Surface morphology of the orbitofrontal cortex in individuals at risk of psychosis: A multicenter study

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Abstract

Changes in the surface morphology of the orbitofrontal cortex (OFC), such as an altered sulcogyral pattern of the 'H-shaped' orbital sulcus and fewer orbital sulci, have been reported in schizophrenia, possibly reflecting abnormal neurodevelopment during gestation. However, whether high-risk subjects for developing psychosis also exhibit these gross morphologic anomalies is not well documented. This multicenter MRI study from 4 scanning sites in Japan investigated the distribution of the OFC sulcogyral pattern, as well as a number of intermediate and posterior orbital sulci in 125 individuals with an at-risk mental state (ARMS) [of whom 22 later developed psychosis (ARMS-P) and 97 did not (ARMS-NP)] and 110 healthy controls. While there was no group difference in OFC pattern distribution, the ARMS group as a whole had a significantly lower number of both orbital sulci compared with the controls, which was associated with prodromal symptomatology. The ARMS-P and -NP groups did not differ in OFC surface morphology. These results suggest that gross morphology of the OFC in high-risk subjects may at least partly reflect neurodevelopmental pathology related to vulnerability to psychosis.

Keywords: Orbitofrontal cortex; Sulcogyral pattern; Magnetic resonance imaging; Multicenter; High-risk; Psychosis

1. Introduction

The surface morphology of the human orbitofrontal cortex (OFC) has large inter-individual variability (Chiavaras and Petrides, 2000), probably reflecting variations in early neurodevelopmental processes (Rakic, 1988). Although not consistently (e.g., Cropley et al., 2015), previous magnetic resonance imaging (MRI) studies of psychotic disorders such as schizophrenia have demonstrated decreased Type I and increased Type III expression in the variation of OFC the 'H-shaped' sulcus [Type I, II, and III; defined by Chiavaras and Petrides, 2000] (Fig. 1) especially on the right hemisphere (Chakirova et al., 2010; Nakamura et al., 2007; Nishikawa et al., 2016; Takayanagi et al., 2010) as well as a decreased number of intermediate orbital sulcus (IOS) (Takahashi et al., 2016) and posterior orbital sulcus (POS) (Bartholomeusz et al., 2014; Takahashi et al., 2016) in the patient group. The altered OFC surface morphology seems to be already present at their first-episode (Bartholomeusz et al., 2014; Chakirova et al., 2010; Takayanagi et al., 2010), and patients with schizotypal disorder, who are genetically related to schizophrenia and may be vulnerable to psychopathology (Siever and Davis, 2004), partly share the OFC findings with schizophrenia (Nishikawa et al., 2016; Takahashi et al., 2016). As gross cortical folding patterns are largely established by birth (Chi et al., 1977), the OFC surface morphology in psychotic disorders may reflect neurodevelopmental pathology.

Previous MRI studies of gross surface morphology in individuals with an at-risk mental state (ARMS; Yung et al., 2003, 2004a), about 35% of whom would later develop psychosis (Fusar-Poli et al., 2012; Nelson et al., 2013), have yielded partly inconsistent results; the ARMS subjects likely exhibit an altered folding pattern of the anterior cingulate cortex (Yücel et al., 2003) and frontal/parietal hyper-gyrification (Tepest et al., 2013) regardless of later transition status, while abnormally shallow olfactory sulcus was specific to those with later psychosis onset (ARMS-P) (Takahashi

et al., 2014). To our knowledge, only one MRI study has examined the OFC surface morphology in ARMS; Lavoie et al. (2014) demonstrated that ARMS-P subjects had decreased Type I and increased Type II patterns on the right hemisphere compared to controls, while a decreased number of IOS/POS was observed in the ARMS individuals without clear relation to psychosis onset. Chakirova et al. (2010) found no group difference in the OFC pattern between genetic high-risk subjects and healthy controls, while decreased Type I pattern may be related to the development of schizophrenia as demonstrated only when the left/right hemispheres and Type II/III (i.e., non-Type I) patterns were grouped together. Taken together, it remains elusive as to whether high-risk subjects for developing psychosis exhibit altered OFC surface morphology, which may reflect aberrant neurodevelopment in the orbitofrontal region, and also whether such gross morphologic anomalies, if present, are related to later transition to psychosis.

