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Short communication

Potential role of orbitofrontal surface morphology on social and cognitive functions in high-risk subjects for psychosis and schizophrenia patients

Tsutomu Takahashi[a,*], Mihoko Nakamura[a], Yumiko Nishikawa[a], Yuko Komori[a], Shimako Nishiyama[a], Yoichiro Takayanagi[a], Atsushi Furuichi[a], Mikio Kido[a], Daiki Sasabayashi[a], Yuko Higuchi[a], Kyo Noguchi[b], Michio Suzuki[a]

[a] Department of Neuropsychiatry, University of Toyama Graduate School of Medicine and Pharmaceutical Sciences, 2630 Sugitani, Toyama 930-0194, Japan
[b] Department of Radiology, University of Toyama Graduate School of Medicine and Pharmaceutical Sciences, 2630 Sugitani, Toyama 930-0194, Japan

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ABSTRACT

This MRI study examined the surface morphology of the orbitofrontal cortex (OFC) and its relation to social and cognitive functions in 38 individuals with at-risk mental state (ARMS) and 63 schizophrenia patients in comparison with 61 healthy controls. The ARMS and schizophrenia groups had increased right OFC Type III expression and fewer orbital sulci, which were partly associated with social and cognitive impairments. OFC underdevelopment may underlie vulnerability to psychosis, as well as the core clinical features of the illness.

1. Introduction

Magnetic resonance imaging (MRI) studies of the surface morphology of the orbitofrontal cortex (OFC), which is thought to reflect variations in early neurodevelopmental processes (Kringelbach and Rolls, 2004), in schizophrenia generally demonstrated increased Type III expression in the variation of the ‘H-shaped’ sulcus (Type I, II, and III) and fewer intermediate and posterior orbital sulci (IOS/POS) (Takahashi and Suzuki, 2018). These findings are evident even in first-episode (e.g., Takayanagi et al., 2010) or clinical high-risk (Lavoie et al., 2014; Nakamura et al., in press) subjects, possibly reflecting neurodevelopmental anomalies related to a vulnerability to psychosis.

Cognitive impairments, particularly in memory and executive function, are a core feature of schizophrenia, and are present during the first-episode (Aas et al., 2014) or even before psychosis onset (Fusar-Poli et al., 2012). Schizophrenia patients with an OFC Type III pattern were reported to have poor cognition (Nakamura et al., 2007), supporting the potential role of the frontal gyrification pattern in cognitive function in schizophrenia (Sasabayashi et al., 2017). However, other OFC studies did not find such a relationship (e.g., Takayanagi et al., 2010; Bartholomeusz et al., 2013). Further, as discussed elsewhere (Nakamura et al., in press), the functional relevance of the IOS/POS counts in healthy subjects as well as in schizophrenia patients is largely unknown.

This MRI study investigated OFC surface morphology in individuals with at-risk mental state (ARMS) and schizophrenia patients in comparison with healthy controls. We aimed to replicate previous OFC findings in an independent cohort and further examine possible relation between the OFC surface morphology and cognitive and social functions.

2. Methods

2.1. Subjects

Thirty-eight ARMS subjects fulfilling the Comprehensive Assessment of At-Risk Mental States (CAARMS) criteria (Yung et al., 2005) were recruited from the Consultation and Support Service in Toyama, a specialized clinical setting for early intervention. Major comorbid DSM Axis I disorder included anxiety disorders ($n = 9$), depressive disorders ($n = 6$), schizotypal personality disorders ($n = 6$), pervasive developmental disorders (PDD) ($n = 4$), and attention-deficit/hyperactivity disorder ($n = 2$). The subjects were prospectively followed up on an as-needed basis (e.g., fortnightly to monthly); four (10.5%) developed schizophrenia during clinical follow-up (mean period = 896.1 ± 841.6 days, range = 35–3803 days).

Sixty-three patients with schizophrenia (illness duration = 5.5 ± 6.0 years) were recruited from Toyama University Hospital and diagnosed using the Structured Clinical Interview for DSM-IV Axis I Disorders Patient Edition (SCID-I/P) (First et al., 1997) and a detailed chart review. The clinical symptoms of the ARMS and schizophrenia subjects were rated using the Positive and Negative Syndrome Scale

* Corresponding author.
E-mail address: tsutomu@med.u-toyama.ac.jp (T. Takahashi).

