European Archives of Psychiatry and Clinical Neuroscience (2019) 269:397–406
https://doi.org/10.1007/s00406-018-0890-6

ORIGINAL PAPER

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

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Received: 13 June 2017 / Accepted: 16 March 2018 / Published online: 23 March 2018

Abstract

Changes in the surface morphology of the orbitofrontal cortex (OFC), such as a fewer orbital sulci and altered sulcogyral pattern of the 'H-shaped' orbital sulcus, 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 four scanning sites in Japan investigated the distribution of the number of intermediate and posterior orbital sulci, as well as the OFC sulcogyral pattern, in 125 individuals with an at-risk mental state (ARMS) [of whom 22 later developed psychosis (ARMS-P) and 89 did not (ARMS-NP)] and 110 healthy controls. The ARMS group as a whole had a significantly lower number of intermediate and posterior orbital sulci compared with the controls, which was associated with prodromal symptomatology. However, there was no group difference in OFC pattern distribution. 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

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Introduction

The surface morphology of the human orbitofrontal cortex (OFC) has large inter-individual variability [1], probably reflecting variations in early neurodevelopmental processes [2]. Although not consistently [3], previous magnetic resonance imaging (MRI) studies of psychotic disorders such as schizophrenia have demonstrated a decreased number of intermediate orbital sulcus (IOS) [4] and posterior orbital sulcus (POS) [4, 5], as well as a 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 [1]) (Fig. 1), especially on the right hemisphere [6–9] in the patient group. The altered OFC surface morphology seems to be already present at their first-episode [5, 6, 9], and patients with schizotypal disorder, who are genetically related to schizophrenia and may be vulnerable to psychopathology [10], partly share the OFC findings with schizophrenia [4, 8]. As gross cortical folding patterns are largely established by birth [11], the OFC surface

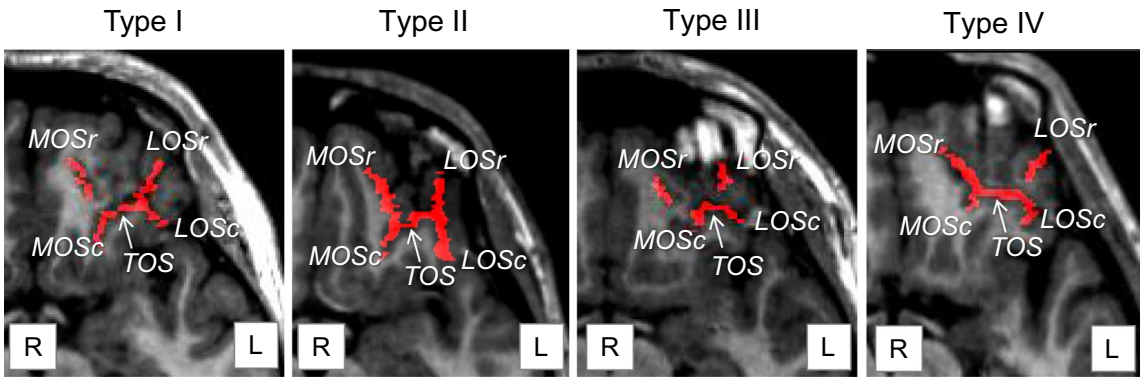

Fig. 1 Classification of the orbitofrontal sulcogyral pattern on an axial view parallel to the anterior commissure–posterior commissure line. Note that these sulci were identified using orthogonal views in three directions and colored on consecutive coronal slices. *c* caudal portion, *LOS* lateral orbital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

morphology in psychotic disorders may reflect neurodevelopmental pathology.