This multicenter MRI study aimed to investigate the OFC sulcogyral pattern and the number of IOS/POS in the ARMS and healthy comparison subjects recruited at 4 scanning sites in Japan. On the basis of a possible role of the OFC surface morphology as an early neurodevelopmental marker of psychosis (Bartholomeusz et al., 2014) as well as previous MRI findings (Chakirova et al., 2010; Lavoie et al., 2014), we predicted that ARMS subjects, especially those who later developed psychosis, would have altered OFC pattern distribution and fewer IOS/POS as compared with healthy subjects. We also investigated the association between the OFC surface morphology and the clinical features of high-risk subjects (e.g., prodromal symptomatology, medication).

2. Methods

2.1. Subjects

One hundred and twenty-five individuals with ARMS were recruited from domestic specialized clinical services for ARMS at Toyama University Hospital, The University of Tokyo Hospital, Toho University Hospital, and Tohoku University Hospital (Koike et al., 2013; Mizuno et al., 2009). Each individual fulfilled the criteria of ARMS for the Comprehensive Assessment of At Risk Mental States (CAARMS) (Yung et al., 2004b) (Toyama and Tohoku) or the Structured Interview for Prodromal Syndromes / Scale of Prodromal Symptoms (SIPS/SOPS) (Miller et al., 2003) (Tokyo and Toho). The ARMS individuals were prospectively followed up regularly at each site and divided into 1) those who subsequently developed overt psychosis [ARMS-P, *n* = 22 (17.6%)], 2) those who did not develop psychosis during a clinical follow-up of at least 2 years (ARMS-NP, *n* = 97), or 3) those with an unknown outcome due to drop out within less than 2 years (ARMS-UK, *n* = 6). Conversion to psychosis was determined at each site according to the CAARMS criteria (i.e., at least one fully positive psychotic symptom several times per week for more than one week) or the SIPS criteria (i.e., the presence of a positive symptom that has been existing for more than one month or accompanying a serious disorganization or danger). The psychosis diagnoses of ARMS-P based on the criteria in the Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-Ⅳ; American Psychiatric Association 1994) were schizophrenia (*n* = 15), delusional disorder (*n* = 1), schizophreniform disorder (*n* = 1), brief psychotic disorder (*n* = 1), and psychotic disorder NOS (*n* = 4). Medication dose, interval between scanning and conversion, and other clinical data are summarized in Table 1.

Gender- and age- matched control individuals consisted of 110 healthy volunteers who were recruited from the community, hospital staff, and university students at each site. The exclusion criteria for both ARMS and healthy subjects were 1) having a lifetime history of serious head injury, neurological illness, or other serious physical

disease, 2) fulfilling the criteria for substance abuse/dependence, and 3) having previous psychotic episodes which met the DSM-IV criteria. The study received approval from the Committee on Medical Ethics at each site. After a complete explanation of the study, written informed consent was obtained from all subjects.

2.2. Magnetic resonance imaging procedures

T1-weighted MRI images of 1-mm sagittal slices were acquired from 4 scanning sites. The scanner field strength was 1.5T for 3 sites (Toyama, Toho, and Tohoku) and 3.0T for one site (Tokyo) (Table 2). The images were processed on a Macintosh computer (Apple Inc., CA, USA) using Dr. View software (Infocom, Tokyo, Japan). Brain images were realigned in three dimensions to standardize for differences in head tilt during image acquisition and were reconstructed into contiguous coronal images with a 1.0-mm thickness, perpendicular to the anterior commissure-posterior commissure line.

2.3. OFC sulcogyral pattern classification and sulcus count

The medial orbital sulcus (MOS), lateral orbital sulcus (LOS), and transverse orbital sulcus (TOS) were highlighted on consecutive 1-mm coronal slices, and then viewed in the axial plane for OFC pattern classification based on the definition by Chiavaras and Petrides (2000). Briefly, the OFC sulcogyral patterns were classified according to the continuity of the ‘H-shaped’ sulcus consisting of the MOS, TOS, and LOS; for Type I the MOS is disconnected while the LOS is intact, for Type II both the MOS and LOS are continuous, and for Type III both the MOS and LOS are disconnected (Fig. 1). In rare instances where the MOS was continuous, but the LOS was disconnected, this pattern was classified as Type IV (Chakirova et al., 2010).

We then identified and counted the number of IOS (single, double, or triple) and POS (absent, single, or double); the IOS was identified anterior to the TOS in between the rostral MOS and rostral LOS, while the POS was posterior to the TOS in between the caudal MOS and caudal LOS (Fig. 2). According to previous reports (Lavoie et al., 2014; Takahashi et al., 2016), a fissure clearly visible in at least 4 coronal and 4 axial slices was defined as a sulcus.

