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Regular Article

Increased pituitary volume in subjects at risk for psychosis and patients with first-episode schizophrenia

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Aim: Enlarged pituitary gland has been reported in schizophrenia, possibly reflecting hypothalamic–pituitary–adrenal hyperactivity. The aim of the present study was to examine whether individuals at risk of psychosis also have similar changes.

Methods: Magnetic resonance imaging was used to examine the pituitary volume in 22 individuals with at-risk mental state (ARMS; 11 male, 11 female), 64 first-episode patients with schizophrenia (FESz; 37 male, 27 female), and 86 healthy controls. The control subjects were divided into age- and gender-matched controls for ARMS (11 male, 11 female) and FESz (37 male, 27 female).

Results: Both the ARMS and FESz groups had a larger pituitary volume compared with matched controls, but no difference was found between the ARMS and FESz subjects. There was no association between the pituitary volume and clinical variables (symptom measures at scanning, daily dosage or duration of antipsychotic medication) in either clinical group. The pituitary volume did not differ significantly between the ARMS individuals who later developed schizophrenia ($n = 5$) and those who did not ($n = 17$). The pituitary volume was larger in women than in men for all diagnostic groups.

Conclusion: The finding of increased pituitary volume in both ARMS and FESz subjects may reflect a common vulnerability to stress in early psychosis. Further work in a larger ARMS sample is required to examine the possible relationship between pituitary volume and emergence of psychosis.

Key words: at-risk mental state, hypothalamic–pituitary–adrenal axis, magnetic resonance imaging, pituitary gland, schizophrenia.

HYPOTHALAMIC–PITUITARY–ADRENAL (HPA) axis hyperactivity is thought to reflect stress-related hormonal dysregulation and has been described in schizophrenia.[1,2] Although not consistently replicated,[3] previous magnetic resonance imaging (MRI) studies have generally demonstrated enlarged pituitary volume[4–6] with ongoing expansion[7,8] early in the course of schizophrenia, presumably reflecting activation of the hormonal stress response. The patients may also exhibit pituitary atrophy during later courses,[9–11] possibly as a result of prolonged HPA activation.[12] Interestingly, recent neuroendocrine findings in clinical subjects at high risk for developing psychosis (i.e. at-risk mental state; ARMS[13]), such as the association of cortisol level with prodromal or psychotic symptoms[14–17] as well as with

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progression to psychosis,[18] suggest that HPA axis dysfunction may pre-date the onset of psychosis in at least some individuals.[19]

In contrast to these hormonal investigations, there have been only a few MRI studies addressing pituitary volume changes prior to psychosis onset and the results have been inconsistent. In the first MRI study of the pituitary gland in clinical high-risk subjects, Garner *et al.* found no significant volume difference between the ARMS subjects (as a whole or those who later developed psychosis) and controls, but pituitary enlargement was associated with later transition to psychosis (predominantly affective psychosis).[4] They also examined the possible relationship of the pituitary volume to anxiety/depressive or psychotic symptoms, but found no significant results. Thompson *et al.* showed that pituitary volume in ARMS did not correlate with the experience of stressful events, plasma cortisol level, or clinical symptoms, but that study lacked a healthy comparison group.[17] A recent study by Büschlen *et al.* did not replicate a significant difference in the pituitary volume between ARMS with and without transition,[4] but their data (controls < ARMS without later transition < ARMS with transition and first-episode psychosis)[20] were in line with hypothesized pituitary enlargement with the emergence of psychosis. Thus, it remains unclear from the current evidence whether these high-risk subjects have significant pituitary volume changes as compared with controls and whether their pituitary volume is related to clinical characteristics.

The present MRI study investigated the pituitary volume in subjects with ARMS and first-episode schizophrenia (FESz) compared with age- and gender-matched healthy controls. On the basis of previous MRI and neuroendocrine findings suggesting HPA hyperactivity prior to the onset of overt psychosis,[19] we predicted that both ARMS and FESz subjects would have increased pituitary volume compared with matched controls. We also explored the relationship between the pituitary volume and clinical characteristics (e.g. symptom severity, later transition into psychosis, and antipsychotic medication) in these participants.

METHODS

Participants

Twenty-two ARMS subjects were recruited from the Consultation Support Service in Toyama (CAST), which was launched in 2006 as a specialized clinical setting to study and treat young people (aged 15–30 years) at risk for developing psychosis.[21] The ARMS subjects, who had no previous episode of overt psychosis and no clear diagnosis of major depression or borderline personality disorder, were diagnosed according to the Comprehensive Assessment of At Risk Mental States (CAARMS);[13] inclusion into the study required one or more of (i) attenuated psychotic symptoms defined by subthreshold intensity or frequency ($n = 21$); (ii) brief limited intermittent psychotic symptoms with spontaneous resolution ($n = 2$); and/or (iii) family history of psychosis or a personal history of schizotypal personality disorder accompanied by a decline in general functioning ($n = 1$). At intake, they were also assessed using the Beck Depression Inventory (BDI) and State Trait Anxiety Inventory (STAI) (Table 1).[23,24] Eighteen ARMS subjects were antipsychotic naïve at the time of scanning, but three subjects were receiving low doses of atypical antipsychotics (risperidone, blonanserin, or aripiprazole) and one was treated with sulpiride. They were also receiving benzodiazepines ($n = 3$), antidepressants ($n = 1$), and/or tandospirone ($n = 3$). The mental condition of each subject was regularly assessed by experienced psychiatrists to check for the emergence of full-blown psychosis at outpatient clinics of the Department of Neuropsychiatry of Toyama University Hospital; five (22.7%) of the ARMS subjects in this group developed schizophrenia fulfilling ICD-10 research criteria[25] and 17 (77.3%) did not develop psychosis during follow up (mean clinical follow-up period after scanning, 15.6 ± 17.4 months).

Sixty-four FESz patients who fulfilled the ICD-10 research criteria,[25] with illness duration ≤1 year ($n = 48$) or under first psychiatric hospitalization ($n = 16$) at the time of scanning,[26–29] were recruited from inpatient and outpatient clinics of the Department of Neuropsychiatry of Toyama University Hospital (Table 1). The diagnosis of schizophrenia was confirmed for all patients at least 6 months after illness onset based on information obtained from a detailed chart review as well as their clinical symptoms rated at the time of scanning. They were also screened for other neuropsychiatric conditions (e.g. depressive/manic symptoms) by experienced psychiatrists. All but two of the patients were on antipsychotic medication; 18 were treated with typical antipsychotics, 43 were receiving atypical antipsychotics and one received both typical and atypical antipsychotics.

Table 1. ARMS and FESz subject data vs matched controls (mean ± SD)

Parameters	ARMS (11 M, 11 F)	Controls (11 M, 11 F)	Group comparisons
Age (years)	19.1 ± 4.1	19.4 ± 4.2	$F(1,42) = 0.05$, $P = 0.830$
Height (cm)	162.2 ± 9.5	164.3 ± 8.5	$F(1,42) = 0.62$, $P = 0.436$
Education (years)	11.1 ± 1.6	13.1 ± 2.6	$F(1,42) = 8.99$, $P = 0.005$
Parental education (years)	13.8 ± 1.7	12.4 ± 1.6	$F(1,42) = 7.68$, $P = 0.008$
Medication dose (HPD equiv., mg/day)†	2.2 ± 3.1 ($n = 4$)	–	–
Duration of medication (months)	2.3 ± 4.1 ($n = 4$)	–	–
Time between intake and scan (days)	50.8 ± 74.4	–	–
Time between scan and onset (months)	8.2 ± 9.9 ($n = 5$)	–	–
STAI trait at intake‡	65.3 ± 10.9	–	–
STAI state at intake‡	58.4 ± 11.3	–	–
BDI at intake‡	24.1 ± 10.0	–	–
SAPS total at scanning	20.4 ± 10.9	–	–
SANS total at scanning	48.5 ± 19.4	–	–
	FESz (37 M, 27 F)	Controls (37 M, 27 F)	Group comparisons
Age (years)	24.0 ± 4.7	25.1 ± 5.0	$F(1,126) = 1.64$, $P = 0.203$
Height (cm)	164.9 ± 7.6	167.0 ± 7.5	$F(1,126) = 2.60$, $P = 0.109$
Education (years)	13.5 ± 1.9	16.5 ± 2.6	$F(1,126) = 57.55$, $P < 0.001$
Parental education (years)	13.0 ± 2.0	13.2 ± 2.5	$F(1,124) = 0.50$, $P = 0.482$
Onset age (years)	23.1 ± 4.7	–	–
Illness duration (months)	11.2 ± 12.2	–	–
Medication dose (HPD equiv., mg/day)	10.3 ± 8.8	–	–
Duration of medication (months)	8.3 ± 12.6	–	–
SAPS total at scanning	27.3 ± 21.9	–	–
SANS total at scanning	53.1 ± 25.2	–	–

†Different typical and atypical antipsychotic dosages are converted into HPD equivalents using the guideline by Toru.[22]
‡Data missing for one participant. ARMS, at-risk mental state; BDI, Beck Depression Inventory; FESz, first-episode schizophrenia; HPD, haloperidol; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; STAI, State Trait Anxiety Inventory.