Previous MRI studies of gross surface morphology in individuals with an at-risk mental state (ARMS) [12, 13], about 35% of whom would later develop psychosis [14, 15], have yielded partly inconsistent results; the ARMS subjects likely exhibit an altered folding pattern of the anterior cingulate cortex [16] and frontal/parietal hyper-gyrification [17] regardless of later transition status, while abnormally shallow olfactory sulcus was specific to those with later psychosis onset (ARMS-P) [18]. To our knowledge, only one MRI study has examined the OFC surface morphology in ARMS; Lavoie et al. [19] demonstrated that a decreased number of IOS/POS was observed in the ARMS individuals without clear relation to psychosis onset, while ARMS-P subjects had decreased Type I and increased Type II patterns on the right hemisphere compared to controls. Chakirova et al. [6] 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 number of IOS/POS and the OFC sulcogyral pattern in the ARMS and healthy comparison subjects recruited at four scanning sites in Japan. On the basis of a possible role of the OFC surface morphology as an early neurodevelopmental marker of psychosis [5] as well as previous MRI findings [6, 19], we predicted that ARMS subjects, especially those who later developed psychosis, would have fewer IOS/POS and altered OFC pattern distribution as compared with healthy subjects. Because the OFC surface morphology possibly reflects maturation process and function of the OFC [1, 2], we also investigated the association between the OFC surface morphology and demographic/clinical variables in both healthy and high-risk subjects.

Materials and methods

Subjects

One hundred and twenty-five individuals with ARMS were recruited from domestic specialized clinical services for ARMS at Toyama University Hospital, Toho University Hospital, Tohoku University Hospital, and the University of Tokyo Hospital [20, 21]. Each individual fulfilled the criteria of ARMS for the Comprehensive Assessment of At Risk Mental States (CAARMS) [22] (Toyama and Tohoku) or the Structured Interview for Prodromal Syndromes/Scale of Prodromal Symptoms (SIPS/SOPS) [23] (Toho and Tokyo). 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, $n = 89$), or (3) those with an unknown outcome due to drop out within less than 2 years (ARMS-UK, $n = 14$). 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 1 week) or the SIPS criteria (i.e., the presence of a positive symptom that has been existing for more than 1 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) [24] 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. In addition, the healthy controls in this study did not have any history of psychiatric illness. 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.

Magnetic resonance imaging procedures

T1-weighted MRI images of 1-mm sagittal slices were acquired from four scanning sites. The scanner field strength was 1.5 T for three sites (Toyama, Toho, and Tohoku) and 3.0 T 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.

Sulcus count and OFC sulcogyral pattern classification

We identified and counted the number of IOS (single, double, or triple) and POS (absent, single, or double); the IOS was identified anterior to the transverse orbital sulcus (TOS) in between the rostral medial orbital sulcus (MOS) and rostral lateral orbital sulcus (LOS), while the POS was posterior to the TOS in between the caudal MOS and caudal LOS (Fig. 2). According to previous reports [4, 19], a fissure clearly visible in at least four coronal and four axial slices was defined as a sulcus.

The MOS, LOS, and 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 [1]. 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 [6].

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.

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 number of IOS/POS (three counts for each sulcus) and OFC pattern distribution (three patterns) were evaluated by 2×3 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 [6, 8]. To examine possible functional significance of the OFC surface morphology, its associations with demographic/clinical variables (age, education, parental education, and medication dose) were analyzed for each hemisphere by ANOVA with the sulcus count or OFC pattern 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 $p<0.05$.

Results

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).