Two raters (MN and TT), who were blind to the subjects' identity, independently performed the OFC sulcogyral pattern classification and sulcus count for all subjects. Intra- (MN) and inter-rater reliabilities (Cronbach's α) in a subset of 15 randomly selected brains (30 hemispheres) were over 0.78 for all assessments. A consensus agreement was reached in all cases even when the initial classification/count differed between the raters.

2.4. Statistical analysis

Clinical and demographic differences between groups were examined by one-way analysis of variance (ANOVA), χ^2 test, or Fisher's exact test (when more than 20% of cells had expected counts less than 5). Group differences in the OFC pattern distribution and number of IOS/POS were evaluated by χ^2 test or Fisher's exact test. The hemispheres with a rare OFC Type IV pattern (n = 6, 1.27% of all hemispheres) were excluded from the statistical analyses (Chakirova et al., 2010; Nishikawa et al., 2016). The relationships between the OFC surface morphology and demographic/clinical variables (age, education, parental education, and medication dose) were analyzed for each hemisphere by ANOVA with the OFC pattern or sulcus count as a between-subject factor. For the CAARMS subscale scores (available for 55 ARMS individuals), age and medication dose were used as covariates. The hemispheres with triple-IOS and/or double-POS in the ARMS subjects were excluded from the ANOVAs due to small

sample size. Statistical significance was defined as $p < 0.05$.

3. Results

3.1. Demographic characteristics

There were no group differences in age, sex, or parental education, but the healthy controls had attained a higher level of education compared with the ARMS individuals (Table 1). The ARMS-P and -NP individuals did not differ in their symptom severity on the basis of CAARMS scores and medication dose (Table 1).

3.2. Group difference in the OFC pattern distribution and sulcus count

There was no significant difference in the OFC pattern distribution between the controls and ARMS as a whole or between the ARMS-P and -NP groups (Table 3). The ARMS individuals were characterized by a significantly lower number of bilateral IOS and left POS compared with controls, but there was no difference between the ARMS-P and -NP groups (Table 4).

The study findings remained essentially the same even when we analyzed only right-handed subjects because of significant group difference in handedness distribution (Table 1) or when we examined only medication-naïve ARMS individuals ($n = 82$).

3.3. OFC surface morphology and demographic/clinical variables

In the controls, right OFC Type II pattern was related to lower education [F (2, 94) = 4.78, $p = 0.011$] compared with Type III (Scheffe's test, $p = 0.011$) and to younger age [F (2, 105) = 5.71, $p = 0.004$] compared with Type I (Scheffe's test, $p = 0.038$) and Type

III (Scheffe's test, $p = 0.005$). However, the sulcus counts did not relate to demographic variables in the controls.

In the ARMS subjects, the right double-IOS pattern was related to younger age [F (1, 113) = 4.31, $p = 0.040$] compared with single-IOS (Scheffe's test, $p = 0.040$). The ARMS individuals with left OFC pattern II ($n = 5$) had a lower global score of disorganized speech [F (2, 48) = 1.39, $p = 0.041$] compared with Type I ($n = 25$; Scheffe's test, $p = 0.024$) and III ($n = 23$; Scheffe's test, $p = 0.040$). Further, those with right absent-POS ($n = 24$) had a lower global score of perceptual abnormalities [F (1, 46) = 28.33, $p < 0.001$] compared with single-POS ($n = 26$; Scheffe's test, $p < 0.001$). The relations between the OFC surface morphology and symptom ratings remained significant even when we examined only medication-naïve ARMS individuals.

The OFC surface morphology did not relate to sex for both healthy controls and ARMS individuals.

3.4. Relationship between the OFC pattern and sulcus counts

Healthy controls with left triple-IOS less frequently had left absent-POS pattern (Fisher’s exact test, $p = 0.010$). Further, right OFC type II was related to a right double-POS pattern in healthy subjects (Fisher’s exact test, $p = 0.005$), but this result was on the basis of only 8 subjects (Table 3). The OFC pattern and IOS/POS counts did not relate to each other in the ARMS subjects (all $p > 0.119$).

4. Discussion

To our knowledge, this is the first multicenter MRI study of the OFC H-shaped sulcogyral pattern and number of orbital sulci in a relatively large sample of clinical high-risk subjects. While no group difference was found in the distribution of the OFC

sulcogyral pattern, the ARMS individuals had a significantly lower number of IOS/POS compared with controls. However, the number of these sulci did not differ between the ARMS individuals with and without later transition to psychosis. These findings suggest that such an altered OFC surface morphology may be a vulnerability marker of psychosis that reflects early neurodevelopmental abnormality.

