score of ≥3 on hallucinations subscale of BPRS), delusions (defined by a score of ≥4 on unusual thought content subscale of BPRS or ≥4 on suspiciousness subscale of BPRS), or it is held with strong conviction, as defined by a score of ≥3 on CASH rating scale for delusions or formal thought disorder (defined by a score of ≥4 on conceptual disorganization subscale of BPRS)
- Frequency of symptoms is at least several times a week to daily
- Duration of mental state change is >1 week

BPRS = brief psychiatric rating scale; CASH = comprehensive assessment of symptoms and history; GAF = global assessment of function scale. People are included if they meet criteria for one or more of the three groups.

(mean = 13 months, maximum = 44 months). After baseline scanning, they were monitored regularly for the onset of psychotic symptoms based on operationalized criteria (Yung et al., 2004) and were then divided into subgroups according to the outcome at 12 months; 39 UHR subjects (28.9%) developed psychosis (UHR-P) and 96 (71.1%) did not (UHR-NP). Family history of psychosis in a first- or second-degree relative was assessed by the interview using the Family Interview for Genetic Studies (FIGS; Maxwell, 1992) as well as interviews with a family member (Wood et al., 2005); 58 and 51 UHR subjects had a positive and negative family history, respectively. Clear evidence of family history was not available for 26 UHR subjects.

All subjects were physically healthy, and none had a lifetime history of serious head trauma, neurological illness, serious medical or surgical illness, or DSM-III-R criteria of alcohol or substance abuse or dependence. Control subjects with a personal or family history of psychiatric illness were excluded. 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

MR 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 = 0.9375 × 0.9375 × 1.5 mm). The intracranial volume (ICV) was measured to correct for differences in head size as previously described (Eritaia et al., 2000; Velakoulis et al., 2006); the four groups (FEP, chronic schizophrenia, UHR, and controls) did not significantly differ in their ICV volumes (Table 3).

For the assessment of the CSP, the image data were processed using the software package Dr. View (AJS, Tokyo, Japan). Brain images were realigned in three dimensions and reconstructed into contiguous coronal images, with a 0.9375-mm thickness, perpendicular to the AC-PC line. Then, one rater (TT) counted the number of coronal slices where a cavum was seen. A CSP equal to or greater than 6 slices (approximately 5.6 mm) was defined as large (Kasai et al., 2004). All analyses were undertaken with the rater blinded to the subject diagnosis. Inter- (TT and IH) and intra-rater intraclass correlation coefficients (ICCs) in 30 randomly selected brains were over 0.96.

As described in detail previously (Yücel et al., 2002, 2003), ACC surface morphology was assessed on several para-sagittal slices using MEDx 3.0 (Sensor System, Stirling, VA, USA). Briefly, depending on the presence or absence of the paracingulate sulcus and its antero-posterior extent, three types of ACC sulcal patterns were identified (prominent, present, or absent). Based on the combination of left and right paracingulate sulcus morphology, an asymmetry index was assigned to each individual in terms of a leftward, symmetric, or rightward bias.

Table 3
Demographic characteristics of the participants

	Controls (n=87)	UHR (n=135)	FEP (n=162)	Chronic Sz (n=89)	Group comparisons
Age (years)	26.9±10.1	20.1±3.6	21.5±3.4	34.9±9.6	F (3, 469)=109.63, p<0.01; Sz>all other groups, controls>UHR and FEP
Male/female	55/32	78/57	108/54	76/13	Chi-square=19.39, p<0.01; males>females in Sz compared with all other groups
Handedness (right/mixed/left) [a]	80/2/5	115/3/14	139/4/17	74/5/6	Chi-square=5.26, p=0.51
Height (cm) [a]	175.3±9.7	171.1±9.0	172.8±9.4	174.3±7.9	F (3, 458)=4.22, p=0.012; controls>UHR
Premorbid IQ [a, b]	102.3±10.5	95.7±13.5	93.9±13.6	95.6±15.1	F (3, 369)=6.72, p<0.01; controls>all other groups
Duration of illness (days) [c]	–	–	54±87 (median=27)	4673±3613 (median=3757)	F (1, 245)=260.44, p<0.01; Sz>FEP
Drug (mg/day, CP equivalent) [d]	–	–	154.7±118.2	842.9±715.8	F (1, 224)=136.66, p<0.01; Sz>FEP
Intracranial volume (cm^3)	1450±143	1428±147	1422±133	1441±130	F (3, 468)=0.84, p=0.47 [e]

The values represent means±SDs. CP, chlorpromazine; FEP, first-episode psychosis; Sz, schizophrenia; UHR, ultra high-risk group.