Group difference in the sulcus count and OFC pattern distribution

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

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	89	14	–	–
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	25	1	–	–
Scanning site 4 (Tokyo)	32	32	3	22	7	–	–
Male/female	54/56	54/71	8/14	40/49	6/8	χ^2 (1) = 0.81, p = 0.366	χ^2 (1) = 0.53, p = 0.467
Age (years)	21.3 (3.2)	21.3 (5.5)	20.2 (4.3)	21.7 (5.9)	20.7 (4.3)	F (1, 233) < 0.01, p = 0.958	F (1, 109) = 1.14, p = 0.287
Education (years)[a]	14.4 (2.6)	12.5 (2.5)	12.6 (2.4)	12.6 (2.6)	12.0 (2.1)	F (1, 202) = 27.84, p < 0.001	F (1, 90) = 0.01, p = 0.908
Parental education (years)[b]	14.2 (2.1)	13.9 (2.1)	13.9 (1.8)	13.9 (2.2)	14.0 (1.8)	F (1, 165) = 0.56, p = 0.455	F (1, 71) = 0.02, p = 0.899
Handedness (right/mix/left)[c]	96/0/1	96/6/5	17/2/2	66/4/2	13/0/1	p = 0.012 (FET)	p = 0.249 (FET)
Duration between scan and onset (months)	–	–	10.0 (9.3)	–	–	–	–
Clinical follow-up period after scanning (months)	–	62.8 (30.9)	61.0 (26.1)	72.0 (24.4)	7.0 (6.0)	–	F (1, 109) = 3.49, p = 0.064
Drug (mg/day, chlorpromazine equivalent)[d]	–	181.5 (143.3) (n = 43)	191.4 (123.2) (n = 10)	155.2 (104.8) (n = 30)	411.0 (337.6) (n = 3)	–	F (1, 38) = 0.82, p = 0.371
Medication type (typical/atypical/mixed)	–	5/36/2	0/10/0	5/24/1	0/2/1	–	p = 0.476 (FET)
CAARMS subscale scores (n = 55)							
Unusual thought global rating	–	2.8 (1.9)	3.4 (2.2)	2.5 (1.8)	3.6 (1.5)	–	F (1, 46) = 2.18, p = 0.147
Unusual thought frequency	–	3.5 (2.0)	3.2 (2.0)	3.5 (2.1)	4.1 (1.3)	–	F (1, 46) = 0.28, p = 0.601
Perceptual abnormalities global rating	–	2.8 (1.6)	2.8 (1.8)	2.8 (1.5)	2.7 (1.6)	–	F (1, 46) < 0.01, p = 0.953
Perceptual abnormalities frequency	–	2.9 (1.8)	2.9 (2.0)	2.8(1.6)	3.3 (2.1)	–	F (1, 46) = 0.02, p = 0.895
Disorganized speech global rating	–	2.0 (1.2)	2.4 (1.3)	2.0(1.3)	1.7 (1.0)	–	F (1, 46) = 0.98, p = 0.328
Disorganized speech frequency	–	3.9 (2.2)	3.6 (2.1)	3.9 (2.3)	4.3 (2.4)	–	F (1, 46) = 0.11, p = 0.738

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 31 individuals (12 healthy and 19 ARMS individuals)

[b]Data missing for 68 individuals (30 healthy and 38 ARMS individuals)

[c]Data missing for 31 individuals (13 healthy and 18 ARMS individuals)

[d]Converted into chlorpromazine equivalents using the guideline by Inada and Inagaki [25]

Table 2 MRI data acquisition

Site	Scanner	Field strength (Tesla)	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
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
Tokyo	GE Signa	3	6.80/1.94	0.938 × 0.938 × 1.0	3D-FSPGR