Our findings on OFC surface morphology are thought to reflect orbitofrontal neural development, because the orbital sulci examined in this study (IOS, POS, and other orbital sulci forming H-shaped sulcus) develop predominantly during the mid-to-late gestation period and remain relatively stable after birth (Armstrong et al., 1995; Chi et al., 1977). One strength of this study is that we examined both the IOS/POS number and OFC H-shaped sulcus pattern, because separate parts of the OFC appear to have somewhat different developmental periods and functions (i.e., mediolateral and posterior-anterior sequence of sulcus maturations; Kringelbach and Rolls, 2004). While the neural mechanisms underlying the inter-individual variability of H-shaped sulcus pattern remain unclear, reduction in sulcus number probably reflects immature sulcus formation due to underdevelopment of the local neural system (Ganella et al., 2015). Interestingly, our previous OFC studies (Nishikawa et al., 2016; Takahashi et al., 2016) demonstrated both fewer IOS/POS and altered OFC pattern distribution in schizophrenia, but the current ARMS cohort as well as schizotypal disorder patients, a milder form of schizophrenia-spectrum, only exhibited the decreased IOS/POS number. These findings may suggest greater and more prolonged neurodevelopmental pathology in patients with full-blown schizophrenia as compared with high-risk or schizotypal subjects.

Although there have been only a few IOS/POS studies in psychotic disorders, our findings of a decreased number of these sulci in the ARMS group are in line with similar findings in subjects with ARMS (Lavoie et al., 2014), first-episode psychosis (Bartholomeusz et al., 2014), and established schizophrenia (Takahashi et al., 2016).

Because this and previous (Lavoie et al., 2014) studies in ARMS found no clear relation between the sulcus number and later psychosis onset, the reduced number of orbital sulci could be regarded as a general risk factor related to vulnerability to psychosis. Given that the cortical folding pattern likely reflects critical neurodevelopmental events such as local neuronal connection and synaptic development (Rakic, 1988; Van Essen, 1997), our findings may partly support the neuroimaging findings of frontal dysconnectivity also in ARMS subjects who did not develop psychosis (Schmidt et al., 2015; Wang et al., 2016) or in non-affected relatives of schizophrenia patients (van der Meer et al., 2014).

Inconsistent with the relatively common finding of decreased Type I and/or increased Type III pattern in the right hemisphere from the prodromal (Lavoie et al., 2014) or early (Bartholomeusz et al., 2014; Takayanagi et al., 2010) phases of psychosis to chronic stages of schizophrenia (Cropley et al., 2015; Nakamura et al., 2007), the current ARMS cohort did not exhibit an altered OFC pattern distribution. It is also reported that decreased Type I may be associated with later development of schizophrenia in genetic high-risk subjects (Chakirova et al., 2010), although their results are not lateralized and of a mild degree. On the other hand, discrepant findings [e.g., increased Type II in schizophrenia (Cropley et al., 2015)] as well as variability in OFC type distribution between control cohorts implicate the influence of methodological differences between the studies (e.g., OFC classification methods, sample characteristics). However, our negative results could not be explained solely by these methodological issues, because our previous study using the identical classification method in a Japanese sample demonstrated altered distribution of the OFC pattern in schizophrenia (Nishikawa et al., 2016). Alternatively, our discrepant findings (i.e., altered OFC pattern in schizophrenia but not in ARMS-P subjects) may raise the possibility that the OFC pattern changes during the development of psychosis, which may conceivably occur subsequent to progressive OFC gray matter reduction (Cannon

et al., 2015; Pantelis et al., 2003, 2005). Indeed, the OFC sulcogyral patterns seem to be associated with the thickness of OFC gray matter in a community sample (Whittle et al., 2014). Taken together, our findings suggest that the OFC H-shaped sulcogyral pattern is unlikely to be a simple neurodevelopmental marker of psychosis, but further longitudinal studies should examine its stability especially in the early stages of psychosis.