[a] Data missing for some participants.

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

[c] Defined as the number of days between the first assessment and magnetic resonance imaging. Data on 4 patients (1 with chronic Sz and 3 with FEP) were not available.

[d] Atypical neuroleptic dosages were converted into CP equivalents using the guideline by Woods (2003). 25 patients (19 with chronic Sz and 6 with FEP) had incomplete medication data.

[e] ANCOVA with age as a covariate and group as a between-subject factor was used.

2.3. Statistical analysis

Clinical and demographic differences between groups were examined with one-way analysis of variance (ANOVA) or chi-square test. Post hoc Scheffé's test was employed to follow-up the significant main effects yielded by ANOVAs. The relationship between the length of the CSP and age, height, or premorbid IQ was examined for each group using Pearson's partial correlation controlling for ICV. For this analysis, the subjects without CSP (17 FEP, 11 chronic schizophrenia, 9 UHR, and 9 control subjects) were regarded as having a CSP of 0.5 mm and then the length of the CSP was log-transformed because of their skewed distribution (Takahashi et al., 2007).

Chi-square tests, or Fisher's exact tests when expected cell sizes were less than five, were used for assessing the frequency of the large CSP. The length of the CSP (log) was analyzed using the analysis of covariance (ANCOVA) with ICV and age as covariates, with diagnosis (FEP, chronic schizophrenia, UHR, and control subjects) and gender as between-subject factors.

ACC data were available for 354 subjects (111 FEP, 71 chronic schizophrenia, 97 UHR, and 75 control subjects). In order to examine the relationship between the CSP and ACC folding pattern, the length of the CSP (log) was analyzed by ANCOVA 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 CSP length and paracingulate asymmetry index (leftward, symmetric, and rightward) was also analyzed using the same model. The effect of the large CSP on these ACC sulcal features was tested by chi-square tests or Fisher's exact tests for each diagnostic group. Statistical significance was defined as $p<0.05$.

3. Results

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 3). Premorbid IQ was negatively correlated with the length of the CSP only for healthy comparisons ($r=-0.243$, $p=0.035$), but the correlation was not significant after Bonferroni correction. The length of the CSP was not correlated with age and height in all the diagnostic groups.

Overall frequency of the CSP in the present sample was 90.3% (427/473); there was no difference in its prevalence among the diagnostic groups [89.5% (145/162) in the FEP patients, 87.6% (78/89) in the chronic schizophrenia patients, 93.3% (126/135) in the UHR individuals, and 89.7% (78/87) in the controls] (chi-

square=2.29, $p=0.51$) (Fig. 1). The prevalence of a large CSP in the present sample was 10.6% (50/473) [9.3% (15/162) in the FEP patients, 11.2% (10/89) in the chronic schizophrenia patients, 11.1% (15/135) in the UHR individuals, and 11.5% (10/87) in the controls], with no between group differences (chi-square=0.46, $p=0.93$). There was no difference in large CSP prevalence among subgroups of the FEP patients [6.5% (3/46) of schizophrenia, 11.1% (6/57) of schizophreniform psychosis, 17.6% (6/34) of affective psychosis, and 0% (0/25) of other psychosis; Fig. 2] ($p=0.12$, Fisher's exact test) or between the UHR-P [7.7% (3/39)] and UHR-NP [12.5% (12/96)] individuals ($p=0.42$, Fisher's exact test). For the UHR subjects whose family history of psychosis was available ($n=109$), no difference in large CSP prevalence was found between the UHR subjects with [13.8% (8/58)] and without [7.8% (4/51)] a family history ($p=0.32$, Fisher's exact test).

ANCOVA of the CSP length (log) revealed no significant main effects for diagnosis [$F(3, 463)=0.73$, $p=0.537$] and gender [$F(1, 463)=0.65$, $p=0.421$]. There was no diagnosis-by-gender interaction [$F(3, 463)=0.66$, $p=0.579$]. The CSP length did not differ among subgroups of the FEP patients [$F(3, 152)=1.17$, $p=0.324$] or between the UHR-P and UHR-NP individuals [$F(1, 129)=0.04$, $p=0.844$].