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

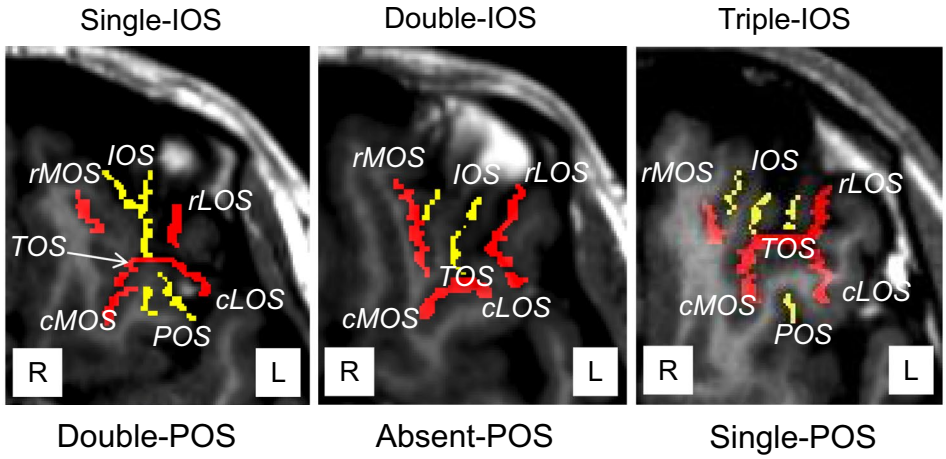

Fig. 2 Variations in the number of intermediate orbital sulcus (IOS) and posterior orbital sulcus (POS) on sample axial views of the orbitofrontal cortex (yellow). *c* caudal portion, *LOS* lateral orbital sulcus, *MOS* medial orbital sulcus, *r* rostral portion, *TOS* transverse orbital sulcus

and -NP groups (Table 3). 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 4).

Our main results of fewer orbital sulci in the ARMS group remained significant for right IOS and left POS even after Bonferroni correction for multiple comparisons [six OFC variations (H-shaped pattern, IOS, and POS for each hemisphere) in two groups; $p < 0.004$ (0.05/12)]. Further, 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 ($n = 82$).

OFC surface morphology and demographic/clinical variables

In the controls, the sulcus counts did not relate to demographic variables. However, right OFC Type II pattern was related to lower education (mean 12.1 years, SD 2.4) [F (2, 94) = 4.78, $p = 0.011$] compared with Type III (mean 15.3 years, SD 2.4; Scheffe's test, $p = 0.011$) and to younger age (mean 18.3 years, SD 2.3) [F (2, 105) = 5.71, $p = 0.004$] compared with Type I (mean 21.2 years, SD 3.1; Scheffe's test, $p = 0.038$) and Type III (mean 22.4 years, SD 3.0; Scheffe's test, $p = 0.005$).

In the ARMS subjects, the right double-IOS pattern was related to younger age (mean 21.0 years, SD 4.9) [F (1, 113) = 4.31, $p = 0.040$] compared with single-IOS (mean 23.3 years, SD 6.6; Scheffe's test, $p = 0.040$). Further, those with right absent-POS ($n = 24$) had a lower global score of perceptual abnormalities (mean 1.8, SD 1.6) [F (1, 46) = 28.33, $p < 0.001$] compared with single-POS ($n = 26$, mean 3.7, SD 1.0; Scheffe's test, $p < 0.001$). While the OFC pattern in the ARMS individuals did not relate to demographic variables (age and parental/personal education), those with left OFC pattern II ($n = 5$) had a lower global score of disorganized speech (mean 0.6, SD 0.9) [F (2, 48) = 3.43, $p = 0.041$] compared with Type I ($n = 25$, mean 2.2, SD 1.3; Scheffe's test, $p = 0.024$) and III ($n = 23$, mean 2.1, SD 1.1; Scheffe's test, $p = 0.040$). 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.

Table 3 Sulcus counts of the orbital sulci in the study participants

	Controls ($n=110$), n (%)	Whole ARMS ($n=125$), n (%)	ARMS-P ($n=22$), n (%)	ARMS-NP ($n=89$), n (%)	ARMS-UK ($n=14$), n (%)	Controls vs whole ARMS			ARMS-P vs ARMS-NP		
						$\chi 2$ (2)	p	Cramer's V	$\chi 2$ (2)	p	Cramer's V
Left IOS						8.37	0.015[a]	0.19	–	1.000[b]	0.02
Single	34 (30.9)	54 (43.2)	9 (40.9)	39 (43.8)	6 (42.9)						
Double	60 (54.5)	65 (52.0)	12 (54.5)	46 (51.7)	7 (50.0)						
Triple	16 (14.5)	6 (4.8)	1 (4.5)	4 (4.5)	1 (7.1)						
Right IOS						11.95	0.003[a]	0.23	–	0.091[b]	0.19
Single	17 (15.5)	33 (26.4)	2 (9.1)	26 (29.2)	5 (35.7)						
Double	68 (61.8)	82 (65.6)	18 (81.8)	58 (65.2)	6 (42.9)						
Triple	25 (22.7)	10 (8.0)	2 (9.1)	5 (5.6)	3 (21.4)						
Left POS						15.31	< 0.001[a]	0.26	–	0.183[b]	0.19
Absent	38 (34.5)	72 (57.6)	10 (45.5)	55 (61.8)	7 (50.0)						
Single	59 (53.6)	49 (39.2)	12 (54.5)	30 (33.7)	7 (50.0)						
Double	13 (11.8)	4 (3.2)	0 (0.0)	4 (4.5)	0 (0.0)						
Right POS						1.00	0.608	0.07	1.1	0.584	0.10
Absent	51 (46.4)	61 (48.8)	13 (59.1)	42 (47.2)	6 (42.9)						
Single	47 (42.7)	55 (44.0)	8 (36.4)	40 (44.9)	7 (50.0)						
Double	12 (10.9)	9 (7.2)	1 (4.5)	7 (7.9)	1 (7.1)						