The control subjects consisted of 86 healthy volunteers recruited from the community, hospital staff, and university students. Given the sexual dimorphism (male < female) and age-related atrophy of the pituitary gland,[30–32] the control subjects comprised two groups that were age- and gender-matched for ARMS ($n = 22$) and for FESz ($n = 64$), respectively (Table 1). Although the controls did not receive a full diagnostic interview, they were given a questionnaire consisting of 15 items concerning their personal (13 items; e.g. a history of obstetric complications, substantial head injury, seizures, neurological or psychiatric diseases, impaired thyroid function, hypertension, diabetes, and substance use) and family (two items) histories of illness.[33] They did not have any personal or family history of psychiatric illness among their first-degree relatives.

All subjects in this study (ARMS, FESz, and controls) were screened using the same exclusion criteria (except family history of psychiatric illness, which was applied only to controls). They were right-handed and physically healthy at the time of the study, and none had a history of serious head trauma, severe obstetric complications, neurological illness, substance abuse disorder, or serious medical disease (e.g. impaired thyroid function, hypertension, and diabetes). The FESz and ARMS participants were screened for these conditions using a detailed chart review at scanning (FESz) or direct interview at study intake (ARMS). None of the participants was pregnant or taking exogenous estrogens at the time of the study, but hormone levels as well as menstrual cycle in female subjects were not assessed in this study. All participants were

Table 2. Intracranial and pituitary volume (mean ± SD)

Variables	ARMS (11 M, 11 F)	Controls for ARMS (11 M, 11 F)	FESz (37 M, 27 F)	Controls for FESz (37 M, 27 F)
Intracranial volume (cm^3)	1460 ± 132	1500 ± 146	1500 ± 147	1502 ± 150
Pituitary volume (mm^3)	763 ± 124†	697 ± 143	802 ± 153†	708 ± 140

†Significantly larger than age- and gender-matched controls. Statistical analysis for the pituitary gland was based on relative volume. Analysis of covariance with age as a covariate and with diagnosis as a between-subject factor was used for the intracranial volume. ARMS, at risk mental state; FESz, first-episode schizophrenia.

also screened for gross brain abnormalities by neuroradiologists.

The clinical symptoms of the ARMS and FESz subjects were rated at the time of scanning using the Scale for the Assessment of Negative Symptoms and the Scale for the Assessment of Positive Symptoms (SANS/SAPS).[34] Of the 172 participants in this study, 60 controls (35 male) and 37 schizophrenia patients (21 male) were also included in our previous pituitary study.[35] This study was approved by the Committee on Medical Ethics of Toyama University. After a complete description of the study was provided, written informed consent was obtained from all subjects.

Magnetic resonance imaging procedures

The subjects were scanned on a 1.5-T Magnetom Vision (Siemens Medical System, Erlangen, Germany) with a 3-D gradient-echo sequence fast low-angle shots (FLASH) yielding 160–180 contiguous T1-weighted slices of 1.0-mm thickness in the sagittal plane. The imaging parameters were as follows: repetition time, 24 ms; echo time, 5 ms; flip angle, 40°; field of view, 256 mm; and matrix size, 256 × 256 pixels. The voxel size was 1.0 × 1.0 × 1.0 mm. The scanner was calibrated weekly with the same phantom to ensure measurement stability.

To assess the pituitary volume, the images were processed on a Linux PC (Fujitsu, Tokyo, Japan) using Dr. View software (AJS, Tokyo, Japan). Brain images were realigned in three dimensions to standardize for differences in head tilt during image acquisition and were then reconstructed into entire contiguous coronal images of 1-mm thickness perpendicular to the anterior commissure–posterior commissure line. The signal intensity histogram distributions from the T1-weighted images across the whole cerebrum were then used to semi-automatically segment the voxels into brain tissue components and cerebrospinal fluid. The intracranial volume (ICV) was measured to correct for differences in head size as described previously;[36] there were no significant group differences for ICV (ARMS vs their controls, $F(1,41) = 0.88$, $P = 0.353$; FES vs their controls, $F(1,125) < 0.01$, $P = 0.984$; and FES vs ARMS vs all controls, $F(2,168) = 0.43$, $P = 0.654$; Table 2).

Pituitary measurements

The pituitary gland volume was manually traced on consecutive 1-mm coronal slices based on a method used by Garner *et al.*[4] Briefly, we traced around the usually well-defined borders of the anterior and posterior pituitary: the diaphragma sellae, superiorly; the sphenoid sinus, inferiorly; and the cavernous sinuses, bilaterally. As presented in Figure 1, the pituitary stalk was excluded from the tracings, but we included a posterior bright spot, corresponding to the posterior pituitary (the intensity of which is thought to reflect the vasopressin concentration). All measurements were carried out by a trained rater (TT) without knowledge of the subjects' identities or the times of their scans. To determine the reliability of the measurement, a second rater (VL) measured the pituitary volume in a subset of 10 randomly selected brains. Each pituitary volume in these 10 brains was then remeasured after at least 4 weeks by the first rater. Inter- (TT and VL) and intra-rater intraclass correlation coefficients were >0.93.

Statistical analysis

The relative volume of the pituitary gland ([absolute volume/ICV) × 100]) was analyzed using analysis of

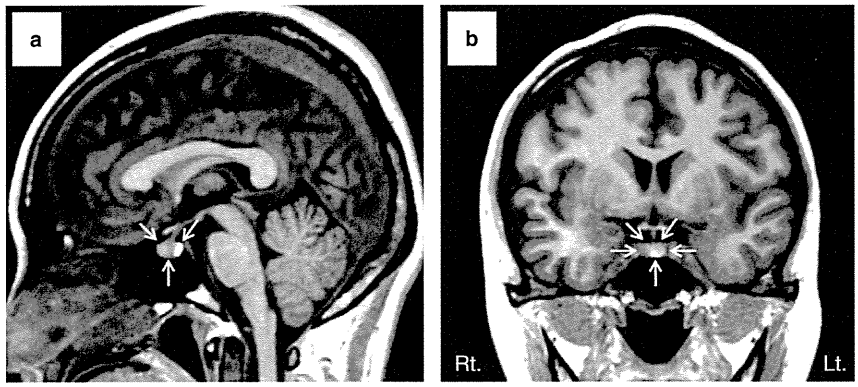

Figure 1. (a) Sagittal and (b) coronal views of the pituitary gland manually traced in this study. The pituitary stalk was excluded from the tracings, but a posterior bright spot was included.

covariance (ANCOVA) with age as a covariate and with diagnosis and gender as between-subject factors. The effect of medication type (typical vs atypical for FESz) and outcome (with vs without later transition for ARMS) on relative pituitary volume was also examined on ANCOVA. Post-hoc Scheffé's tests were carried out to follow up any significant main effects or interactions. Spearman's rank correlations were calculated to examine relationships between relative pituitary volume and the clinical variables. Statistical significance was defined as $P < 0.05$ (two-tailed).

RESULTS

Group comparisons of the pituitary volume

ANCOVAs of the pituitary volume showed significant main effects for diagnosis (ARMS vs their controls, $F(1,39) = 4.94$, $P = 0.032$; FESz vs their controls, $F(1,123) = 15.58$, $P < 0.001$) and gender (ARMS vs their controls, $F(1,39) = 26.39$, $P < 0.001$; FESz vs their controls, $F(1,123) = 113.58$, $P < 0.001$) but not diagnosis × gender interaction (ARMS vs their controls, $F(1,39) = 0.91$, $P = 0.346$; FESz vs their controls, $F(1,123) = 0.66$, $P = 0.417$). Post-hoc analyses showed that both the ARMS ($P = 0.030$) and FESz ($P < 0.001$) groups had a larger pituitary volume compared with matched controls, and female subjects had a larger volume than male subjects ($P < 0.001$; Table 2; Fig. 2). Direct comparison of the pituitary volume between ARMS and FESz showed no significant group difference ($F(1,81) = 1.58$, $P = 0.213$).