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Table 1
Demographic/clinical data and orbitofrontal surface morphology in the ARMS, schizophrenia, and control subjects

	Controls (n = 61)	ARMS (n = 38)	Sz (n = 63)	Group difference
Age	25.6 ± 3.2	18.4 ± 3.9	28.0 ± 9.4	F (2, 159) = 27.01, p < 0.001; ARMS < Contols, Sz
Male/female	32/29	24/14	29/34	Chi-square = 2.79, p = 0.248
Height (cm)	166.0 ± 8.3	165.3 ± 9.0	163.2 ± 8.4	F (2, 159) = 1.80, p = 0.168
JART-IQ	110.2 ± 5.9	98.0 ± 10.2	99.5 ± 9.7	F (2, 159) = 32.91, p < 0.001; ARMS, Sz < Controls
Handedness (right/mixes/left)	40/15/6	22/12/4	52/9/2	Fisher's exact test, p = 0.064
Medication dose (HPD equiv., mg/day)	-	2.0 ± 1.6 (n = 11)	11.3 ± 7.8 (n = 51)	F (1, 59) = 15.15, p < 0.001; ARMS < Sz
Medication type (atypical/typical/mixed)	-	9/1/1	45/1/5	Fisher's exact test, p = 0.372
Duration of medication (years)	-	0.7 ± 1.3 (0.0 to 4.8; n = 14)[a]	5.2 ± 6.2 (0.0 to 25.0; n = 53)[a]	F (1, 64) = 0.05, p = 0.820
PANSS positive	-	11.4 ± 3.6 (2 to 18)	13.9 ± 5.6 (7 to 30)	F (1, 98) = 5.20, p = 0.024; ARMS < Sz
PANSS negative	-	15.4 ± 6.7 (2 to 29)	16.3 ± 5.6 (7 to 32)	F (1, 98) = 3.97, p = 0.049; not significant (post-hoc test)
PANSS general	-	30.4 ± 8.1 (18 to 49)	31.0 ± 9.7 (16 to 55)	F (1, 98) = 1.38, p = 0.243
SOFAS[b,c]	-	52.2 ± 10.8 (30 to 70)	48.2 ± 13.9 (30 to 85)	F (1, 97) = 4.52, p = 0.036: not significant (post-hoc test)
SCoRS global rating score[b]	-	5.4 ± 2.4 (1 to 9)	5.2 ± 2.5 (1 to 9)	F (1, 97) = 0.49, p = 0.487
BACS subdomain z-scores[d]				Group × domain interaction, F (5, 495) = 5.64, p < 0.001
Verbal memory	-	−0.9 ± 1.6 (−5.0 to 2.4)	−1.3 ± 1.4 (−5.2 to 1.4)	p = 0.933
Working memory	-	−0.8 ± 1.4 (-4.7 to 1.5)	−1.0 ± 1.4 (-5.1 to 1.2)	p = 1.000
Motor function	-	−0.8 ± 1.4 (−4.0 to 2.4)	−1.9 ± 1.5 (−5.9 to 1.0)	p = 0.009; Sz < ARMS
Verbal fluency	-	−1.0 ± 1.6 (-4.7 to 1.6)	−0.8 ± 1.1 (-3.5 to 1.5)	p = 1.000
Attention and processing speed	-	−0.3 ± 1.3 (-4.4 to 2.2)	−1.4 ± 1.5 (-5.0 to 2.0)	p = 0.013; Sz < ARMS
Executive function	-	−0.5 ± 1.3 (-6.1 to 1.3)	−0.8 ± 1.6 (−7.3 to 1.7)	p = 1.000
Left OFC sulcogyral pattern [n (%)]				Chi-square = 7.53, p = 0.112
Type I	39 (63.9)	25 (65.8)	31 (49.2)	
Type II	5 (8.2)	6 (15.8)	6 (9.5)	
Type III	16 (26.2)	7 (18.4)	26 (41.3)	
Type IV	1 (1.6)	0 (0)	0 (0)	
Right OFC sulcogyral pattern [n (%)]				Chi-square = 11.64, p = 0.020[e]
Type I	42 (68.9)	20 (52.6)	28 (44.4)	
Type II	6 (9.8)	3 (7.9)	4 (6.3)	
Type III	12 (19.7)	15 (39.5)	31 (49.2)	
Type IV	1 (1.6)	0 (0)	0 (0)	
Left IOS [n (%)]				Chi-square = 16.42, p = 0.003[f]
Single	15 (24.6)	18 (47.4)	30 (47.6)	
Double	33 (54.1)	19 (50.0)	30 (47.6)	
Triple	13 (21.3)	1 (2.6)	3 (4.8)	
Right IOS [n (%)]				Chi-square = 20.03, p < 0.001[f]
Single	9 (14.8)	15 (39.5)	25 (39.7)	
Double	40 (65.6)	21 (55.3)	37 (58.7)	
Triple	12 (19.7)	2 (5.3)	1 (1.6)	
Left POS [n (%)]				Chi-square = 5.33, p = 0.255
Absent	27 (44.3)	21 (55.3)	38 (60.3)	
Single	27 (44.3)	15 (39.5)	23 (36.5)	
Double	7 (11.5)	2 (5.3)	2 (3.2)	
Right POS [n (%)]				Chi-square = 22.05, p > 0.001[f]
Absent	18 (29.5)	19 (50.0)	38 (60.3)	
Single	29 (47.5)	18 (47.4)	23 (36.5)	
Double	14 (23.0)	1 (2.6)	2 (3.2)	