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, χ^2 (1) = 6.55, $p=0.010$; right, χ^2 (1) = 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, χ^2 (1) = 4.19, $p=0.041$] and absent-POS [left, χ^2 (1) = 12.49, $p<0.001$] patterns less often than the ARMS group

[b]Fisher's exact test was used

Table 4 Distribution of OFC sulcogyral pattern in the study participants

	Controls ($n=110$), n (%)	whole ARMS ($n=125$), n (%)	ARMS-P ($n=22$), n (%)	ARMS-NP ($n=89$), n (%)	ARMS-UK ($n=14$), n (%)	Controls vs whole ARMS			ARMS-P vs ARMS-NP		
						χ^2 (2)	p	Cramer's V	χ^2 (2)	p	Cramer's V
Left hemisphere						0.71	0.703	0.06	0.17	0.922	0.04
Type I	60 (54.5)	61 (48.8)	10 (45.5)	46 (51.7)	5 (35.7)						
Type II	9 (8.2)	12 (9.6)	2 (9.1)	7 (7.9)	3 (21.4)						
Type III	40 (36.4)	50 (40.0)	9 (40.9)	35 (39.3)	6 (42.9)						
Type IV	1 (0.9)	2 (1.6)	1 (4.5)	1 (1.1)	0 (0.0)						
Right hemisphere						2.96	0.228	0.11	1.19	0.550	0.10
Type I	72 (65.5)	70 (56.0)	14 (63.6)	47 (52.8)	9 (64.3)						
Type II	8 (7.3)	9 (7.2)	2 (9.1)	6 (6.7)	1 (7.1)						
Type III	28 (25.5)	45 (36.0)	6 (27.3)	35 (39.3)	4 (28.6)						
Type IV	2 (1.8)	1 (0.8)	0 (0.0)	1 (1.1)	0 (0.0)						

ARMS at-risk mental state, *NP* non-psychosis, *P* psychosis, *UK* unknown outcome

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 eight subjects (Table 3). The OFC pattern and IOS/POS counts did not relate to each other in the ARMS subjects (all $p>0.119$).

Discussion

In this multicenter MRI study, we investigated the number of orbital sulci and OFC H-shaped sulcogyral pattern in a relatively large sample of clinical high-risk subjects. While the ARMS individuals had a significantly lower number of IOS/POS compared with controls, the number of these sulci did not differ between the ARMS individuals with and without later transition to psychosis. No group difference was found in the distribution of the OFC sulcogyral pattern. 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 [11, 26]. 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 [27]). Indeed, a recent functional MRI study of reward type-dependent activation demonstrated functional organization in specific OFC sulci locations [28]; primary (erotic) and secondary (monetary) experienced value signals were located in the rostral and more caudal portions of the MOS, respectively. 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 [29]. Interestingly, our previous OFC studies [4, 8] 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. Given the association between the OFC surface morphology and symptomatology in the high-risk subjects [6] as well as established schizophrenia patients [4, 7] as described below, the anatomo-functional relation of the OFC and its potential abnormalities should be further examined in various stages of psychosis.