These results remained essentially the same even when we added medication dose and duration as covariates, and there was no difference in the pituitary volume between the FESz patients treated with typical ($n = 18$) and atypical ($n = 43$) antipsychotics

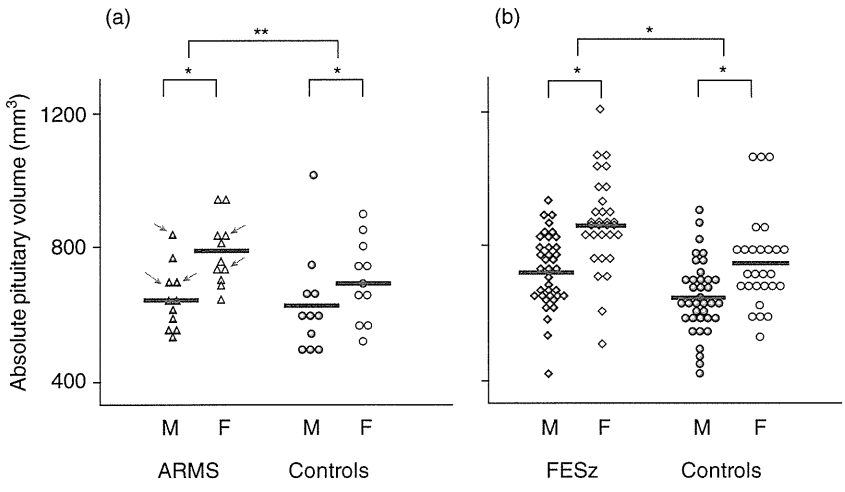

Figure 2. Absolute pituitary volume in the at-risk mental state (ARMS) individuals, controls for ARMS, first-episode schizophrenia (FESz) patients, and controls for FESz. Arrows, ARMS individuals with later transition into psychosis. Horizontal lines, mean. Post-hoc test: $*P < 0.01$, $**P = 0.03$ (statistical analysis for the pituitary gland was based on relative volume).

($F(1,58) = 0.30$, $P = 0.586$). Although the ARMS subjects who were taking antipsychotics at scanning ($n = 4$; pituitary volume, 843 ± 128 mm^3) had a larger pituitary volume than antipsychotic-naïve ARMS subjects ($n = 18$; pituitary volume, 746 ± 120 mm^3), the difference was not statistically significant ($F(1,19) = 1.73$, $P = 0.204$). The comparison of the pituitary volume between the antipsychotic-naïve ARMS and FESz subjects showed no significant group difference ($F(1,77) = 1.60$, $P = 0.209$). When we examined only antipsychotic-naïve ARMS subjects ($n = 18$) and 18 age- and gender-matched controls, pituitary expansion did not reach significance ($F(1,31) = 3.48$, $P = 0.072$). The pituitary volume did not differ significantly between the ARMS subjects who later developed schizophrenia ($n = 5$; pituitary volume, 803 ± 78 mm^3) and those who did not ($n = 17$; pituitary volume, 752 ± 134 mm^3; $F(1,19) = 0.87$, $P = 0.362$).

Correlation analysis

The relative pituitary volume did not correlate with age, education, or parental education in all groups. No significant correlation was found between the pituitary volume and the BDI or STAI (state, trait) score in the ARMS subjects. In the FESz group, the pituitary volume was not significantly correlated with onset age or illness duration. In both the ARMS and FESz groups, no significant correlation was found between the pituitary volume and the total scores for the SANS/SAPS or medication (daily dose at scanning, duration of antipsychotic treatment).

DISCUSSION

This MRI study identified an enlarged pituitary volume in both subjects with ARMS and patients with FESz compared with healthy controls. The effect of medication is an important consideration for pituitary findings,[7,9,10,37] but we found no significant effect of daily dose or duration of antipsychotic treatment on the pituitary volume. Consistent with previous reports,[4,17] the pituitary volume did not correlate with clinical symptoms in either clinical group. Despite the relatively small number of subjects with ARMS, the present findings suggest that these high-risk subjects may share HPA hyperactivity with FESz patients as a possible indicator of common stress vulnerability.

Pituitary volume in early psychosis

The present finding of enlarged pituitary volume in FESz is consistent with previous MRI studies,[5,6,8,20] supporting the role of HPA hyperactivity in the development of psychosis.[2,18] To our knowledge, however, there have been only two MRI studies of the pituitary volume in ARMS as compared with healthy controls, which have yielded partly inconsistent results. Garner *et al.* found no significant group difference in the pituitary volume between the ARMS and controls, but the ARMS subjects who later developed psychosis (ARMS-T) had a larger pituitary volume than those who did not (ARMS-NT).[4] The present results were similar to those of Büschlen *et al.*, who reported that the pituitary volume increased in the order of healthy controls to ARMS-NT to ARMS-T and first-episode psychosis, although the difference between the ARMS-T and -NT was not statistically significant.[20] As discussed by Büschlen *et al.*,[20] these inconsistencies may be partly due to different ascertainment strategies, as well as different characteristics, of regional psychiatric services. In fact, Garner *et al.*, who included ARMS subjects with a comorbid diagnosis of major depression or borderline personality disorder, suggested the role of the pituitary volume as a predictor of psychotic major depression,[4] whereas the ARMS-T subjects in the present study and those of Büschlen *et al.*,[20] neither of whom included ARMS subjects with those comorbidities, predominantly developed schizophrenic psychosis. Nevertheless, these MRI studies generally imply that these clinical high-risk subjects could exhibit pituitary expansion at least in some individuals, supporting the notion that an enhanced HPA axis response to stress appears to be part of the biological vulnerability to psychosis.[19] This notion may also be supported by hormone[38–40] and neuroimaging[35] findings in subjects with schizotypal personality disorder (SPD) who have a higher incidence of developing psychosis than the general population,[41] suggesting that distress related to social deficits or incipient psychotic experience could activate the stress response even without florid psychosis.

Possible underlying mechanism of the pituitary expansion

The present structural MRI study could not address the mechanism for pituitary volume changes, but a recent study by Habets *et al.* showed that higher pitu-

itary volume was associated with increased emotional stress reactivity especially in patients with psychotic disorder.[42] It may be possible that pituitary expansion in the present study reflects HPA axis hyperactivity and a subsequent increase in the size and number of corticotrophs (cells producing adrenocorticotropic hormone; ACTH), which can be explained by an activation of the hormonal stress response.[5,6] Estrogen treatment, hypothalamic tumor, pregnancy, and primary hypothyroidism also lead to pituitary expansion,[43,44] but these common causes of pituitary enlargement were excluded in the present subjects.

Antipsychotic medication could also influence HPA activation,[2,45,46] but the effect of medication on the pituitary volume remains controversial. Recent MRI studies suggested that atypical antipsychotics might reduce pituitary volume in the course of psychosis,[9,10,37] consistent with the notion that antipsychotic medication generally dampens HPA activity in schizophrenia.[1,2,46] In contrast, some antipsychotics may increase pituitary volume, possibly by activating prolactin-secreting cells.[5,7,47] Although we did not find a direct relation between the pituitary volume and medication (daily dose at scanning, duration of antipsychotic treatment), almost all of the present FESz patients had been taking antipsychotics for a substantial period at the time of scanning (mean, 8.3 months) and significant pituitary expansion of the ARMS subjects diminished when we investigated only antipsychotic-naïve ARMS subjects. Thus, the possibility still exists that the pituitary expansion in the present study was partly related to the effect of antipsychotic medication, which should be further examined.

Pituitary volume and clinical characteristics

In contrast to neuroendocrine observations demonstrating the association of plasma or salivary cortisol levels with prodromal (including depressive and anxiety) or psychotic symptoms in ARMS subjects,[14–17] this and previous MRI studies in ARMS found no significant correlation between the pituitary volume and global psychopathology, general functioning, or psychotic symptomatology.[4,17] Direct comparison of plasma and MRI findings in ARMS also showed that pituitary volume did not correlate with either plasma cortisol level or number of glucocorticoid receptors.[17] Our previous study, however, identified a significant relationship between ongoing pituitary expansion and treatment response or severity of positive psychotic symptoms in FESz,[8] suggesting that it is longitudinal pituitary changes during early phases of the illness that are relevant to clinical manifestations of psychosis. Interestingly, a recent study of cortisol level emphasized the role of longitudinal HPA changes in the development of psychosis.[18] Thus, further study of the association of longitudinal pituitary volume changes with HPA functioning and clinical characteristics (e.g. symptom severity, later transition into psychosis) is required to examine the potential role of HPA activity in the emergence of psychosis in vulnerable individuals.

Methodological considerations

A few possible methodological considerations in this study should be taken into account. First, the sample size of the present ARMS group (especially those who later developed psychosis) was relatively small and the clinical follow-up period was short for some individuals. Although we found no significant difference in pituitary volume between the ARMS subjects with and without later transition to psychosis, whether the baseline pituitary volume could predict onset of psychosis should be tested in a larger, well-defined high-risk cohort. Second, although the present findings of pituitary enlargement in early psychosis are thought to reflect state-related HPA axis dysregulation, we did not directly assess pituitary function. The pituitary gland is also considered to be sensitive to prolactin-elevating antipsychotics[7,47] and a recent study reported hyperprolactinemia in antipsychotic-naïve ARMS subjects.[48] The present findings replicated the sexual dimorphism of the pituitary gland volume (female > male),[32] potentially reflecting different endogenous estrogen levels.[49] We did not, however, assess prolactin or estrogen level in this study. Thus, additional assessment of both pituitary volume and hormone levels (e.g. cortisol, ACTH, prolactin, and estrogen) is required. The present study might be also limited by a lack of urine toxicology screening for substance use. Finally, given that HPA axis functioning also appears to be affected in major depressive disorders[50–52] and that Garner *et al.* found an enlarged pituitary volume prior to the onset of psychotic major depression,[4] further investigation of the disease specificity of pituitary findings is warranted.