For the relationship between the CSP and ACC folding pattern, ANCOVAs of the CSP length revealed no main effects of ACC sulcal features [left sulcal pattern, $F(2, 340)=2.83$, $p=0.060$; right sulcal pattern, $F(2, 340)=1.91$, $p=0.149$; and asymmetry index, $F(2, 340)=0.64$, $p=0.527$] or diagnosis-by-ACC [left sulcal pattern, $F(6, 340)=0.62$, $p=0.711$; right sulcal pattern, $F(6, 340)=1.04$, $p=0.397$; and asymmetry index, $F(6, 340)=0.35$, $p=0.912$] interactions. Fisher's exact tests did not reveal any significant effects of the large CSP on these ACC sulcal features.

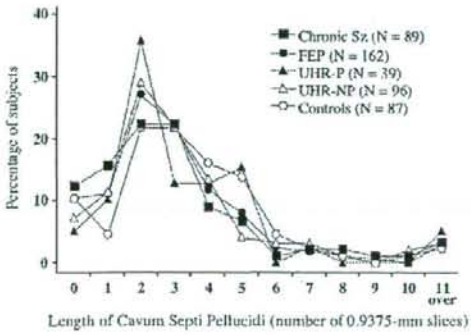

Fig. 1. Length of the cavum septi pellucidi (CSP) in 473 participants. A CSP equal to or greater than 6 slices (approximately 5.6 mm) was defined as large. Abbreviations: FEP=first-episode psychosis; Sz=schizophrenia; UHR-P=ultra high-risk individuals who developed psychosis; UHR-NP=ultra high-risk individuals who did not develop psychosis.

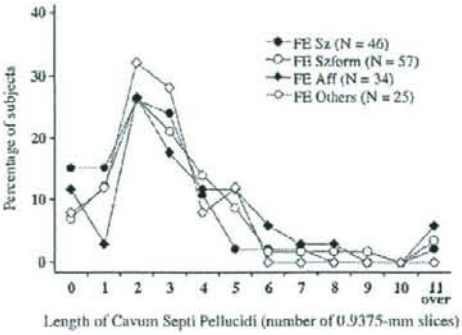

Fig. 2. Length of the cavum septi pellucidi (CSP) in subgroups of 162 patients with first-episode psychosis. Abbreviations: FE=first-episode; Sz=schizophrenia; Szform=schizophreniform; Aff=affective psychosis; other=other psychoses.

4. Discussion

The current study did not identify any difference in the prevalence of a large CSP between patients with first-episode psychosis, patients with chronic schizophrenia, or ultra high-risk (UHR) subjects as compared with healthy comparisons. In addition, there was no group difference in the length of the CSP. Our findings suggest that a large CSP is not a neurodevelopmental marker of psychosis and that there is no diagnostic specificity of abnormal CSP between schizophrenic versus affective psychoses.

As discussed elsewhere (Takahashi et al., 2007), the wide variance in the prevalence of the large CSP in schizophrenia reported to date (approximately from 4% to 30%) could be partly explained by differences in imaging techniques or sample characteristics (e.g., race, gender) among the reports, but our results were comparable with those in a large Japanese sample balanced by gender, where 6.5% (10/154) of schizophrenia patients and 7.4% (12/163) of healthy comparisons had a large CSP (Takahashi et al., 2007).

In this study, we found no CSP abnormalities in UHR subjects compared with healthy subjects. In addition, family history of psychosis is not likely to affect the CSP findings in our UHR sample. These observations are consistent with previous MRI studies showing no higher prevalence of a large CSP in other clinical (Borgwardt

et al., 2007; Choi et al., 2008) or genetic (Choi et al., 2008; Keshavan et al., 2002; Rajarethinam et al., 2008) high-risk cohorts. The findings of this study are also generally in line with our previous MRI study that reported no difference in the prevalence of the large CSP between subjects with schizotypal personality disorder (SPD) [10.6% (5/47)] and healthy controls (Takahashi et al., 2007), as SPD subjects with decreased functioning also fulfill the UHR criteria (Yung et al., 2004). These findings suggest that abnormal CSP may not play a major role in the vulnerability to psychosis, but do not exclude the possibility that other midline cerebral malformations such as an absence of the adhesio interthalamica (AI) (de Souza Crippa et al., 2006) could be a marker of neurodevelopmental pathology of psychotic disorders. In fact, only 4/473 subjects (chronic schizophrenia patients) in the current study presented both large CSP and absence of the AI (unpublished data), implicating that abnormalities in these two midline structures are not closely associated with each other in the neurobiology of psychotic disorders.