Our results suggested that the OFC surface morphology could be related to the severity of the subthreshold symptoms in the high-risk cohort. We found a relation between the left OFC Type II pattern and severity of disorganized speech, although this result was based on only five ARMS subjects. Type III seems to be associated with psychosis-like symptoms in a genetic high-risk cohort (Chakirova et al., 2010) or severity of symptoms and cognitive impairments in schizophrenia (Nakamura et al., 2007), but healthy subjects with Type III are reported to have better cognitive functioning (Ganella et al., 2015). Significant relation between absent-POS and less severe perceptual abnormalities in our ARMS cohort was an unexpected finding, because an absent-POS pattern implies more severe neurodevelopmental pathology related to negative symptomatology in the schizophrenia spectrum (Takahashi et al., 2016). On the other hand, more POS pattern was also associated with aberrant neurodevelopment due to preterm birth (Ganella et al., 2015) or more severe depressive symptoms in the general population (Whittle et al., 2014). Thus, the functional significance of each OFC surface morphology variation and its relation to normal/pathological mental status is largely unknown and requires further examination.

A few possible confounding factors in this study should be taken into account. First, this multicenter study used different MRI scanners with different acquisition sequences. Although the orbital sulci assessed in this study could be readily identified in all cases using high-resolution 3D T1 images from the 4 scanning sites, the possibility exists that differing image quality (e.g., different voxel size) has affected the results. It is also

possible that a different proportion of controls and ARMS individuals, as well as different criteria (i.e., CAARMS or SIPS/SOPS) for the ARMS diagnosis at each site, biased the findings. However, there was no significant effect of site on the OFC surface morphology in both healthy and ARMS subjects in this study (data not shown). Second, a proportion of the ARMS subjects in this study were taking antipsychotics at scanning, which could affect brain morphology (Moncrieff and Leo, 2010) as well as prodromal symptomatology (Kobayashi et al., 2009). However, our main findings did not change even when we examined only medication-naïve ARMS subjects. Finally, as altered distribution of OFC pattern and fewer orbital sulci are also reported in autism spectrum disorders (Watanabe et al., 2014) and anxiety trait in panic disorder (Roppongi et al., 2010), the disease specificity of our findings should be further examined.

In conclusion, this multicenter MRI study demonstrated that ARMS individuals are characterized by fewer IOS/POS in the OFC surface, which may be partly associated with subthreshold psychotic symptoms. However, the OFC surface morphology is not associated with later transition into psychosis. These findings are suggestive of early disruption of the cortical folding processes and its relation to general vulnerability to psychopathology. Additional longitudinal studies would be required for a fuller understanding of the nature of OFC gross morphology in the course of psychosis.

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Figure Legends

Fig. 1. Classification of the orbitofrontal sulcogyral pattern on an axial view parallel to the anterior commissure-posterior commissure line. Note that these sulci were identified using orthogonal views in three directions and colored on consecutive coronal slices. c, caudal portion; LOS, lateral orbital sulcus; MOS, medial orbital sulcus; r, rostral portion; TOS, transverse orbital sulcus.

Fig. 2. Variations in the number of intermediate orbital sulcus (IOS) and posterior orbital sulcus (POS) on sample axial views of the orbitofrontal cortex (yellow). c, caudal portion; LOS, lateral orbital sulcus; MOS, medial orbital sulcus; r, rostral portion; TOS, transverse orbital sulcus.

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Contributors

In this study, Drs. Suzuki, Kasai, Mizuno, and Matsumoto conceived the idea and methodology of the study. Dr. Nakamura conducted the statistical analyses and wrote the manuscript. Drs. Takayanagi, Furuichi, Kido, Nishikawa, Sasabayashi, Katagiri, Sakuma, Obara, Koike, and Yamasue recruited subjects, and were involved in clinical and diagnostic assessments. Drs. Nakamura and Takahashi analyzed the MRI data. Dr. Noguchi provided technical support for the MRI scanning and data processing. Drs. Takahashi, Takayanagi, and Suzuki contributed to the 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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Figure 1

