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Reduced pineal gland volume across the stages of schizophrenia

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ABSTRACT

A few magnetic resonance imaging (MRI) studies reported reduced pineal gland volume in chronic schizophrenia (Sz), implicating the involvement of melatonin in the pathophysiology of the illness. However, it is not known whether this abnormality, if present, exists at the early illness stages and/or develops progressively over the course of the illness. This MRI study examined pineal gland volume in 64 patients with first-episode schizophrenia (FESz), 40 patients with chronic Sz, 22 individuals with at-risk mental state (ARMS), and 84 healthy controls. Longitudinal changes in pineal volume (mean inter-scan interval = 2.5 ± 0.7 years) were also examined in a subsample of 23 FESz, 16 chronic Sz, and 21 healthy subjects. In the cross-sectional comparison, the ARMS, FESz, and chronic Sz groups had significantly smaller pineal volume to the same degree as compared with healthy controls. A longitudinal comparison demonstrated that pineal volume did not change over time in any group. There was no association between pineal volume and clinical variables (e.g., symptom severity, medication) in the ARMS and Sz groups. The results suggest that a smaller pineal gland may be a static vulnerability marker of Sz, which probably reflects an early neurodevelopmental abnormality.

1. Introduction

Various evidence has suggested that abnormal function of the pineal gland, a neuroendocrine organ that regulates circadian rhythms and sleep by secretion of melatonin (Borjigin et al., 2012; Cajochen et al., 2003), may be implicated in the pathophysiology of schizophrenia (Sz) (Anderson and Maes, 2012; Pacchierotti et al., 2001). Although not consistently replicated (Afonso et al., 2011; Viganò et al., 2001), at least some subtypes of Sz [e.g., paranoid subtype (Monteleone et al., 1997)] may exhibit decreased plasma levels (Monteleone et al., 1997; Robinson et al., 1991) or altered urine secretion peaks (Wulff et al., 2012) of melatonin. These findings are unlikely to be related to medication status or symptom severity (reviewed by Morera-Fumero and Abreu-Gonzalez, 2013). A recent in vitro study (Galván-Arrieta et al., 2017) suggested that low melatonin levels during gestation may underlie impaired neurodevelopment, which was associated with the etiology of Sz (Catts et al., 2013). As pineal gland volume, which correlates with melatonin levels in healthy subjects (Liebrich et al., 2014; Nölte et al., 2009), likely increases until infancy but remains stable thereafter in normal development (Sumida et al., 1996), it seems worthwhile to examine the potential role of functional/structural abnormalities of the pineal gland as a static vulnerability marker of Sz.

In contrast to hormonal investigations, there have been only a few magnetic resonance imaging (MRI) studies addressing pineal volume differences in Sz and the results have been inconsistent; an early study by Rajarethinam et al. (1995) found no significant volume difference between chronic patients and controls, while subsequent studies by Bersani et al. (2002) and Fındıklı et al. (2015) reported reduced pineal volume in chronic Sz. The reason for these discrepancies remains unclear, but rather small sample sizes (15 to 17 patients) and two-dimensional estimation of the pineal volume (Sumida et al., 1996) in the latter studies (Bersani et al., 2002; Fındıklı et al., 2015), as well as different exclusion criteria for subjects with pineal cyst, which likely exists in approximately 20–40% of healthy subjects (Carpenter et al., 2017; Pu et al., 2007), may have affected the findings. On the other hand, both previous studies reporting reduced pineal volume in Sz (Bersani et al., 2002; Fındıklı et al., 2015) hypothesized early neurodevelopmental pathology to explain their findings, because clinical variables such as illness duration, medication, and symptom severity did not affect pineal volumes. However, further studies in both cross-sectional and longitudinal designs, ideally in various illness stages (including prodromal phase), are needed to clarify whether pineal volume is a static marker of neurodevelopmental abnormality in Sz.