Studies of incidental MRI findings in patients with schizophrenia are largely consistent with the findings of the current study. Our own work in a large sample has identified no increased prevalence of incidental findings in UHR individuals or first-episode patients compared to control subjects (Lubman et al., 2002; Patrikios, unpublished data). Nearly half of the patients with chronic schizophrenia exhibited incidental findings, which were more likely to have been acquired rather than have developmental origin (Lubman et al., 2002).

Our previous studies of the surface morphology in anterior cingulate cortex (ACC) have shown that UHR individuals share abnormalities in ACC sulcus/gyral folding, which are thought to represent prenatal neurodevelopmental insult, with established schizophrenia (Yücel et al., 2002, 2003). In this study, we found no direct relationship between the CSP and ACC surface morphology, suggesting different biological processes responsible for these potential neurodevelopmental markers. Given that ACC folding is almost complete by the third trimester of gestation (Chi et al., 1977) while fusion of the septi pellucidi occurs within 3–6 months of birth (Shaw and Alvord, 1969), our findings in these structures may provide a clue to the timing of neurodevelopmental abnormalities underlying psychosis.

Several limitations of the current study should be taken into account. First, we examined the anterior–posterior length of the CSP in this study but did not assess its overall size. As suggested by Choi et al. (2008), the possibility exists that only the length of the CSP might not be sensitive enough to detect existing changes of the CSP in high-risk subjects or patients with psychotic disorders. However, a recent study using high-resolution MRI indicated that the length the CSP is highly correlated with its volume in both schizophrenia and healthy control subjects (de Souza Crippa et al., 2006). Second, detailed clinical data of the patients with FEP and chronic schizophrenia such as the symptomatology at the scanning, family history of psychosis, or information on obstetric complications were not available, representing a limitation of this study. In addition, a larger number of subjects with a large CSP are needed to further explore the association of an abnormal CSP with other structural abnormalities (Kwon et al., 1998; Kasai et al., 2004) and with the cognitive and clinical characteristics (Flashman et al., 2007; Nopoulos et al., 2000) of psychotic disorders.

In conclusion, we found no difference in the prevalence of abnormal CSP as well as the size of the CSP in a large sample of chronic schizophrenia, first-episode psychosis, and ultra high-risk individuals compared with healthy comparisons. The negative findings of the present study thus suggest that the CSP is unlikely to be related to the neurobiology of emerging psychotic disorders.

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Contributors

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

Conflict of interest

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

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統合失調症の二段階仮説

Two-hit hypothesis of schizophrenia

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要 約

脳形態画像研究などにより，統合失調症においては，神経発達早期の障害を示唆する変化だけでなく，特に病初期に進行性の脳形態変化が生じていることが報告されている。そこから，発達早期の固定的病変がfirst hitとなって脆弱性を形成し，さらに思春期の頃に何らかの病的過程がsecond hitとして加わることにより発症に至る，と説明する二段階仮説(two-hit hypothesis)が提唱されている。この仮説の根拠となる知見について，脳形態画像研究を中心に概説し，二段階仮説の1つである側頭ー前頭二段階発症仮説を紹介する。

Key Words 統合失調症，神経発達障害仮説，二段階仮説(two-hit hypothesis)，磁気共鳴画像(MRI)，進行性形態変化，早期介入

はじめに

統合失調症の病態仮説として，神経発達障害仮説が広く知られている。これは，そもそもは統合失調症患者の脳に認められる軽微な形態学的変化が，胎生期を中心とした神経発達の障害に由来すると考えられるいくつかの所見に基づいて，1980年代後半に提唱されたものである[1,2]。すなわち，CTスキャンなどにより脳室拡大が病初期から認められること，病理学的検索により嗅内皮質などに胎生中期の障害を示唆する神経細胞の配列異常などがみられること，グリオーシスが認められないこと，などである。提唱された当初は，発達早期の固定的病変を想定し，それによって神経系が成熟を迎える思春期後になって機能障害が引き起こされるという考えにより，統合失調症の発症を説明していた。しかし，その後の磁気共鳴画像(MRI)による研究の進展により，統合失調症では特に病初期に進行性の脳形態変化が生じていることが強く示唆され，従来の神経発達障害仮説は修正を迫られるに至った。そこで，発達早期の固定的病変(first hit)が脆弱性を形成し，さらに思春期の頃に何らかの病的過程(second hit)が加わることにより統合失調症が発症するという考えが登場した(図1)。これが二段階仮説(two-hit hypothesis)の骨子である[3]。しかし，病的過程の生じる時期ではなく，遺伝要因(first hit)と環境要因(second hit)の双方が関与することで発症を説明し，two-hit hypothesisと呼ぶこともある[4]。ここでは前者の立場から，脳形態画像における知見を中心に，統合失調症の二段階仮説に関して述べたい。