Conclusion

Both the ARMS and FESz subjects had significant enlargement of the pituitary gland, presumably reflecting activation of the hormonal stress response during early psychosis. Given that the pituitary gland is a dynamic organ reflecting state-related HPA axis dysregulation, longitudinal study of the pituitary volume and its relation to clinical characteristics, as well as hormone levels, is required to further understand the role of HPA functioning in the emergence of psychosis.

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Brief report

Longitudinal MRI study of the midline brain regions in first-episode schizophrenia

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ABSTRACT

This magnetic resonance imaging (MRI) study investigated the prevalence and size of the adhesio interthalamica (AI) and cavum septi pellucidi (CSP) in 64 first-episode schizophrenia patients and 64 controls, of whom longitudinal data were available for 20 patients and 21 controls. The AI was shorter in the patients and showed longitudinal decline in both groups; there was also a trend for AI atrophy to correlate with negative symptoms. The CSP showed no group difference. These results suggest a role for the AI as a possible neurodevelopmental marker of schizophrenia.

1. Introduction

The adhesio interthalamica (AI), a midline structure connecting the medial surfaces of the thalami, is variable in size among individuals and missing in about 20% of human brains (Carpenter and Sutin, 1983). Previous neuroimaging studies have demonstrated that schizophrenia patients are more likely to have a smaller AI (reviewed by Trzesniak et al., 2011a), possibly reflecting early developmental abnormalities. A large cavum septi pellucidi (CSP) ($\geq$6 mm; Takahashi et al., 2007), which is formed by the incomplete fusion of the septum pellucidi (Rakic and Yakovlev, 1968), may also be related to fetal neurodevelopmental abnormalities in schizophrenia (Trzesniak et al., 2011b). Our previous magnetic resonance imaging (MRI) studies showed smaller AI and a higher rate for it to be absent, but no difference in the size and prevalence of CSP, in a large sample of chronic schizophrenia patients compared with controls (Takahashi et al., 2007, 2008a), but these results may have been partly biased by the effects of medication and illness chronicity. A recent longitudinal MRI study demonstrated the possibility that the size of these midline regions could change during the course of the illness (Trzesniak et al., 2012), whereas Davidson et al. (2012) reported longitudinal stability in the CSP length in first-episode schizophrenia.

This MRI study aimed to replicate our earlier observations described above in a cohort of first-episode schizophrenia and to investigate the changes over time in the size of these midline regions. Given their potential role as neurodevelopmental markers, we posited no diagnosis-by-time interaction in these regions.

2. Methods

2.1. Participants

Sixty-four schizophrenia patients fulfilling the ICD-10 research criteria (World Health Organization, 1993), whose illness duration was 1 year or less (n=48) or under first psychiatric hospitalization (n=16), were recruited from inpatient and outpatient clinics of the Department of Neuropsychiatry of Toyama University Hospital. Sixty-four healthy volunteers were recruited from the community, hospital staff, and university students. The controls were given a questionnaire consisting of 15 items concerning their personal and family histories of illness; none had a personal or family history of psychiatric illness among their first-degree relatives. All subjects were right-handed and physically healthy, and did not have any history of serious head trauma, neurological illness, substance abuse, or serious medical disease. Of the 128 participants, 37 patients and 60 controls were included in our previous cross-sectional studies of the CSP (Takahashi et al., 2007) and AI (Takahashi et al., 2008a). Follow-up MRI data were available for 20 patients and 21 controls; the characteristics of this sub-sample were largely comparable with those of the whole sample of this study (Table 1). The controls were also assessed using the questionnaire at follow-up to ensure that none had any neuropsychiatric disorder during the period between scans.

The patients' clinical symptoms were rated at the time of scanning (baseline and follow-up) using the Scale for the Assessment of Negative and Positive Symptoms (SANS/SAPS; Andreasen, 1984). The diagnosis of schizophrenia was confirmed in all patients at least 6 months after the illness onset based on

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Table 1
Sample characteristics and brain measurements of the participants.

	Cross-sectional sample			Longitudinal sample		
	Controls	Schizophrenia	Group comparisons	Controls	Schizophrenia	Group comparisons
Male/female	37/27	37/27	Chi-square=0.00, $p=1.000$	13/8	14/6	Chi-square=0.30, $p=0.585$
Age (years)	25.1 ± 5.0	24.0 ± 4.7	$F(1, 126)=1.64$, $p=0.203$	24.5 ± 5.0	23.8 ± 5.0	$F(1, 39)=0.19$, $p=0.664$
Height (cm)	167.0 ± 7.5	164.9 ± 7.6	$F(1, 126)=2.60$, $p=0.109$	167.3 ± 7.6	166.2 ± 6.6	$F(1, 39)=0.27$, $p=0.606$
Education (years)	16.5 ± 2.6	13.5 ± 1.9	$F(1, 126)=57.55$, $p<0.001$	15.6 ± 2.4	13.0 ± 1.6	$F(1, 39)=17.24$, $p<0.001$
Parental education (years)[a]	13.2 ± 2.5	13.0 ± 2.0	$F(1, 124)=0.50$, $p=0.482$	12.8 ± 2.6	12.5 ± 2.1	$F(1, 39)=0.10$, $p=0.756$
Inter-scan interval (years)	–	–		2.5 ± 0.4	2.7 ± 0.8	$F(1, 39)=1.30$, $p=0.261$
Onset age (years)	–	23.1 ± 4.7	–	–	22.7 ± 5.1	–
Illness duration at baseline (months)	–	11.2 ± 12.2	–	–	10.2 ± 9.4	–
Medication type (T/AT/mixed)						
At baseline	–	18/43/1[b]	–	–	6/12/2	–
During follow-up	–	–	–	–	3/13/4	–
Medication dose (haloperidol equivalent)						
At baseline (mg/day)	–	10.3 ± 8.8	–	–	14.6 ± 11.7	–
Cumulative dose during follow-up (mg)	–	–	–	–	9852 ± 8727	–
Duration of medication at baseline (months)	–	8.3 ± 12.6	–	–	8.3 ± 10.1	–
SAPS total at baseline	–	27.3 ± 21.9 ($N=61$)	–	–	33.0 ± 24.0 ($N=17$)	–
SAPS total at follow-up	–	–	–	–	19.1 ± 17.5 ($N=19$)	–
SANS total at baseline	–	53.1 ± 25.2 ($N=61$)	–	–	53.7 ± 27.1 ($N=17$)	–
SANS total at follow-up	–	–	–	–	38.0 ± 24.0 ($N=19$)	–
AI absent [N (%)]	7 (10.9)	10 (15.6)	Chi-square=0.61, $p=0.435$	3 (14.3)	4 (20.0)	$p=0.627$, Fisher's exact test
AI length at baseline (mm) (median)	8.9 ± 3.5 (10.0)	7.3 ± 3.2 (7.0)	$F(1, 122)=11.08$, $p=0.001$	8.4 ± 3.5 (8.0)	6.9 ± 3.3 (6.5)	$F(1, 35)=1.40$, $p=0.245$
AI length at follow-up (mm) (median)	–	–	–	8.1 ± 3.4 (7.0)	6.8 ± 3.1 (6.5)	$F(1, 35)=1.71$, $p=0.200$
AI change during follow-up (mm)[c]	–	–	–	−0.3 ± 0.6	−0.2 ± 0.7	$F(1, 33)=1.39$, $p=0.247$
large CSP [N (%)]	8 (12.5)	3 (4.7)	$p=0.115$, Fisher's exact test	2 (9.5)	1 (5.0)	$p=0.578$, Fisher's exact test
CSP length at baseline (mm) (median)	4.7 ± 10.1 (2.0)	3.1 ± 6.5 (2.0)	$F(1, 122)=0.26$, $p=0.611$[d]	4.8 ± 11.4 (2.0)	3.4 ± 5.9 (2.0)	$F(1, 35)=0.00$, $p=0.970$[d]
CSP length at follow-up (mm) (median)	–	–	–	4.9 ± 11.6 (2.0)	3.2 ± 5.7 (2.0)	$F(1, 35)=0186$, $p=0.669$[d]
CSP change during follow-up (mm)[c]	–	–	–	+0.1 ± 0.5	−0.2 ± 0.7	$F(1, 33)=0.10$, $p=0.753$
Intracranial volume (cm^3)	1501.9 ± 150.4	1499.8 ± 147.1	$F(1, 125)<0.01$, $p=0.983$	1501.1 ± 158.3	1482.2 ± 133.2	$F(1, 38)=0.08$, $p=0.774$

Values represent means ± S.D.'s unless otherwise stated.
AI, adhesio interthalamica; AT, atypical; CSP, cavum septum pellucidum; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; T, typical.