This MRI study investigated pineal gland volume in first-episode (FE) Sz, chronic Sz, and subjects at clinical high-risk for developing psychosis [i.e., at-risk mental state (ARMS; Yung et al., 2005)], compared to

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healthy controls. We also investigated pineal cyst prevalence between the groups. Further, pineal volume changes over time were examined in a longitudinal subsample of FESz, chronic Sz, and healthy controls. On the basis of previous findings in chronic patients (Bersani et al., 2002; Fındıklı et al., 2015) and the potential role of melatonin in the neurodevelopmental etiology of Sz ((Galván-Arrieta et al., 2017), we predicted that patients would exhibit reduced pineal volume in both early and chronic phases of Sz, and that pineal volume would not change over time during the course of the illness. We also explored the relationship between pineal volume and various clinical factors (e.g., symptom severity, antipsychotic medication) in ARMS and Sz groups.

2. Methods

2.1. Subjects

One-hundred and four patients with Sz (64 FE and 40 chronic cases) who met the ICD-10 research criteria (World Health Organization, 1993) were recruited from the inpatient and outpatient clinics of the Department of Neuropsychiatry of Toyama University Hospital. Patients were diagnosed following a structured clinical interview by psychiatrists using the Comprehensive Assessment of Symptoms and History (Andreasen et al., 1992). Patients were defined as FESz when illness duration was ≤1 year ($N = 48$) or they were under first psychiatric hospitalization ($N = 16$) (Hirayasu et al., 2000; Schooler et al., 2005), while patients with illness duration >3 years ($N = 40$) were categorized as chronic Sz. The diagnosis of Sz was confirmed for all FESz patients at least 6 months after illness onset based on information obtained from a detailed chart review as well as the clinical symptoms rated at the time of scanning. Medication and other clinical data are summarized in Table 1.

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 (Mizuno et al., 2009). The ARMS subjects, who had no previous episode of overt psychosis, were diagnosed according to the Japanese version of the

Table 1
Demographic/clinical characteristics and brain measurements of the cross-sectional sample.