1 早期神経発達障害(first hit)

脳形態画像において統合失調症患者に認められる形態

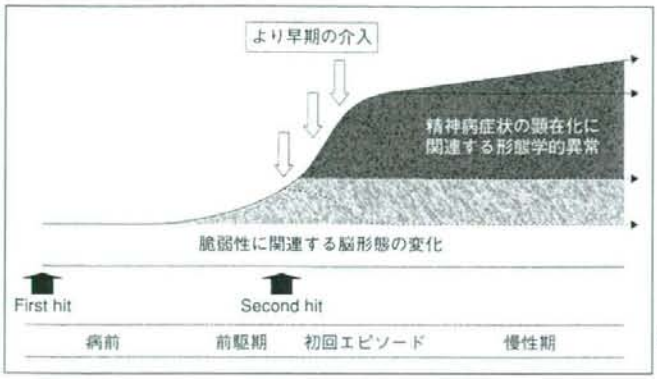

図1．統合失調症の縦断的経過と想定される脳形態の変化

学的変化としては，前頭－側頭辺縁－傍辺縁領域を中心に，広範囲に認められる軽度の体積減少が多く報告されている[3]。これらの体積変化は，早期の神経発達障害によっても生じているかもしれないが，後述のように病初期の進行性変化が加わっている可能性を考えると，どこまでが早期神経発達障害によるかを識別することはできない。ほかに繰り返し報告されている所見として，大脳半球間の左右差の異常がある。脳の左右差は出生時にすでに明瞭に認められることから，側頭平面体積の左半球優位性の減退あるいは逆転などの所見は，早期神経発達障害を示すものと解されてきた[6]。しかし，上側頭回では左側優位の進行性変化が報告されているので[7,8]，体積を指標にする限り，これも純粋な早期神経発達障害の所見とはいいがたい。一方で，透明中隔腔の拡大，視床間橋の欠損などの大脳正中構造の異常は，胎生期の発達異常を示唆する所見といえるであろう[9,10]。また大脳脳回のgyrification index(脳断面において脳溝まで入り込んで計測した脳周囲長の，脳回の頂点を結んで計測した脳周囲長に対する比)が増大し，hypergyriaが認められるという所見[11]や，左前部帯状回の脳溝の分枝(paracingulate sulcus)が減少し，左半球優位性が失われているという所見[12]も，比較的早期の神経発達障害の指標と考えられる。これらの所見から，統合失調症では早期神経発達障害により，大脳半球間あるいは半球内の機能的結合に何らかの変化が生じていることが示唆される。

患者の発病前に検査を行うことは困難なので，脳体積の変化も含め，発病前から存在すると推定される脆弱性に関わる脳形態変化について窺い知るために，遺伝的リスクのある者(患者の近親者)や統合失調症スペクトラム障害患者を対象にした検討が行われている。患者親族では，メタ解析により，海馬あるいは扁桃体－海馬複合体の体積減少が最も一致した所見として認められている[13]。われわれが検討した統合失調型障害患者では，扁桃体，海馬，上側頭回などの体積減少が見出された[14-16]。

2 思春期以降の進行性形態変化(second hit)

慢性統合失調症患者で報告されている脳形態異常のほとんどは，初回エピソード患者においてすでに認められることから[5]，かつては発症後の進行性変化はないか，あってもわずかと考えられていた。しかし，初回エピソード患者を対象にした研究であっても，罹病期間が数年に及ぶ者も含んでいることが多いため，発症後に生じる変化を明らかにするためには，同一患者の縦断的比較が必要となる。MRIによる脳室系の縦断的検討では，進行性変化を認めているものが多い。脳実質についての初回エピソード患者の縦断的研究は多くなく，結果も一致しているとはいえないが，そのなかで進行性形態変化が比較的明瞭に示されている部位は上側頭回である。Kasaiら[7,8]によると，13例の初回エピソード患者において，1.5年の間に，左上側頭回体積が9.6%減少し，細分化して計測すると左Heschl回体積が6.9%，左側頭平面体積が7.2%減少したという。われわれは，縦断的検討ではないが，未