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 [effect size relative to controls (Cramer's V) = 0.07 to 0.26 (small to medium)] are in line with similar findings in subjects with ARMS (Cramer's V = 0.17 to 0.33) [19], first-episode psychosis (Cramer's V = 0.06 to 0.24) [5], and established schizophrenia (Cramer's V = 0.24 to 0.39) [4]. Because this and previous [19] 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 [2, 29], our findings may partly support the neuroimaging findings of frontal dysconnectivity also in ARMS subjects who did not develop psychosis [30, 31] or in non-affected relatives of schizophrenia patients [32].

Inconsistent with the relatively common finding of decreased Type I and/or increased Type III pattern in the right hemisphere from the prodromal [19] or early [5, 9] phases of psychosis to chronic stages of schizophrenia [3, 7], 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 [6], although their results are not lateralized and of a mild degree. On the other hand, discrepant findings (e.g., increased Type II in schizophrenia [3]) 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 [8]. 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 [33–35]. Indeed, the OFC sulcogyral patterns seem to be associated with the thickness of OFC gray matter in a community sample [36]. Further, our findings in healthy subjects suggested possible effect of aging and education on the OFC pattern, which may support that environmental factors could affect frontal maturation process (e.g., synaptic pruning) during adolescence [35, 37]. Taken together, our findings suggest that the OFC H-shaped sulcogyral pattern is unlikely to be a simple neurodevelopmental marker, but further longitudinal studies should examine its stability in both normal and pathological conditions (e.g., 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 [6] or severity of symptoms and cognitive impairments in schizophrenia [7], but healthy subjects with Type III are reported to have better cognitive functioning [27]. 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 [4]. On the other hand, more POS pattern was also associated with aberrant neurodevelopment due to preterm birth [27] or more severe depressive symptoms in the general population [36]. 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 four 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 [38] as well as prodromal symptomatology [39]. However, our main findings did not change even when we examined only medication-naïve ARMS subjects. Third, for the relation between the OFC morphology and clinical/demographic variables, the possibility of Type I error due to multiple exploratory analyses needs to be taken into account. Further studies with clear hypotheses would be required to clarify the functional significance of OFC surface morphology in both healthy and high-risk subjects. Finally, as altered distribution of OFC pattern and fewer orbital sulci are also reported in autism spectrum disorders [40] and anxiety trait in panic disorder [41], 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.

Acknowledgements This work was supported by JSPS KAKENHI Grant Number JP26461739 to TT, JP26461738 to YT, JP24390281 to MS, JP16H06395, 16H06399, 16K21720, and 16H06280 to KK, the SENSHIN Medical Research Foundation [Psychiatry 16 (general): 2–30] to YT, and by the Health and Labour Sciences Research Grants for Comprehensive Research on Persons with Disabilities from the Japan Agency for Medical Research and Development (AMED) Grant Number 16dk0307029h0003 to MS, KM and MM The study was also supported in part by the Brain Mapping by Integrated Neurotechnologies for Disease Studies (Brain/MINDS) from AMED Grant Number 17dm0207004h0004, UTokyo Center for Integrative Science of Human Behavior (CiSHuB), and by World Premier International Research Center Initiative (WPI), MEXT, Japan to KK. The funding agencies had no role in the design and conduct of the study, collection, management, analysis and interpretation of the data, or preparation, review and approval of the manuscript. The authors are grateful to the staff of the Consultation and Support Service in Toyama (CAST), Il Bosco of Toho University Omori Medical Center, Sendai At-risk Mental State and First Episode (SAFE) service, and the University of Tokyo Hospital for their assistance in the diagnostic and psychopathological assessments of the study participants.

Compliance with ethical standards

Conflict of interest There are no conflicts of interest for any of the authors including any financial, personal or other relationships with other people or organizations within 3 years of beginning the submitted work that could inappropriately influence, or be perceived to influence, our work.

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