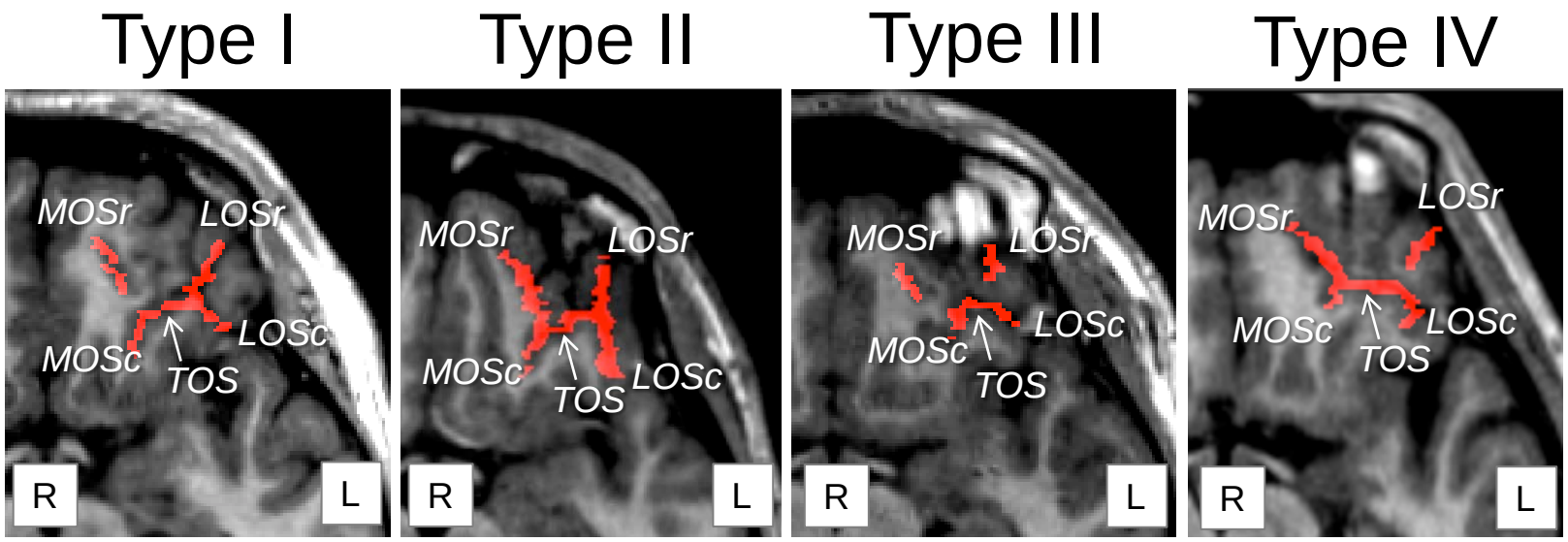

Figure 2

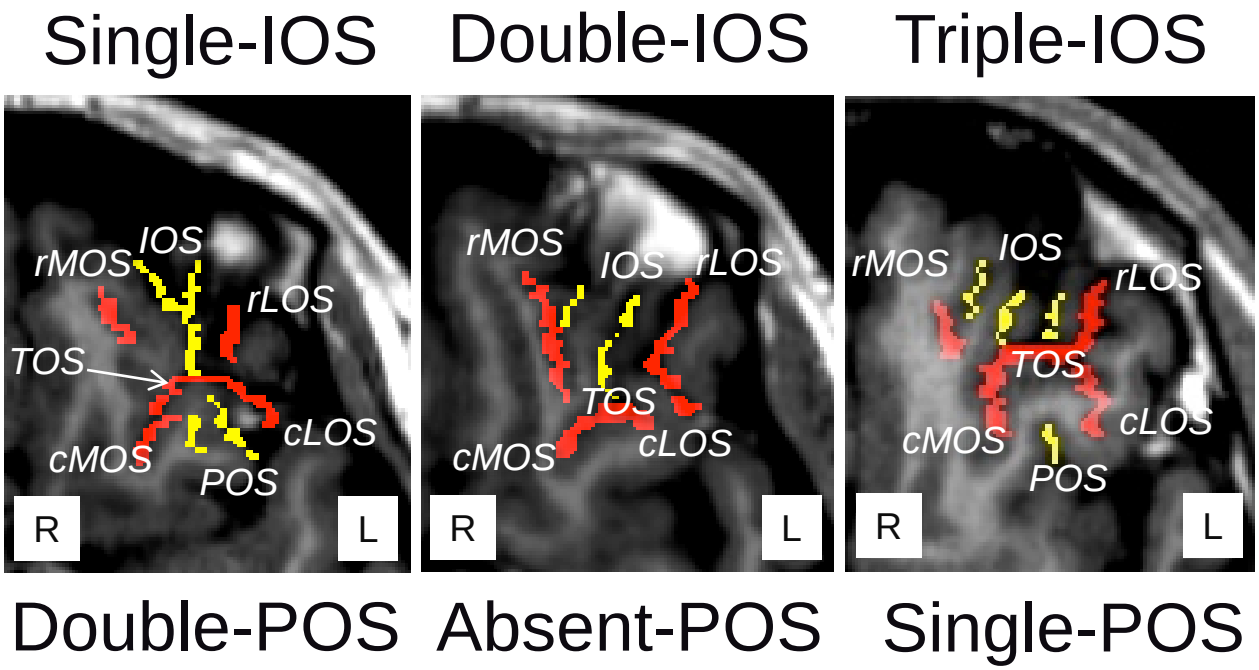
Single-IOS
Double-IOS
Triple-IOS
rMOS
IOS
rLOS
TOS
cLOS
cMOS
POS
R
L
Double-POS
Absent-POS
Single-POS

Table 1. Characteristics of the study participants.