治療精神病期間(duration of untreated psychosis；DUP)が長いほど左側頭平面体積が小さいことを見出しており[17]，病初期(特に未治療期間)にこの部位で進行性体積減少が生じていることが示唆される。この進行性変化のメカニズムは不明であり，N-methyl-D-aspartate(NMDA)受容体機能低下に起因するグルタミン酸による興奮毒性も想定されているが[9]，議論のあるところである[18]。

前頭葉に進行性変化が認められるかが問題であるが，結果は一致していない。73例という比較的多数の発症早期の患者を3年余り追跡したHoら[19]の研究では，健常者との間に有意差が認められているものの，前頭葉体積の年間変化率は健常者が+0.8%であったのに対し，統合失調症患者では−0.2%と非常に軽微な変化である。前頭前野などにおいては，思春期後もシナプス剪定(pruning)や髄鞘化などの成熟過程が進行していると考えられる。統合失調症患者では，このような成熟過程が過剰に生じているという仮説[20]があり，それを示唆する研究報告もあるが，今後明らかにすべき重要な課題である。

近年，精神病への早期介入が推進されるとともに，初回エピソードより早期のat risk mental state(ARMS)，すなわち前駆状態の可能性がある者を対象とした検討が行われつつある。Pantelisら[21]は，ARMSの基準を満たし，後に統合失調症などの精神病を発症した10例について，1回目のスキャン(発症の平均172日前)と2回目のスキャン(発症の平均202日後)のvoxel-based morphometry(VBM)による縦断的比較を行い，両側の帯状回，左側の内側側頭葉(海馬傍回と紡錘状回)，眼窩前頭皮質，小脳の灰白質減少を報告した。前駆状態において，脳形態の変化の進行が初めて示されたことは意義深く，今後はこのような研究を推進し，より多数例について詳細な検討を行う必要がある。

3 側頭−前頭二段階発症仮説

われわれは，軽度あるいは萌芽的な統合失調症様症状を有するが，明らかで持続的な精神病(陽性)症状を示さないことを特徴とする統合失調型障害患者の脳形態について，統合失調症患者との比較検討を行ってきた[22]。その結果，統合失調型障害と統合失調症に共通する，脆弱性に関わると考えられる変化は，前述のように扁桃体，海馬，上側頭回などの体積減少であった[14-16]。一方，前頭前野においては，統合失調症では広範囲に体積減少が認められたのに対し，統合失調型障害ではほぼ保たれていた[14,15]。これらの所見から，統合失調症では前頭前野の変化が加わることにより，側頭葉の変化が臨床的に顕在化し，精神病症状として発現しているという病態生理が想定できる。そこから患者親族における研究結果なども考慮し，統合失調症においては，脆弱性としての側頭葉の変化が先行し，思春期に前頭葉の変化が加わることによって発症に至るという縦断的過程が生じているのではないか，というのが側頭—前頭二段階発症仮説[23,24]である。この仮説では，前頭葉の変化が陰性症状を引き起こすとともに，陽性症状の顕在化をもたらすと考えることにより，多くの統合失調症患者に陰性症状と陽性症状の両方が認められることも説明できる。この仮説は，統合失調症の発症前後における，縦断的な脳形態画像研究によって検証される必要がある。

おわりに

統合失調症において，first hitを形成すると考えられる胎生期などの神経発達早期における障害には，遺伝要因と周産期合併症，母体のウイルス感染などの環境要因の両方が関与すると考えられる。発症前後における進行性変化については未解明な部分が多いが，脳の成熟過程の過剰進行，神経毒性によるシナプス成分の退縮など，複数の機序が仮説として提唱されている。そうなると，second hitにとどまらずthird hitを想定する必要があるかもしれない。このような進行性変化にも，遺伝要因と，ストレスや乱用薬物など種々の環境要因との双方が関与していると考えられる。近年，統合失調症の疾患感受性候補遺伝子が数多く見出され[25]，脳形態を中間表現型とした関連研究が盛んになっている。上述のように，統合失調症における脳形態変化の意義は多様であると考えられるので，遺伝子との関連も縦断的経過を考慮して検討される必要がある。さらに，エピジェネティックな機序

による遺伝－環境相互作用が重要な役割を演じているかもしれない。最後に，統合失調症に対する早期介入を推進する意義は，二段階仮説に基づけば，second hit を最小限にすることによって長期転帰の改善を図ることにある，といえるであろう（図1）。