Values represent Means ± SDs (range) unless otherwise stated.
ARMS, at-risk mental state; BACS, Brief Assessment of Cognition in Schizophrenia; HPD, haloperidol; IOS, intermediate orbital sulcus; JART, Japanese version of National Adult Reading Test; OFC, orbitofrontal cortex; PANSS, Positive and Negative Syndrome Scale; POS, posterior orbital sulcus; SCoRS, Schizophrenia Cognition Rating Scale; SOFAS, Social and Occupational Functioning Assessment Scale; Sz, schizophrenia.

[a] Some participants were medication-free at the time of scanning but had a history of antipsychotic medication.
[b] Data missing for one schizophrenia patient.
[c] Healthy subjects generally have a score ranged 90–100 (Madeira et al., 2016).
[d] The primary measure from each test of the BACS was standardized by creating z-scores, whereby the mean score of Japanese healthy controls was set to zero and the standard deviation set to one (Kaneda et al., 2013).
[e] No group difference between the ARMS and Sz groups (χ^2 = 0.91, p = 0.635). The ARMS (χ^2 = 4.42, p = 0.036) and Sz (χ^2 = 11.53, p < 0.001) groups had increased Type III expression compared to controls. The Sz group also had decreased Type I expression compared to controls (χ^2 = 8.18, p = 0.004). When we excluded four ARMS individuals with pervasive developmental disorder (PDD), the ARMS group had a trend towards increased Type III expression compared to controls (χ^2 = 3.70, p = 0.055).
[f] No group differences between the ARMS and Sz groups (all p > 0.287). When they were grouped together as a clinical group, the triple-IOS [left, p < 0.001 (Fisher's exact test); right, p = 0.002 (Fisher's exact test)] and double-POS [right, p < 0.001 (Fisher's exact test)] patterns were more common in the controls than in the clinical group. These results of sulcus number remained essentially the same even when we excluded the ARMS individuals with PDD (n = 4). The controls had single-IOS (left, χ^2 = 8.41, p = 0.003; right, χ^2 = 11.13, p < 0.001) and absent-POS (right, χ^2 = 11.09, p = 0.001) patterns less often than the clinical group.

(PANSS) (Kay et al., 1987). Medication and other clinical data are summarized in Table 1.

Sixty-one healthy volunteers, without family history of psychiatric illness among first-degree relatives, were recruited from members of the local community and hospital staff. They were screened using the SCID-I Non-patient Edition (First et al., 1997) and a questionnaire consisting of 19 items concerning personal and family histories of illness.