[a] Data missing for one control and one schizophrenia subjects.
[b] Two patients were medication free at the time of scanning.
[c] Negative value indicates a decrease in length. The statistical analyses reported herein were based on repeated measures ANCOVA with time (baseline, follow-up) as a within-subject variable (see text). The main effect of time was $F(1, 37)=4.95$, $p=0.032$ for the AI and $F(1, 37)=0.02$, $p=0.883$ for the CSP.
[d] The CSP measures were log-transformed for statistics because of their skewed distribution ($p<0.01$, Kolmogorov–Smirnov test). The skewness and kurtosis statistics of baseline CSP length were 4.82 and 24.12 before transformation and 1.00 and 2.49 after transformation, respectively.

information obtained from a detailed chart review. Other clinical information, including cumulative neuroleptic dosage during the study, was also collected in this chart review. Medication and other clinical data are summarized in Table 1.

This study was approved by the Committee on Medical Ethics of Toyama University. After a complete description of the study was provided, written informed consent was obtained from all subjects.

2.2. Magnetic resonance imaging procedures

The subjects were scanned on a 1.5-T Magnetom Vision (Siemens Medical System, Inc., Erlangen, Germany) with a three-dimensional gradient-echo sequence FLASH (fast low-angle shots) yielding 160-180 contiguous T1-weighted slices of 1.0-mm thickness in the sagittal plane. The imaging parameters were as follows: repetition time=24 ms; echo time=5 ms; flip angle=40°; field of view=256 mm; and matrix size=256 × 256 pixels. The voxel size was $1.0 \times 1.0 \times 1.0\ mm^3$. The follow-up data were acquired using the same scanner/parameters as described above. The scanner was calibrated weekly with the same phantom to ensure measurement stability.

To assess the AI and CSP, the images were processed using Dr. View software (AJS, Tokyo, Japan) as described elsewhere (Takahashi et al., 2007, 2008a). Briefly, brain images were realigned in three dimensions and then reconstructed into entire contiguous coronal images with a 1-mm thickness, perpendicular to the anterior commissure-posterior commissure (AC-PC) line. One rater (TT), who was blind to the subjects' identity and time of scan, counted the number of coronal slices where each midline region was clearly seen. The length of the AI and CSP (in mm) was equal to the number of these slices. We considered the AI as present when it could be identified on three or more slices on both coronal and axial views (Takahashi et al., 2008a). A CSP equal to or greater than 6 mm was defined as large on the basis of previous reports (e.g., Nopoulos et al., 1997; Kwon et al., 1998; Kasai et al., 2004). Intra- and inter-rater (TT and KN) intraclass correlation coefficients for the AI and CSP lengths ($n=30$) in randomly selected brains were over 0.97.

2.3. Statistical analysis

Chi-square tests, or Fisher's exact tests when expected cell sizes were less than five, were used to assess the frequency of the AI and large CSP. The length of each

midline region was analyzed using analysis of covariance (ANCOVA), with intracranial volume (ICV) and age as covariates and with diagnosis and gender as between-subject factors. Gender was used as a between-subject factor on the basis of possible gender effect on the AI size (Allen and Gorski, 1991). The CSP measures were log-transformed because of their skewed distribution (eFig. 1, Table 1). Longitudinal changes were analyzed using repeated measures ANCOVAs with age at first scan, ICV, inter-scan interval, and cumulative dose of antipsychotics during scans as covariates, diagnosis and gender as between-subject factors, and time (baseline, follow-up) as a within-subject variable. Post-hoc Scheffé's tests (Scheffé, 1959) were used to follow up these analyses. The relationships between the midline regions (baseline length, absolute length change during scans) and clinical variables were examined by Pearson's partial correlation coefficients controlling for age and ICV. Inter-scan interval and cumulative medication dose were also used as controlling factors for correlational analyses between length change and clinical variables. Statistical analyses reported here were performed using the STATISTICA software package (Statsoft, Tulsa, OK); the statistical modeling was based on its manual (Statsoft, 1994) as in our previous publications (e.g., Takahashi et al., 2009). Statistical significance was defined as $p < 0.05$.

3. Results

There was no group difference in the prevalence of an absent AI (Table 1), but ANCOVA of the baseline AI length revealed significant main effects for diagnosis [$F(1, 122)=11.08$, $p=0.001$] and gender [$F(1, 122)=5.36$, $p=0.022$] but not their interaction. Post hoc analyses showed that the patients had a shorter AI than controls ($p=0.004$) (eFig. 2) and males had a shorter AI than females ($p < 0.001$). However, the main effect for diagnosis was not significant when we added medication duration and dose also as covariates [$F(1120)=1.20$, $p=0.276$]. Longitudinal analyses of the AI revealed a significant effect of time [$F(1, 37)=4.95$, $p=0.032$], but no diagnosis-by-time interaction, indicating its atrophy over time in both groups ($p=0.032$). The AI length, but not CSP length, at the baseline was negatively correlated with age for both controls ($r=-0.343$, $p=0.005$) and patients ($r=-0.277$, $p=0.027$). In the patients, the AI length was not correlated with the onset age, illness duration, medication (duration and dose), or total SANS/SAPS scores. The cumulative medication dose did not correlate with the AI change over time. Overall, although not statistically significant [$n=16$, $F(1,15)=2.34$, $p=0.147$], negative symptoms (total SANS score) reduced over time (Table 1), but greater AI atrophy over time was correlated at a trend level with less improvement in negative symptoms ($r=0.619$, $p=0.032$), though this did not survive Bonferroni correction (Dunn, 1961).

For the CSP (length and prevalence), we found no effect of diagnosis, time, or gender (Table 1, eFig. 1). The CSP categories (absent, present, or large) changed during follow-up in one control [from absent to present (1 mm)] and one patient [from present (2 mm) to absent]. The CSP length did not correlate with any clinical variables.

The ANCOVA results of length change over time remained the same for both AI and CSP even when we added baseline medication dose or deleted cumulative medication dose as the covariate.

4. Discussion

Consistent with previous findings in first-episode schizophrenia (Trzesniak et al., 2012) or clinical high-risk subjects (Takahashi et al., 2008b), baseline results in this study demonstrated shorter length of the AI in schizophrenia patients in the early illness stages. A lack of correlation with medication and illness duration, as well as no disease-specific progressive changes, also supports the concept that AI malformation may at least partly represent early neurodevelopmental disturbance in schizophrenia (Weinberger, 1987). On the other hand, we did not identify any differences in the CSP measures between the groups, suggesting that it may not play a major role in the neurobiology of schizophrenia (Takahashi et al., 2007, 2008c).

The present study and a previous (Trzesniak et al., 2012) longitudinal analysis found AI atrophy over time in both schizophrenia and controls, supporting the notion that the AI develops during early gestation, but also undergoes increasing atrophy with age (Rosales et al., 1968; O'Rahilly and Müller, 1990). This study also replicated that men had shorter AI than women (Allen and Gorski, 1991). While the functional significance of the AI, as well as the nature of its atrophy, remains unclear, the midline nuclei of the thalamus including the AI have efferent connections with the amygdaloid nuclei (Graff-Radford, 1997) and are involved in the regulation of the dopamine release of the basal ganglia (Romo et al., 1984). A trend-level correlation between longitudinal AI atrophy and negative symptoms may support a relationship between AI abnormalities and negative symptoms in schizophrenia (Meisenzahl et al., 2000, 2002; Takahashi et al., 2008a), but this effect needs to be replicated. Also, this possible correlation would suggest a role in schizophrenia for accelerated atrophy in AI during adulthood in addition to the hypothesized role as an early neurodevelopmental marker. Although we found no diagnosis-by-time interaction in AI length, it is possible that the reduced AI length apparent at the first episode is due to accelerated AI atrophy at or before illness onset and our sample size or duration is underpowered to examine this effect.

The present study supported the role of the AI as a neurodevelopmental marker of schizophrenia, although possible medication effect on the AI morphology should be further examined. In addition, our longitudinal analyses should be considered preliminary due to the small sample size. For example, in contrast to the negative CSP findings in this study, several previous studies have found CSP abnormalities in schizophrenia (reviewed by Trzesniak et al., 2011b) and Trzesniak et al. (2012) demonstrated significant expansion of the CSP in 52 first-episode patients even during a shorter follow-up period (18 months). As Choi et al. (2008) reported abnormal CSP in subjects at risk for psychosis using the CSP grading system, which integrated CSP length, width, and overall size, the possibility also exists that measuring only the length of the CSP might not be a sensitive enough approach to detect existing changes of the CSP. Another limitation of this study is that neighboring structures are not measured, so it cannot be ruled out that differences in AI are accounted for by differences in thalamic or ventricular volume or orientation. Additional longitudinal studies in a larger cohort in various illness stages (e.g., prodromal and chronic phases) are required to further understand the nature of midline brain abnormalities in the course of schizophrenia.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.pscychresns.2012.12.001.

