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

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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
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 Yakovelev, 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-NP) and did not (UHR-PP) 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., 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), 153 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 Multidimensional 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 Yung, 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 Multidimensional 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.

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Table 1

Sample characteristics and olfactory sulcus measures of the participants.

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>UHR-NP</th>
<th>UHR-P</th>
<th>FEP</th>
<th>Chronic Sz</th>
<th>Group comparisons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>26.9 (10.1)</td>
<td>20.4 (3.6)</td>
<td>19.6 (3.5)</td>
<td>21.5 (3.4)</td>
<td>34.9 (9.6)</td>
<td>F(4, 468) = 82.32, p &lt; 0.001; Sz &gt; controls &gt; UHR-P, FEP; UHR-NP, and FEP</td>
</tr>
<tr>
<td>M/F</td>
<td>55/32</td>
<td>48/35</td>
<td>30/22</td>
<td>108/54</td>
<td>76/13</td>
<td>Chi-square = 19.39, p &lt; 0.001; M &gt; F in Sz compared with all other groups</td>
</tr>
<tr>
<td>Handedness (right/mixed/left)</td>
<td>80/2/5</td>
<td>69/3/10</td>
<td>46/0/4</td>
<td>139/4/17</td>
<td>74/5/6</td>
<td>F(4, 457) = 3.22, p = 0.013; controls &gt; UHR-NP</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>175.3 (9.7)</td>
<td>170.8 (9.1)</td>
<td>171.6 (8.8)</td>
<td>172.8 (9.4)</td>
<td>174.3 (7.9)</td>
<td>F(4, 368) = 5.19, p &lt; 0.001; controls &gt; FEP</td>
</tr>
<tr>
<td>Premorbid IQa,b</td>
<td>102.3 (10.5)</td>
<td>96.6 (13.7)</td>
<td>94.3 (13.2)</td>
<td>93.9 (13.6)</td>
<td>95.6 (15.1)</td>
<td>F(1, 132) = 0.38, p = 0.538</td>
</tr>
<tr>
<td>BPRS total at intake</td>
<td>–</td>
<td>43.7 (8.3)</td>
<td>44.6 (8.3)</td>
<td>–</td>
<td>–</td>
<td>F(1, 132) = 1.80, p = 0.164</td>
</tr>
<tr>
<td>BPRS psychotic subscale at intake</td>
<td>–</td>
<td>8.1 (2.5)</td>
<td>8.8 (2.8)</td>
<td>–</td>
<td>–</td>
<td>F(1, 132) = 3.52, p = 0.063</td>
</tr>
<tr>
<td>SANS total at intake</td>
<td>–</td>
<td>17.3 (12.7)</td>
<td>21.5 (8.3)</td>
<td>–</td>
<td>–</td>
<td>F(1, 132) = 3.52, p = 0.063</td>
</tr>
<tr>
<td>Duration of illness (days)b</td>
<td>54 (87)</td>
<td>467 (3613)</td>
<td>1547 (1182)</td>
<td>842.9 (715.8)</td>
<td>F(1, 245) = 260.44, p &lt; 0.001; Sz &gt; FEP</td>
<td></td>
</tr>
<tr>
<td>Drug (mg/day, CP equivalent)c</td>
<td>1450 (143)</td>
<td>1424 (148)</td>
<td>1435 (146)</td>
<td>1422 (133)</td>
<td>1441 (130)</td>
<td>F(1, 224) = 136.66, p &lt; 0.001; Sz &gt; FEP</td>
</tr>
<tr>
<td>Intracranial volume (ml)</td>
<td>1361 (140)</td>
<td>1315 (137)</td>
<td>1324 (135)</td>
<td>1305 (123)</td>
<td>1325 (119)</td>
<td>F(4, 467) = 0.68, p = 0.609</td>
</tr>
<tr>
<td>Whole brain volume (ml)</td>
<td>44.9 (3.9)</td>
<td>44.1 (5.2)</td>
<td>44.9 (4.8)</td>
<td>44.6 (4.8)</td>
<td>43.3 (5.1)</td>
<td>F(4, 467) = 3.27, p = 0.011; C &gt; FEP</td>
</tr>
<tr>
<td>Olfactory sulcus length (mm)</td>
<td>45.6 (4.0)</td>
<td>45.3 (4.9)</td>
<td>45.7 (4.9)</td>
<td>45.7 (5.0)</td>
<td>44.3 (5.2)</td>
<td>F(4, 461) = 1.04, p = 0.385</td>
</tr>
<tr>
<td>Olfactory sulcus depth (mm)</td>
<td>11.5 (1.3)</td>
<td>11.4 (1.2)</td>
<td>10.5 (1.1)</td>
<td>9.6 (1.0)</td>
<td>9.2 (1.0)</td>
<td>F(4, 461) = 95.50, p &lt; 0.001; controls and UHR-NP &gt; UHR-P &gt; FEP &gt; Sz</td>
</tr>
</tbody>
</table>

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 (Yucel 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 using 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 Scheffe’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 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 \( (r = 0.376, p < 0.001 \); 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 \( (r = 0.330, p = 0.002 \). 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
neurodevelopment early in gestation. Interestingly, only olfactory sulcus depth and ACC folding in patients with ultra high risk (UHR) cohort shares abnormalities in the olfactory sulcus (Turetsky et al., 2009b). 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 (PPT)], 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 pellucidum 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 (Burnön 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 anomalies in psychiatric disorders may also reflect progressive brain changes during and after the onset of illness. Additional longitudinal studies would be required to understand 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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