	Controls	Whole ARMS	ARMS-P	ARMS-NP	ARMS-UK	Controls vs whole ARMS	ARMS-P vs ARMS-NP
Number of subjects (total)	110	125	22	97	6	-	-
Scanning site 1 (Toyama)	45	22	5	11	6	-	-
Scanning site 2 (Toho)	16	36	5	31	0	-	-
Scanning site 3 (Tohoku)	17	35	9	26	0	-	-
Scanning site 4 (Tokyo)	32	32	3	29	0	-	-
Male/female	54/56	54/71	8/14	43/54	3/3	$\chi^2 = 0.81$, $p = 0.366$	$\chi^2 = 0.47$, $p = 0.495$
Age (years)	21.3 (3.2)	21.3 (5.5)	20.2 (4.3)	21.7 (5.7)	19.6 (5.4)	F (1, 233) < 0.01, $p = 0.958$	F (1, 117) = 1.20, $p = 0.276$
Education (years)[a]	14.4 (2.6)	12.5 (2.5)	12.6 (2.4)	12.7 (2.5)	10.5 (1.6)	F (1, 202) = 27.84, $p < 0.001$	F (1, 98) = 0.04, $p = 0.833$
Parental education (years)[a]	14.2 (2.1)	13.9 (2.1)	13.9 (1.8)	14.0 (2.2)	13.2 (0.9)	F (1, 165) = 0.56, $p = 0.455$	F (1, 79) = 0.08, $p = 0.781$
Handedness (right/mix/left)[a]	96/0/1	96/6/5	17/2/2	73/4/3	6/0/0	$p = 0.012$ (FET)	$p = 0.212$ (FET)
Duration between scan and onset (months)	-	-	10.0 (9.3)	-	-	-	-
Drug (mg/day, Chlorpromazine equivalent)[b]	-		191.4 (123.2) [n = 10]	178.5 (150.5) [n = 33]	-	-	F (1, 41) = 0.06, $p = 0.806$
Medication type (typical/atypical/mixed)	-	5/36/2	0/10/0	5/26/2	0/0/0	-	$p = 0.736$ (FET)
CAARMS subscale scores (n = 55)							
Unusual thought global rating	-	2.8 (1.9)	3.4 (2.2)	2.4 (1.7)	4.0(1.1)	-	F (1, 47) = 2.42, $p = 0.127$
Unusual thought frequency	-	3.5 (2.0)	3.2 (2.0)	3.5 (2.1)	4.3(1.4)	-	F (1, 47) = 0.26, $p = 0.611$
Perceptual abnormalities global rating	-	2.8 (1.6)	2.8 (1.8)	2.7 (1.6)	3.2(1.2)	-	F (1, 47) < 0.01, $p = 0.930$
Perceptual abnormalities frequency	-	2.9 (1.8)	2.9 (2.0)	2.7 (1.7)	3.8(1.7)	-	F (1, 47) = 0.07, $p = 0.791$
Disorganized speech global rating	-	2.0 (1.2)	2.4 (1.3)	1.9 (1.3)	2.0(0.6)	-	F (1, 47) = 1.23, $p = 0.273$
Disorganized speech frequency	-	3.9 (2.2)	3.6 (2.1)	3.8 (2.3)	5.0(1.5)	-	F (1, 47) = 0.03, $p = 0.855$

Values represent means (SDs) unless otherwise stated. ARMS, at-risk mental state; FET, Fisher's exact test; NP, non-psychosis; P, psychosis; UK, unknown outcome.

[a] Data missing for some participants.

[b] Converted into Chlorpromazine equivalents using the guideline by Inada and Inagaki (2015).

Table 2. MRI data acquisition

Site	Scanner	Field Strength (Tesra)	TR/TE (ms)	Voxel Dimensions (mm)	Sequence
Toyama	Siemens Magnetom Vision	1.5	24.0/5.0	1.0 × 1.0 × 1.0	3D-FLASH
Tokyo	GE Signa	3	6.80/1.94	0.938 × 0.938 × 1.0	3D-FSPGR
Toho	Toshiba EXCELART Vantage	1.5	24.4/5.5	0.98 × 0.98 × 1.0	3D-FE
Tohoku	Phillips Achieva	1.5	30.0/5.0	1.0 × 1.0 × 1.0	3D-FFE

FE, field echo; FFE, fast field echo; FLASH, fast low-angle shots with gradient echo; FSPGR, fast-spoiled gradient recalled acquisition with steady state; TR/TE, repetition time/echo time; 3D; Three-dimensional.