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Altered depth of the olfactory sulcus in first-episode schizophrenia

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ABSTRACT

A shallow olfactory sulcus has been reported in chronic schizophrenia, possibly reflecting abnormal forebrain development during early gestation. However, it remains unclear whether this abnormality exists at the early illness stage and/or develops progressively over the course of the illness. This magnetic resonance imaging (MRI) study investigated the length and depth of the olfactory sulcus in 64 first-episode schizophrenia patients and 64 controls, of whom longitudinal MRI data (mean inter-scan interval = 2.6 years) were available for 20 patients and 21 controls. In the cross-sectional comparison at the baseline, the schizophrenia patients had a significantly shallower olfactory sulcus compared with the controls bilaterally, but there was no group difference in its anterior–posterior length. A longitudinal comparison demonstrated that the sulcus length and depth did not change over time in either group. The olfactory sulcus measures of the patients did not significantly correlate with clinical variables such as onset age, medication or symptom severity. These findings suggest that the olfactory sulcus depth, but not length, may be a static vulnerability marker of schizophrenia that reflects early neurodevelopmental abnormality.

1. Introduction

The depth of the olfactory sulcus, which appears in the fetal forebrain at around 16 weeks gestation (Chi et al., 1977), relates to olfactory function in healthy subjects and is usually deeper on the right hemisphere in association with functional lateralization in the olfactory system (Hummel et al., 2003). It is known that patients with congenital anosmia have a shallow olfactory sulcus, probably reflecting abnormal development of the olfactory system (Abolmaali et al., 2002; Huart et al., 2011). Given the evidence that schizophrenia patients exhibit olfactory dysfunction as a possible vulnerability marker (Brewer et al., 2001, 2003; Kamath et al., in press; Turetsky et al., 2009b), as well as the fetal stage of the sulcus formation at which neurodevelopmental disruption could increase the risk for schizophrenia (Fatemi and Folsom, 2009), the olfactory sulcus morphology in schizophrenia as a potential early neurodevelopmental marker is worth investigating.

To our knowledge, only two magnetic resonance imaging (MRI) studies have examined the olfactory sulcus depth in schizophrenia; Turetsky et al. (2009a) demonstrated an abnormally shallow olfactory sulcus in chronic patients of both genders, especially on the right hemisphere, whereas Nguyen et al. (2011) found a normal sulcus depth in male chronic patients. This inconsistency may be partly explained by different sample characteristics, as well as technical issues, as Nguyen et al. (2011) measured the sulcus depth using a single slice based on external landmarks [i.e., the plane of the posterior tangent through the eyeballs (PPTE)]. The results of Turetsky et al. (2009a) were based on the measurement of the entire structure, but their findings need replication, ideally in first-episode patients in a longitudinal design, in order to clarify the nature of olfactory sulcus abnormalities in schizophrenia.

This cross-sectional and longitudinal MRI study investigated the length and average depth of the olfactory sulcus in first-episode schizophrenia compared with healthy controls. On the basis of previous findings in chronic patients (Turetsky et al., 2009a) and the potential role of the sulcus depth as a neurodevelopmental marker, we predicted that patients would have a shallower olfactory sulcus compared with the controls at the baseline, and that the sulcus morphology would not change over time in either group. We also explored the relationship between the sulcus morphology and several clinical factors (e.g., symptom severity, antipsychotic medication) in schizophrenia.

Abbreviations: ANCOVA, analysis of covariance; ANOVA, analysis of variance; CSP, cavum septi pellucidi; ICV, intracranial volume; MRI, magnetic resonance imaging; PPTE, plane of the posterior tangent through the eyeballs; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms.

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2. Methods

2.1. Participants

Sixty-four first-episode schizophrenia patients who fulfilled the ICD-10 research criteria (World Health Organization, 1993) were recruited from inpatient and outpatient clinics of the Department of Neuropsychiatry of Toyama University Hospital. In accordance with the literature (Hirayasu et al., 2000; Kasai et al., 2003; Schooler et al., 2005; Yap et al., 2001), first-episode patients were defined as patients experiencing their first episode of schizophrenia whose illness onset was within 1 year of baseline scanning ($N=48$) or those undergoing their first psychiatric hospitalization ($N=16$). The diagnosis of schizophrenia was confirmed for all patients at least 6 months after the illness onset based on information obtained from a detailed chart review. Their clinical symptoms were rated at the time of scanning using the Scale for the Assessment of Negative Symptoms and the Scale for the Assessment of Positive Symptoms (SANS/SAPS; Andreasen, 1984). Medication and other clinical data are summarized in Table 1. Four patients were also receiving mood stabilizers [lithium carbonate ($N=1$), sodium valproate ($N=1$), or carbamazepine ($N=2$)] at the time of baseline scanning.

The control subjects consisted of 64 healthy volunteers recruited from the community, hospital staff, and university students. They were given a questionnaire consisting of 15 items concerning their personal (13 items; e.g., history of obstetric complications, substantial head injury, seizures, neurological or psychiatric diseases, impaired thyroid function, hypertension, diabetes, and substance use) and family (2 items) histories of illness. They did not have any personal or family history of psychiatric illness among their first-degree relatives.

All subjects were right-handed and physically healthy, and none of the participants were pregnant or taking exogenous estrogens at the time of the study. None had a history of serious head trauma, neurological illness, substance abuse disorder, or serious medical disease. All participants were also screened for gross brain abnormalities by neuroradiologists. Follow-up MRI data were available for 20 patients and 21 controls; the characteristics of this sub-sample were largely comparable with those of the whole sample of this study (Table 1). The controls had attained a higher level of education than the patients, but the groups were matched for age, gender, height, parental education, and inter-scan interval (Table 1).

This study was approved by the Committee on Medical Ethics of Toyama University. After a complete description of the study was provided, written informed consent was obtained from all subjects.

2.2. MRI procedures

The subjects were scanned on a 1.5-T Magnetom Vision (Siemens Medical System, Inc., Erlangen, Germany) with a three-dimensional gradient-echo sequence FLASH (fast low-angle shots) yielding 160–180 contiguous T1-weighted slices of 1.0-mm thickness in the sagittal plane. The imaging parameters were as follows: repetition time = 24 ms; echo time = 5 ms; flip angle = 40°; field of view = 256 mm; and matrix size = 256 × 256 pixels. The voxel size was 1.0 × 1.0 × 1.0 mm. The follow-up data were acquired using the same scanner/parameters as described above. The scanner was calibrated weekly with the same phantom to ensure measurement stability. The intracranial volume (ICV) was measured to correct for differences in head size as described previously (Zhou et al., 2003); there was no group difference in the ICV (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 then reconstructed into entire contiguous coronal images with a 1-mm thickness, perpendicular to the anterior commissure–posterior commissure line. One rater (TT), who was blind to the subjects' identity and time of scan, measured the depth of the olfactory sulcus, which could be readily identified in the coronal view, in all 1-mm 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). While previous

Table 1
Sample characteristics of the participants.

	Cross-sectional analysis			Longitudinal analysis		
	Controls	Schizophrenia	*p*	Controls	Schizophrenia	*p*
Male/Female	37/27	37/27	1.000	13/8	14/6	0.585
Age (years)	25.1 (5.0)	24.0 (4.7)	0.203	24.5 (5.0)	23.8 (5.0)	0.664
Height (cm)	167.0 (7.5)	164.9 (7.6)	0.109	167.3 (7.6)	166.2 (6.6)	0.606
Education (years)	16.5 (2.6)	13.5 (1.9)	<0.001	15.6 (2.4)	13.0 (1.6)	<0.001
Parental education (years)[a]	13.2 (2.5)	13.0 (2.0)	0.482	12.8 (2.6)	12.5 (2.1)	0.756
Inter-scan interval (years)	–	–		2.5 (0.4)	2.7 (0.8)	0.261
Onset age (years)	–	23.1 (4.7)	–	–	22.7 (5.1)	–
Illness duration at baseline (months)	–	11.2 (12.2)	–	–	10.2 (9.4)	–
Medication type (typical/atypical/mixed)						
At baseline	–	18/43/1[b]	–	–	6/12/2	–
During follow-up	–	–	–	–	3/13/4	–
Medication dose (haloperidol equivalent)[c]						
At baseline (mg/day)	–	10.3 (8.8)	–	–	14.6 (11.7)	–
Cumurative dose during follow-up (mg)	–	–	–	–	9852 (8727)	–
Duration of medication at baseline (months)	–	8.3 (12.6)	–	–	8.3 (10.1)	–
SAPS total at baseline[a]	–	27.3 (21.9)	–	–	33.0 (24.0)	–
SAPS total at follow-up[a]	–	–	–	–	19.1 (17.5)	–
SANS total at baseline[a]	–	53.1 (25.2)	–	–	53.7 (27.1)	–
SANS total at follow-up[a]	–	–	–	–	38.0 (24.0)	–
Intracranial volume (cm^3)[d]	1501.9 (150.4)	1499.8 (147.1)	0.983	1501.1 (158.3)	1482.2 (133.2)	0.774

Values represent mean (SD) unless otherwise stated. SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms.
[a] Data missing for some participants.
[b] Two patients were medication free at the time of scanning.
[c] Different typical and atypical antipsychotic dosages were converted into haloperidol equivalents using the guideline by Toru (2008).
[d] Age was used as a covariate for ANCOVA analysis.