	C	ARMS	FESz	Chronic Sz	Group comparisons
Age (years)	23.7 ± 5.4	19.1 ± 4.1	24.0 ± 4.7	29.0 ± 5.5	$F(3, 208) = 19.58$, $p < 0.001$; ARMS < C, FESz < Chronic Sz
Gender [male/female (% male)]	48/38 (55.8%)	11/11 (50.0%)	37/27 (57.8%)	20/20 (50.0%)	Chi-square = 0.85, $p = 0.838$
Height (cm)	166.3 ± 7.8	162.2 ± 9.5	164.9 ± 7.6	164.8 ± 8.0	$F(3, 208) = 1.70$, $p = 0.167$
Education (years)	15.7 ± 3.0	11.1 ± 1.6	13.5 ± 1.9	13.6 ± 2.2	$F(3, 208) = 24.36$, $p < 0.001$; ARMS < FESz, Chronic Sz < C
Parental education (years)[a]	13.0 ± 2.3	13.8 ± 1.7	13.0 ± 2.0	11.7 ± 1.7	$F(3, 205) = 5.95$, $p < 0.001$; Chronic Sz < other groups
Onset age (years)	–	–	23.1 ± 4.7	20.9 ± 4.4	$F(1, 102) = 5.52$, $p = 0.021$
Illness duration (months)	–	–	11.2 ± 12.2	96.8 ± 39.8	$F(1, 102) = 255{,}13$, $p < 0.001$
Medication dose (HPD equivalent, mg/day)	–	2.2 ± 3.1 ($N = 4$)	10.3 ± 8.8	10.4 ± 9.3	$F(2, 123) = 13.32$, $p < 0.001$; ARMS < FESz, Chronic Sz
Duration of medication (months)	–	2.3 ± 4.1 ($N = 4$)	8.3 ± 12.6	72.4 ± 47.6	$F(2, 123) = 75.20$, $p < 0.001$; ARMS < FESz < Chronic Sz
Medication type (typical/atypical/mixed)	–	1/3/0	18/43/1[b]	19/18/3	Fisher's exact test, $p = 0.09$
Time between intake and scan (days)	–	50.8 ± 74.4	–	–	–
Time between scan and onset (months)	–	8.2 ± 9.9 ($N = 5$)	–	–	–
STAI trait score at intake[c]	–	65.3 ± 10.9	–	–	–
STAI state score at intake[c]	–	58.4 ± 11.3	–	–	–
BDI score at intake[c]	–	24.1 ± 10.0	–	–	–
SAPS scores[d]					Subscale-by-group interaction; $F(6, 354) = 2.12$, $p = 0.050$
Hallucinations	–	3.7 ± 3.6	7.0 ± 8.0	8.9 ± 7.9	Post-hoc test; ARMS < FESz, chronic Sz
Delusions	–	9.3 ± 4.4	12.6 ± 10.4	11.3 ± 6.7	Post-hoc test; ARMS < FESz
Bizarre behavior	–	4.8 ± 3.6	4.3 ± 4.1	4.4 ± 4.1	–
Positive formal thought disorder	–	2.6 ± 4.3	3.5 ± 5.5	5.5 ± 7.8	–
Total score	–	20.4 ± 10.9	27.3 ± 21.9	30 ± 19.2	$F(2, 118) = 1.70$, $p = 0.186$
SANS scores[d]					Subscale-by-group interaction; $F(8, 472) = 3.30$, $p = 0.001$
Blunted affect	–	11.8 ± 6.9	15.4 ± 9.3	11.4 ± 8.0	Post-hoc test; ARMS, chronic Sz < FESz
Alogia	–	8.5 ± 5.0	7.5 ± 5.0	5.9 ± 3.8	Post-hoc test; chronic Sz < ARMS
Avolition-apathy	–	10.8 ± 4.8	10.5 ± 5.1	9.9 ± 4.0	–
Anhedonia-asociality	–	12.1 ± 7.1	11.2 ± 6.7	10.5 ± 6.3	–
Attention deficit	–	5.3 ± 4.1	8.7 ± 4.5	8.2 ± 4.5	Post-hoc test; ARMS < FESz, chronic Sz
Total score	–	48.5 ± 19.4	53.1 ± 25.2	45.5 ± 18.7	$F(2, 118) = 1.41$, $p = 0.248$
Pineal volume [mm^3 (Cohen's d relative to C)]	131.1 ± 60.1	102.7 ± 43.2 (−0.54)	102.3 ± 46.2 (−0.54)	105.7 ± 46.4 (−0.47)	$F(3, 202) = 4.80$, $p = 0.003$; other groups < C[e]
Cyst (≥2 mm) [N(%)]	25 (29.1%)	3 (13.6%)	11 (17.2%)	10 (25%)	Chi-square = 4.17, $p = 0.243$
Small cystic change (<2 mm) [N(%)]	12 (14.0%)	7 (31.8%)	17 (26.6%)	7 (17.5%)	Chi-square = 5.69, $p = 0.128$
Pineal volume in subjects without cystic change [mm^3 (Cohen's d relative to C)]	106.7 ± 40.6	89.8 ± 25.9 (−0.54)	79.8 ± 21.8 (−0.83)	91.7 ± 38.1 (−0.38)	$F(3, 110) = 3.35$, $p = 0.022$; FESz < C
Intracranial volume (cm^3)	1502 ± 148	1460 ± 132	1500 ± 147	1513 ± 173	$F(3, 207) = 0.30$, $p = 0.828$[f]

Values represent means ± SDs unless otherwise stated.
ARMS, at-risk mental state; BDI, Beck Depression Inventory; C, controls; FE, first-episode; HPD, haloperidol; SANS, scale for the assessment of negative symptoms; SAPS, scale for the assessment of positive symptoms; STAI, State Trait Anxiety Inventory; Sz, schizophrenia.
[a] Data missing for one control, one FESz, and one chronic Sz subjects.
[b] Two patients were medication-free at the time of scanning.
[c] Data missing for one participant.
[d] Data missing for two FESz and three chronic Sz patients. Groups were compared using ANOVA with subscale as a within-subject variable.
[e] The pineal volume was log-transformed for statistics because of its skewed distribution ($p < 0.01$, Shapiro-Wilk test). The skewness and kurtosis statistics were 1.39 and 2.23 before transformation and 0.24 and −0.20 after transformation, respectively. The pineal volume was normally distributed after transformation ($p = 0.279$, Shapiro-Wilk test).
[f] Age was used as a covariate.