All subjects were physically healthy and none had a lifetime history of serious head trauma, neurological illness, serious medical or surgical illness, substance abuse, or steroid use. There is no sample overlap between this and our previous study (Nakamura et al., 2018), which examined the OFC surface morphology in ARMS individuals recruited from 4 different sites. This study received approval from the Committee on Medical Ethics of Toyama University. Written informed consent was obtained from all subjects. When participants were under the age of 20, written consent was also obtained from the parent/guardian.

2.2. Magnetic resonance imaging procedures

MR scans were acquired with a 3-T Magnetom Verio (Siemens, Erlangen, Germany) with a 3D MPRAGE sequence, which yielded 176 contiguous T1-weighted slices of 1.2-mm thickness in the sagittal plane (TR = 2300 ms, TE = 2.9 ms, Flip = 9°, FOV = 256 mm, Matrix = 256 × 256, and Voxel size = 1.0 × 1.0 × 1.2 mm). Using Dr. View software (Infocom, Tokyo, Japan), brain images were realigned in three dimensions and then reconstructed into entire contiguous coronal images, 1-mm thick, perpendicular to the anterior commissure-posterior commissure line.

The OFC pattern classification (Type I, II, and III) and sulcus counts of the IOS/POS were based on Chiavaras and Petrides (2000) (eFig. 1). One rater (TT) assessed the OFC surface morphology with no knowledge of the subject's identity. Intra- and inter-rater (TT and MN) reliabilities (Cronbach's α) for the OFC pattern and sulcus counts in a subset of 30 hemispheres were over 0.81.

2.3. Assessment of social and cognitive functions

The ARMS and schizophrenia groups were assessed using the Brief Assessment of Cognition in Schizophrenia (BACS) (Keefe et al., 2004), the Schizophrenia Cognition Rating Scale (SCoRS), an interview-based measure of cognitive abilities related to daily-living functioning (Keefe et al., 2006; Higuchi et al., 2017), and the Social and Occupational Functioning Assessment Scale (SOFAS) (Goldman et al., 1992).

2.4. Statistical analysis

Group differences in the OFC pattern distribution and number of IOS/POS were evaluated by χ^2 test. Hemispheres with a rare OFC Type IV pattern were excluded from the statistical analyses (Chakirova et al., 2010). The relationships between the OFC surface morphology and clinical variables [onset age and illness duration (for schizophrenia), dose and duration of medication, and PANSS subscores] and social/cognitive measures (SOFAS, SCoRS, and BACS scores) were analyzed for each hemisphere by ANOVA, with the OFC pattern or sulcus count as a between-subject factor. Because of small number of the subjects with Type II, the OFC pattern was categorized as Type III *vs* non-Type III or Type I *vs* non-Type I. Hemispheres with triple-IOS and/or double-POS in the ARMS and schizophrenia subjects were excluded from the ANOVAs due to small sample size (n = 1 to 3). Post hoc Scheffé's tests were used. Significance was defined as $p < 0.05$.

3. Results

Both schizophrenia and ARMS groups had an increased right Type III OFC pattern and a lower number of IOS/POS compared with controls, but there was no difference in the OFC surface morphology between these groups (Table 1). The schizophrenia group was also characterized by a decreased right Type I expression compared to controls (Table 1).

In schizophrenia, a right Type III [F (1, 60) = 5.39, p = 0.024] or right non-Type I [F (1, 60) = 11.62, p = 0.001] pattern was significantly related to lower SOFAS score. Further, patients with a left absent-POS had a lower BACS score compared with those with a left single-POS [F (1, 59) = 5.01, p = 0.029], but no interaction was found between the POS pattern and BACS subdomain. These relations remained significant even when we used illness duration and PANSS positive score as the covariates to control for major state effects on cognitive and social functions. The OFC surface morphology was not associated with SOFAS or BACS score in the ARMS group, or with clinical variables and SCoRS score in the schizophrenia and ARMS groups. When the ARMS and schizophrenia subjects were grouped together, subjects with right Type III had a lower BACS score compared with those with non-Type III [F (1, 99) = 4.26, p = 0.042], with no interaction between the OFC pattern and BACS subdomain.