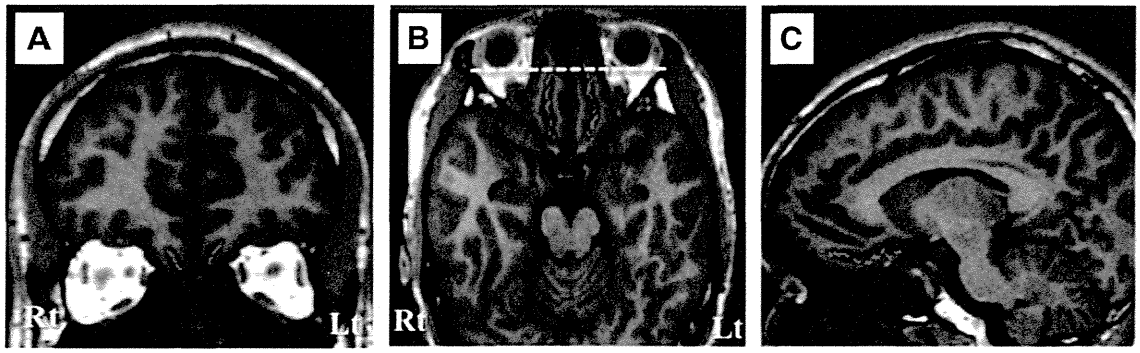

Fig. 1. Olfactory sulci on coronal (A), axial (B), and sagittal (C, left hemisphere) views, colored on 1-mm consecutive coronal slices. Panel A and the dotted line on panel B show the plane of the posterior tangent through the eyeballs (PPTE).

studies measured the sulcus depth by drawing a straight line (Huart et al., 2011; Rombaux et al., 2009), we traced the surface of the intrasulcal gray matter in order to reflect the contour of the sulcus into the measurement. The length of the sulcus in the anterior–posterior direction (mm) was equal to the number of these coronal slices. Intra- and inter-rater (TT and YN) intraclass correlation coefficients for the length and depth of the olfactory sulcus in 10 randomly selected brains were over 0.83.

2.4. Statistical analysis

Clinical and demographic differences between groups were examined with 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 at the baseline were analyzed using the repeated measures analysis of covariance (ANCOVA), with age and ICV as covariates, diagnosis and gender as between-subject factors, and hemisphere as a within-subject variable. The longitudinal changes in the sulcus depth and length were analyzed using repeated measures ANCOVA with age at first scan, ICV, inter-scan interval, and cumulative dose of antipsychotics during scans as covariates, diagnosis and gender as between-subject factors, and time (baseline, follow-up) and hemisphere as within-subject variables. Post-hoc Scheffé's tests were used to follow-up these analyses.

The relationships between baseline measures of the olfactory sulcus and clinical variables were examined by Pearson's partial correlation coefficients controlling for age and ICV. The association between the annual change in the sulcus length and depth, which was calculated as [100 × (measures at follow-up − measures at baseline)/measures at baseline]/inter-scan interval (year), and total SANS/SAPS scores (absolute score change between scans, score at follow-up) was examined using Spearman's rho due to the skewed distribution of these variables (tested by Kolmogorov–Smirnov tests). The association between the annual changes and cumulative dose of antipsychotics during scans was also analyzed using Spearman's rho. Statistical significance was defined as $p<0.05$.

3. Results

ANCOVA of the olfactory sulcus length showed no significant effect involving diagnosis (Table 2), but that for depth revealed significant main effects of diagnosis [F (1, 122) = 120.41, $p<0.001$] and hemisphere [F (1, 124) = 66.67, $p<0.001$] and an interaction between these factors [F (1, 124) = 9.04, $p=0.003$]. Post-hoc analyses showed that the olfactory sulcus depth was significantly shallower in the patients for both hemispheres ($p<0.001$) and deeper in the right hemisphere (controls, $p<0.001$; schizophrenia, $p=0.005$) (Fig. 2). These results did not change even when only the patients whose illness onset was within 1 year of baseline scanning ($N=48$) were included in the analyses, when we added medications (dose and duration) as covariates, or when we excluded the patients taking mood stabilizers ($N=4$). The patients who were receiving typical ($N=18$) and atypical ($N=43$) antipsychotics at baseline scanning did not differ significantly in their sulcus depth [F (1, 55) = 0.55, $p=0.463$]. We found significant effects of diagnosis [F (1, 35) = 47.27, $p<0.001$] and hemisphere [F (1, 37) = 14.30, $p<0.001$] in the baseline sulcus depth in our longitudinal sub-sample (20 patients and 21 controls), which were comparable to the results of the whole sample.

ANCOVA of the longitudinal analysis did not show either main effect of time for length [F (1, 37) = 0.23, $p=0.632$] or depth [F (1, 37) = 0.28, $p=0.600$], or any interaction involving time, showing no significant longitudinal changes in the sulcus morphology in either controls or schizophrenia patients (Fig. 3). We then examined possible longitudinal changes of the sulcus depth only in schizophrenia patients, but found no significant effect of time [F (1, 18) = 0.25, $p=0.619$; Scheffé's test, $p=0.588$].

Table 2
Olfactory sulcus measures.

	Baseline measures (mm)		Diagnosis effect	Change during follow-up (mm)[a]		Diagnosis × time interaction
	Controls	Schizophrenia		Controls	Schizophrenia	
	(N=64)	(N=64)		(N=21)	(N=20)	
Olfactory sulcus length			$F(1,122)=1.67$, $p=0.198$			$F(1,37)=0.43$, $p=0.514$
Left	41.6 (2.9)	42.3 (3.3)		0.0 (1.2)	0.0 (0.7)	
Right	42.1 (3.1)	42.4 (3.3)		−0.4 (1.3)	−0.2 (0.8)	
Olfactory sulcus depth			$F(1,122)=120.41$, $p<0.001$			$F(1,37)=1.26$, $p=0.268$
Left	13.4 (1.1)[b]	11.5 (1.4)		0.1 (0.4)	0.0 (0.3)	
Right	14.4 (1.1)[b,c]	12.0 (1.4)[d]		0.2(0.4)	−0.1 (0.5)	

Values represent mean (SD). [a]Negative value indicates a decrease in length. The statistical analyses reported here were based on repeated measures ANCOVA with time (baseline, follow-up) as a within-subject variable (see text). Post-hoc tests showed: [b]$p<0.001$, deeper than in schizophrenia; [c]$p<0.001$, deeper than in left hemisphere; and [d]$p=0.005$, deeper than in left hemisphere.

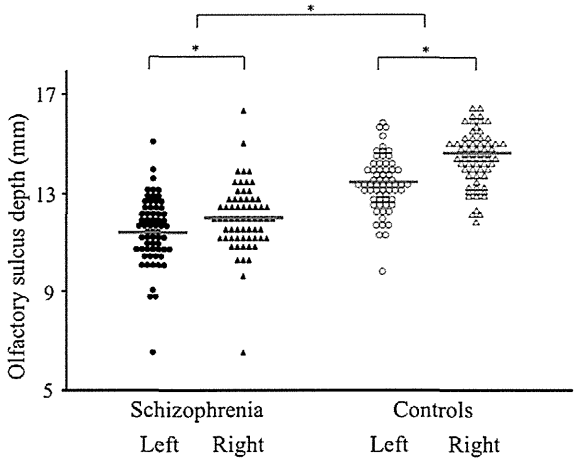

Fig. 2. Olfactory sulcus depth in the patients with schizophrenia and healthy controls at baseline. Horizontal lines indicate mean values. Post hoc Scheffé's test: *$p<0.01$.

The olfactory sulcus length and depth did not correlate with age in either group at the baseline. In the patients, the olfactory sulcus measures (baseline measures, annual change) did not significantly correlate with clinical variables [onset age, medication (dose, duration), illness duration, and total SANS/SAPS scores] after Bonferroni's correction for multiple comparisons. The sulcus length and depth were significantly correlated with each other only in the patients in the left hemisphere ($r=0.449$, $p<0.001$), but this relation was not significantly different from that of the controls ($p=0.267$, Fisher's z transformation).