Table 3. Distribution of the OFC sulcogyral pattern in the study participants.

	Controls (*n* = 110)	whole ARMS (*n* = 125)	ARMS-P (*n* = 22)	ARMS-NP (*n* = 97)	ARMS-UK (*n* = 6)	Controls vs whole ARMS		ARMS-P vs ARMS-NP	
						X^2	*p*	X^2	*p*
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)				
Left hemisphere						0.71	0.703	0.09	0.958
Type I	60 (54.5)	61 (48.8)	10 (45.5)	49 (50.5)	2 (33.3)				
Type II	9 (8.2)	12 (9.6)	2 (9.1)	9 (9.3)	1 (16.7)				
Type III	40 (36.4)	50 (40.0)	9 (40.9)	38 (39.2)	3 (50.0)				
Type IV	1 (0.9)	2 (1.6)	1 (4.5)	1 (1.0)	0 (0.0)				
Right hemisphere						2.96	0.228	1.16	0.559
Type I	72 (65.5)	70 (56.0)	14 (63.6)	51 (52.6)	5 (83.3)				
Type II	8 (7.3)	9 (7.2)	2 (9.1)	7 (7.2)	0 (0.0)				
Type III	28 (25.5)	45 (36.0)	6 (27.3)	38 (39.2)	1 (16.7)				
Type IV	2 (1.8)	1 (0.8)	0 (0.0)	1 (1.0)	0 (0.0)				

ARMS, at-risk mental state; NP, non-psychosis; OFC, orbitofrontal cortex; P, psychosis; UK, unknown outcome.

Table 4. Sulcus counts of the orbital sulci in the study participants.

	Controls (*n* = 110)	whole ARMS (*n* = 125)	ARMS-P (*n* = 22)	ARMS-NP (*n* = 97)	ARMS-UK (*n* = 6)	Controls vs whole ARMS		ARMS-P vs ARMS-NP	
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	χ^2	*p*	χ^2	*p*
Left IOS						8.37	0.015[a]	0.07	0.967
Single	34 (30.9)	54 (43.2)	9 (40.9)	42 (43.3)	3 (50.0)				
Double	60 (54.5)	65 (52.0)	12 (54.5)	50 (51.5)	3 (50.0)				
Triple	16 (14.5)	6 (4.8)	1 (4.5)	5 (5.2)	0 (0.0)				
Right IOS						11.95	0.003[a]	-	0.098[b]
Single	17 (15.5)	33 (26.4)	2 (9.1)	29 (29.9)	2 (33.3)				
Double	68 (61.8)	82 (65.6)	18 (81.8)	62 (63.9)	2 (33.3)				
Triple	25 (22.7)	10 (8.0)	2 (9.1)	6 (6.2)	2 (33.3)				
Left POS						15.31	< 0.001[a]	-	0.281[b]
Absent	38 (34.5)	72 (57.6)	10 (45.5)	58 (59.8)	4 (66.7)				
Single	59 (53.6)	49 (39.2)	12 (54.5)	35 (36.1)	2 (33.3)				
Double	13 (11.8)	4 (3.2)	0 (0.0)	4 (4.1)	0 (0.0)				
Right POS						1.00	0.608	1.02	0.602
Absent	51 (46.4)	61 (48.8)	13 (59.1)	46 (47.4)	2 (33.3)				
Single	47 (42.7)	55 (44.0)	8 (36.4)	44 (45.4)	3 (50.0)				
Double	12 (10.9)	9 (7.2)	1 (4.5)	7 (7.2)	1 (16.7)				

ARMS, at-risk mental state; IOS, intermediate orbital sulcus; NP, non-psychosis; P, psychosis; POS, posterior orbital sulcus; UK, unknown outcome.

[a] The triple-IOS (left, $\chi^2 = 6.55$, $p = 0.010$; right, $\chi^2 = 10.01$, $p = 0.002$) and double-POS [left, $p = 0.012$ (Fisher's exact test)] patterns were more common in the controls than in the ARMS group. The controls had single-IOS (right, $\chi^2 = 4.19$, $p = 0.041$) and absent-POS (left, $\chi^2 = 12.49$, $p < 0.001$) patterns less often than the ARMS group.

[b] Fisher's exact test was used.