4. Discussion

The present study demonstrated that the gross morphology of the OFC was significantly associated with social and cognitive functions in schizophrenia. We also found that individuals with ARMS share a characteristic OFC surface morphology with schizophrenia.

This study replicated an increased Type III expression and fewer orbital sulci in various stages of psychosis, which is thought to reflect early disruption of neurodevelopment predominantly during the mid-to-late gestation period (Kringelbach and Rolls, 2004). Progressive gray matter changes during the early stages of psychosis (Takahashi and Suzuki, 2018) may affect cortical folding, but previous OFC findings suggest that surface morphology is independent of regional volume (Takayanagi et al., 2010) or illness stages (Lavoie et al., 2014; Nishikawa et al., 2016). While it is possible that the OFC findings are more evident in ARMS individuals with later psychosis onset (Lavoie et al., 2014), our results suggest that OFC gross morphology may be a common vulnerability marker of psychosis that reflects early neurodevelopmental abnormalities. It is also reported that schizotypal disorder patients, who have a biological vulnerability to psychosis (Siever and Davis, 2004), partly share the OFC surface morphology with schizophrenia patients (Takahashi et al., 2016), but further study will be needed especially in individuals with a genetic or familial liability to develop psychosis to clarify its potential role as a vulnerability marker.

In this study, an OFC Type III and absent-POS patterns were associated with cognitive deficits in schizophrenia patients or in a combined group of high-risk and schizophrenia subjects. Given that the cortical folding pattern likely reflects critical neurodevelopmental events, such as local neuronal connection and synaptic development (Rakic, 1988), our OFC findings may partly support neuroimaging findings that suggested a relation between frontal dysconnectivity and core cognitive deficits in various stages of psychosis, including clinical high-risk status (Hubl et al., 2018), and both first-episode (Pérez-Iglesias et al., 2010) and chronic (Spoletini et al., 2009) phases. The schizophrenia patients with right Type III (or non-Type I) pattern were also characterized by poor social functioning, partly supporting previous findings of poor local orbitofrontal connectivity (Eack et al., 2017) and specific role of this region on social impairment in schizophrenia (Chemerinski et al., 2002). However, as the present study only explored one specific region in frontal cortex, functional relevance of OFC surface morphology should be further tested ideally in combination with functional and/or connectivity analyses in more diverse brain areas.

Our study was partly limited by a lack of cognitive and functional assessment for healthy control subjects, possible Type I error due to multiple exploratory analyses, and factors related to comorbid diagnosis of ARMS individuals (i.e., no SCID assessment, rather high rate of PDD diagnosis). Probably due to short clinical follow-up periods (< 1 year) for a substantial number of ARMS cases ($n = 12$), our ARMS cohort was characterized by rather low transition rate (10.5%) and small sample size for those who developed psychosis ($n = 4$), which limited our ability to reliably examine the relation between OFC surface morphology and a later transition into psychosis. Possible role of the OFC findings in identifying neurobiological predictors of future transition, which would allow specific and targeted preventive strategies, should be further examined on a larger and well-characterized ARMS cohort.

Contributors

In this study, Drs. Suzuki and Takahashi conceived the idea and methodology of the study. Dr. Takahashi conducted the statistical analyses and wrote the manuscript. Drs. Nakamura, Nishikawa, Nishiyama, Sasabayashi, and Higuchi recruited subjects, and were involved in clinical and diagnostic assessments. Ms. Komori assessed the socio-cognitive functions of the study participants. Drs. Furuichi, Nishikawa, and Nakamura managed the MRI and clinical data. Drs. Takahashi, Nakamura, and Kido analyzed the MRI data. Dr. Noguchi provided technical support for MRI scanning and data processing. Drs. Suzuki, Higuchi, and Takayanagi contributed to the writing and editing of the manuscript. All authors contributed to, and have approved, the final manuscript.

Conflict of interest

No conflicts of interest to declare.

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Supplementary materials

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