4. Discussion

To our knowledge, this is the first MRI study to report olfactory sulcus morphology in first-episode schizophrenia with both cross-sectional and longitudinal designs. In the baseline comparison, the patients had a shallower olfactory sulcus compared with healthy controls bilaterally, while the sulcus length did not differ between the groups. In the longitudinal comparison, the sulcus length and depth did not change over time in either group. We did not find any significant relation between the sulcus morphology and clinical variables (e.g., onset age, medication, and symptom severity) in the patients. These findings suggest that altered depth, but not length, of the olfactory sulcus may be a static vulnerability marker of schizophrenia related to neurodevelopmental pathology.

Our baseline findings replicated and expanded the findings by Turetsky et al. (2009a) in showing that schizophrenia patients had abnormally shallow olfactory sulci, which could be due to a disturbance in olfactory system formation during neurodevelopment (Abolmaali et al., 2002; Hummel et al., 2003), even at the early illness stage. We also found a significant diagnosis-by-hemisphere interaction for the sulcus depth, supporting the concept that schizophrenia patients had a reduced normal right-sided lateralization of the olfactory sulcus depth (Turetsky et al., 2009a). Nguyen et al. (2011) did not find altered olfactory sulcus depth on PPTE slices in chronic schizophrenia, but this single-slice approach using external landmarks (i.e., eyeballs) may be partly biased by subtle brain tilt and/or the positional relation between the eyeballs and brain. The present and previous (Turetsky et al., 2009a) MRI findings based on the entire sulcus measures 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). Given the recent neuroimaging evidence suggesting that brain morphologic changes, including abnormalities in sulcogyral pattern (Yucel et al., 2003), predate the onset of psychosis (Fusar-Poli et al., 2011; Smieskova et al., 2010), the olfactory sulcus morphology in high-risk subjects for developing psychosis and its possible relation to clinical characteristics (e.g., severity of prodromal symptoms, later transition into psychosis) seem worthy of examination in future studies.

On the other hand, dynamic brain changes, including excessive cortical thinning (van Haren et al., 2011) or gray matter reduction (Mane et al., 2009) over time in the frontal area, may also occur during or after the onset of schizophrenia (Pantelis et al., 2007). 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. However, the present longitudinal analyses demonstrated no progressive changes in the olfactory sulcus measures in either first-episode schizophrenia or controls. Antipsychotic medication can significantly affect brain morphology (reviewed by Moncrieff and Leo, 2010), especially regarding progressive brain changes (Takahashi et al., 2010; van Haren et al., 2011) in schizophrenia, but we did not find any medication effect on the length and depth of the olfactory sulcus. Our longitudinal analyses thus revealed that olfactory sulcus morphology may be static, at least during the early illness stage of schizophrenia.

Given that olfactory sulci on the human orbitofrontal cortex appear at 16 weeks gestation and are prominent at 25 weeks (Chi et al., 1977), our results offer a clue regarding the estimation of gestational age at which neurodevelopmental insults occur in schizophrenia. On the basis of gyral development of the human brain (Chi et al., 1977; Garel et al., 2001), previous findings of abnormal cingulate cortex folding in schizophrenia (Fujiwara et al., 2007; Yucel et al., 2002) also suggest neurodevelopmental disturbance by the third trimester of gestation, whereas the orbital sulci, which are not recognizable until 36 weeks of gestation, are of a normal depth in patients (Turetsky et al., 2009a). Our own results of midline brain structures in schizophrenia (Takahashi et al., 2008a,b) partly parallel these findings; abnormally small adhesio interthalamica that develops during early gestation (Rosales et al., 1968) and normal cavum septi pellucidi (CSP), which is related to fusion of the septum pellucidi within 3–6 months of birth (Shaw and Alvord, 1969), support the idea that schizophrenia is more closely related to aberrant neurodevelopment early in gestation. Since discrepant findings, such as altered orbital sulcus pattern (Nakamura et al., 2007; Takayanagi et al., 2010) and increased prevalence of large CSP (Trzesniak et al., 2011), have been also reported in schizophrenia, further comprehensive assessment of these potential neurodevelopmental markers in the same cohort of schizophrenia patients is required in future studies ideally in various illness stages (including prodromal phase).

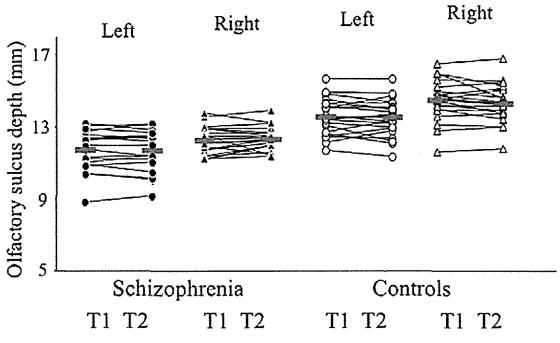

Fig. 3. Scatterplots of absolute olfactory sulcus depth in the patients with schizophrenia and healthy controls. Values of baseline (T1) and follow-up scan (T2) in each subject are connected with a straight line. Horizontal lines indicate means of each group.

A few possible confounding factors in this study should be taken into account. First, although our findings on altered depth of the olfactory sulcus may reflect embryonic disruption of the olfactory system, we did not assess olfactory function or other olfactory structures. Reduced olfactory bulb volume in schizophrenia patients (Nguyen et al., 2011; Turetsky et al., 2000) 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 (Duprez and Rombaux, 2010; Rombaux et al., 2009), but our T1-weighted images did not allow reliable measurement of the bulb. Also, we could not reliably assess the average depth of the orbital sulci because of their variability and complexity (Chiavaras and Petrides, 2000). Second, some of our first-episode patients had been psychotic for several years and already received substantial amounts of antipsychotics at baseline scanning owing to our definition of the first-episode. Although the results did not change even when we included only the patients whose illness duration is ≤1 year in the analyses and we did not find any effect of medication on the sulcus morphology in our sample, the patients with shorter illness duration and/or medication naïve patients should be examined in the future. Third, although we found no relation between the olfactory sulcus morphology and symptom severity at scanning, the possibility exists that it relates to an even later clinical course of schizophrenia. Finally, given that olfactory dysfunction may help to discriminate among various psychiatric disorders as discussed by Nguyen et al. (2011), disease specificity of the olfactory sulcus abnormalities is worthy of further examination.

5. Conclusion

The present study demonstrated a shallow olfactory sulcus in schizophrenia, which already existed in first-episode patients, and this showed no active progressive changes after the illness onset. Our results, as well as the time point at which the sulcus develops during the gestation period, suggest that the olfactory sulcus depth could be a marker of early neurodevelopmental abnormalities in schizophrenia.

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Neuroimaging-aided differential diagnosis of the depressive state

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ABSTRACT

A serious problem in psychiatric practice is the lack of specific, objective biomarker-based assessments to guide diagnosis and treatment. The use of such biomarkers could assist clinicians in establishing differential diagnosis, which may improve specific individualised treatment. This multi-site study sought to develop a clinically suitable neuroimaging-guided diagnostic support system for differential diagnosis at the single-subject level among multiple psychiatric disorders with depressive symptoms using near-infrared spectroscopy, which is a compact and portable neuroimaging method. We conducted a multi-site, case–control replication study using two cohorts, which included seven hospitals in Japan. The study included 673 patients (women/men: 315/358) with psychiatric disorders (major depressive disorder, bipolar disorder, or schizophrenia) who manifested depressive symptoms, and 1007 healthy volunteers (530/477). We measured the accuracy of the single-subject classification in differential diagnosis among major psychiatric disorders, based on spatiotemporal characteristics of fronto-temporal cortical haemodynamic response patterns induced by a brief (<3 min) verbal fluency task. Data from the initial site were used to determine an optimal threshold, based on receiver-operator characteristics analysis, and to generate the simplest and most significant algorithm, which was validated using data from the remaining six sites. The frontal haemodynamic patterns detected by the near-infrared spectroscopy method accurately distinguished between patients with major depressive disorder (74.6%) and those with the two other disorders (85.5%; bipolar disorder or schizophrenia) that presented with depressive symptoms. These results suggest that neuroimaging-guided differential diagnosis of major psychiatric disorders developed using the near-infrared spectroscopy method can be a promising biomarker that should aid in personalised care in real clinical settings. Potential confounding effects of clinical (e.g., age, sex) and systemic (e.g., autonomic nervous system indices) variables on brain signals will need to be clarified to improve classification accuracy.

Introduction

Among non-communicable diseases, neuropsychiatric conditions, including depression, contribute most significantly to overall disability-adjusted life years (DALYs), surpassing both cardiovascular disease and cancer (Mathers and Loncar, 2006; Prince et al., 2007). Therefore, early and accurate diagnosis and treatment are critical in psychiatric disorders, for which the development of specific biomarkers is of special importance. Currently, however, the diagnostic process in psychiatry is mainly based on patients' reports of symptoms, observed behaviours and disease course. Overcoming the limitations of relying on clinical interviews alone for the diagnosis of psychiatric disorders has been a great challenge.

To complicate this issue further, the manifestation of only a major depressive episode hampers the reliable differentiation of major depressive disorder (MDD) from bipolar disorder (BP) or

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