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就任講演

統合失調症の脳病態に即した早期診断・早期治療の実現のために

鈴木道雄

Toward early diagnosis and treatment of schizophrenia based on its brain pathology

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要　旨

統合失調症は思春期から成年早期に好発し，約120人に1人が罹患する疾患であり，慢性化した場合は健全な社会生活が困難となることが多い。統合失調症の病因を明らかにし，より有効な治療法を確立することは，精神医学におけるもっとも重要な課題のひとつである。磁気共鳴画像（MRI）を用いて，脳形態の観点から，統合失調症の発症機序を明らかにしようとする研究と，MRIによる統合失調症の客観的な補助診断法を開発する試みの概略を述べた。また，統合失調症の早期診断・早期治療を推進するために行っている「こころのリスク相談」および「こころのリスク外来」について紹介した。さらに統合失調症の長期予後を改善するために，脳形態などの神経生物学的変化を改善する治療法の可能性について述べた。

Key words : schizophrenia, brain morphology, MRI, early intervention

■はじめに

統合失調症は思春期から成年早期に好発し，約120人に1人が罹患する疾患である（生涯発病率は約0.85%）。世界にはおよそ2千400万人の患者がいるといわれ，日本における患者数は約73万4千人，入院患者は約20万人である（厚生労働省平成14年患者調査）。薬物療法および心理社会療法は進歩しつつあるものの，依然として，症状の持続や再燃に苦しみ，社会的機能やQOLの低下を余儀なくされる患者が少なくない。病態仮説として神経発達障害仮説が有力であり，脆弱性をもった個体に，さまざまなストレスが作用して，特徴的な症状が出現すると考えられる。しかし，脆弱性の本態や発症に関わる脳機構は充分に解明されていない。統合失調症の病因を明らかにし，有効な治療法を確立することは，精神医学におけるもっとも重要な課題のひとつである。

■脳形態画像による統合失調症の病態生理

X線CTや磁気共鳴画像（MRI）の普及に伴い，研究が活発に行われた結果，統合失調症患者の脳に軽度ながら形態学的異常が存在することは共通の認識となった。前頭―側頭―辺縁系領域を中心に体積減少が認められること[1]など，その特徴もある程度明らかになってきた[2]。しかしながら，脳の構造的変化の成因，生じる時期，脳機能との関連や臨床的意義などについてはまだ不明な点が多い。

統合失調症スペクトラムという概念は，統合失調症の原因はさまざまであり，複数の脆弱性遺伝子と環境因子との相互作用により，多彩な表現型が生じるという考えに基づいている。統合失調型障害schizotypal disorderは，統合失調症スペクトラムの中核とも考えられ，統合失調症と類似した，より軽度の萌芽的な症状を特徴とし，明らかで持続性の精神病症状を呈さない。また統合失調症患者の近親者に比較的多くみられる。統合失調症スペクトラムに共通の神経生物学的特徴は，統合失調症への脆弱性を形成し，さらに何らかの病的変化が加わることにより統合失調症が発症すると考えられる。

そこで，我々は，統合失調型障害患者と統合失調症患者の脳形態について，MRIを用いて詳細な比較検討を行った[3]。その結果，扁桃体，海馬，上側頭回などの領域では，統合失調型障害と統合失調症にほぼ同様の体積減少がみられた[4~6]。これらは統合失調症スペクトラムに共通の形態学的基盤であり，おそらく脆弱性を表すと考えられる。一方，前頭前野は，統合失調症では広範囲に体積減少が認められたのに対し，統合失調型障害では

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ほぼ保たれていた[4,5]。以上の所見から，統合失調症において，前頭前野の広範な体積減少に伴う抑制機能障害によって，側頭葉の異常が臨床的に顕在化し，精神病症状として発現しているという病態生理が想定できる。この点をさらに解明するためには，統合失調症の発症前後における，縦断的追跡研究が必要である。また下頭頂小葉（縁上回と角回）の体積も，統合失調型障害では保たれ，統合失調症では減少していた[7]ことからは，前頭頭頂ネットワーク，あるいは上側頭回も含む異種モダリティー連合野の機能障害と，精神病症状との関連も示唆される。なお統合失調型障害において，中前頭回など一部の領域に認められた体積増大の所見[5]は，精神病症状の発現回避に関与する可能性がある。

■思春期健常者における脳の形態学的発達

統合失調症の発症に関連する縦断的な脳形態の変化があるとすれば，正常発達における脳形態の変化，特に統合失調症の好発年齢にさしかかる思春期における変化を明らかにすることが重要と考えられる。我々は，MRIにより，思春期早期（13～14歳）の健常者と思春期後期（18～20歳）の健常者の脳形態を比較した。その結果，思春期における前頭前野を中心とした灰白質減少とともに，海馬・扁桃体の体積増大が認められた[8]。

前頭前野などにおいては，思春期およびその後もシナプス剪定（pruning）や髄鞘化などの成熟過程が進行していると考えられる。統合失調症では，このような成熟過程が過剰に生じているという仮説があるが，pruningなどの脳機構には不明な点が多い。また，海馬・扁桃体における体積増大の所見から，辺縁系でも思春期に形態学的発達が進行していることが示唆される。思春期における海馬や扁桃体の成熟過程への何らかの侵襲が，統合失調症への脆弱性の形成あるいは促進に関与している可能性が考えられる。前頭前野と辺縁系の間には，密接な解剖学的・機能的連絡があるので，このネットワークの形態学的成熟の異常が，統合失調症の発症に関連するのかもしれない（図1）。思春期における脳の正常発達とその障害の脳機構を明らかにすることは，統合失調症の発症機序を解明するための，非常に重要な課題である。

■統合失調症の客観的補助診断法の開発

統合失調症の診断は，現代においても，臨床症状と経過だけに基づいて行われている。脳形態MRIは，侵襲性が低く，安静を保つだけで被検者に特段の努力を要求せず，再現性の高い豊富な客観的情報を提供し，比較的短時間で施行が可能であることが利点である。このようなMRIを統合失調症の補助診断に応用できれば有意義である。しかし，実際のところ，統合失調症に認められる脳形態の変化は，統計学的に検出される軽微なものであり，健常者とオーバーラップが大きいため，そのままでは診断に役立たない。そのため，これまでは，脳形態画像はもっぱら統合失調症の病態研究に用いられ，臨床診断に応用しようという試みは，ほとんど行われて来なかった。しかし，我々は解析法を工夫することにより，MRIを統合失調症の客観的補助診断法として応用することを試みてきた[9]。

まず統合失調症患者57例と健常対照者47名のMRIから，乳頭体をよぎる冠状断面において，大脳縦裂，側脳室体部，第三脳室，側脳室下角，シルビウス裂，上側頭回灰白質および白質，側頭葉全体の左右合わせて14の関心領域の面積を計測し，それらの値を用いて健常対照者と統合失調症患者の判別分析を行った。その結果，男性患者の30例中24例（80%），男性健常者の25名中20名（80%）が正しく判別された。また女性患者の27例中21例（77.8%），女性健常者の22名中19名（86.4%）が正しく判別された[10]。

次に男性の統合失調症患者30例と健常対照者30名のMRIから，voxel-based morphometry（VBM）とmultivariate linear model（MLM）を用いて，両群間の違いをもっともよく表す灰白質分布パターン（eigenimage）を抽出した。そのeigenimageにより，統合失調症患者

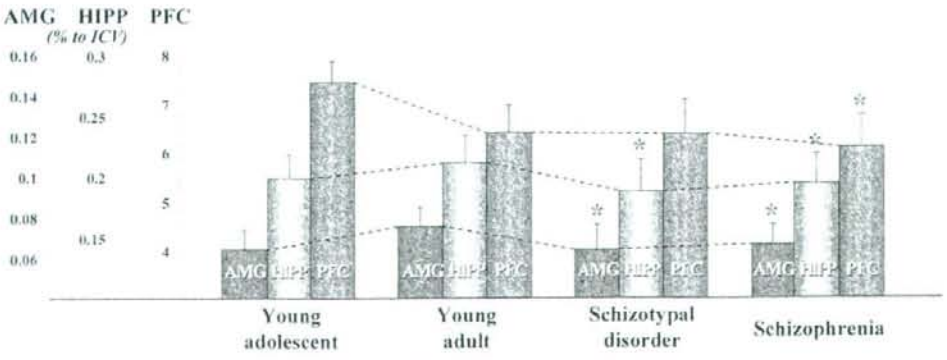

図1 前頭前野と辺縁系の形態学的発達と統合失調症の発症
AMG，扁桃体；HIPP，海馬；ICV，頭蓋内容積；PFC，前頭前野