Comprehensive Assessment of At Risk Mental States (CAARMS) (Miyakoshi et al., 2009); inclusion into the study required one or more of attenuated psychotic symptoms (APS) ($N = 21$), brief and limited intermittent psychotic symptoms (BLIPS) ($N = 2$), and/or genetic risk and deterioration syndrome (GRD) ($N = 1$) (i.e., one participant fulfilled both the APS and BLIPS criterion, and one fulfilled both the APS and GRD criterion). At intake, subjects were also assessed using the Beck Depression Inventory (BDI) (Beck et al., 1961) and State Trait Anxiety Inventory (STAI) (Spielberger et al., 1983). The clinical symptoms of the Sz and ARMS subjects were rated by trained psychiatrists 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). Eighteen ARMS subjects were antipsychotic naïve at the time of scanning, but three were receiving low doses of atypical antipsychotics (risperidone, blonanserin, or aripiprazole) and one was treated with sulpiride. 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 developed Sz fulfilling the ICD-10 research criteria (World Health Organization, 1993) and 17 (77.3%) did not develop psychosis during follow up (mean clinical follow-up period after scanning, 15.6 ± 17.4 months).

The control subjects, consisting of 84 healthy volunteers recruited from the community, hospital staff, and university students, were given a questionnaire consisting of 15 items concerning their personal (13 items; including a history of obstetric complications, substantial head injury, seizures, neurological or psychiatric disease, impaired thyroid function, hypertension, diabetes, and substance abuse) and family (2 items) histories of illness (Takahashi et al., 2008). Subjects with any personal or family history of psychiatric illness among first-degree relatives were excluded.

All subjects in this study (FESz, chronic Sz, ARMS, and controls) were screened using the same exclusion criteria (except family history of psychiatric illness, which applied only to controls). The subjects were 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 Sz and ARMS participants were screened for these conditions using a detailed chart review at scanning (Sz) or direct interview at study intake (ARMS). All participants were also screened for gross brain abnormalities by neuroradiologists. Subjects with pineal cysts were not excluded.

Follow-up MRI data were available for 23 FESz patients, 16 chronic Sz patients, and 21 healthy controls (Table 2); the sample size was rather small because we recruited these longitudinal subjects only within a specific time period. There are substantial sample overlaps between the participants in this study (212 cross-sectional and 60 longitudinal subjects) and those in a series of our MRI studies of cortical and other structures (Takahashi and Suzuki, 2018), however this is the first study of the pineal gland using our MRI data. 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 years, written consent was also obtained from the parent/guardian.

2.2. Magnetic resonance imaging procedures

MR images were obtained using a 1.5T 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. Voxel size was 1.0 × 1.0 × 1.0 mm. The scanner was calibrated weekly with the same phantom to ensure measurement stability.

Table 2
Demographic/clinical characteristics and brain measurements of the longitudinal sample.

	C	FESz	Chronic Sz	Group comparisons
	(13 M, 8F)	(15 M, 8F)	(7 M, 9F)	
Age (years)	24.5 ± 5.0	23.5 ± 4.8	31.6.5 ± 7.1	$F(2, 57) = 11.27$, $p < 0.001$; C, FESz < Chronic Sz
Height (cm)	167.3 ± 7.6	165.0 ± 7.9	163.7 ± 9.3	$F(2, 57) = 0.97$, $p = 0.387$
Education (years)	15.6 ± 2.4	13.1 ± 1.6	14.3 ± 2.6	$F(2, 57) = 7.49$, $p = 0.001$; FESz < C
Parental education (years)	12.8 ± 2.6	12.7 ± 2.1	11.8 ± 1.5	$F(2, 57) = 1.11$, $p = 0.337$
Inter-scan interval (years)	2.5 ± 0.4	2.6 ± 0.8	2.2 ± 0.8	$F(2, 57) = 1.71$, $p = 0.189$
Onset age (years)	–	22.4 ± 4.8	23.0 ± 5.9	$F(1, 37) = 0.09$, $p = 0.764$
Illness duration at baseline (months)	–	9.5 ± 9.1	98.2 ± 38.0	$F(1, 37) = 117.68$, $p < 0.001$
Duration of medication at baseline (months)	–	7.8 ± 9.7	80.2 ± 60.3	$F(1, 37) = 35.167$, $p < 0.001$
Medication type during follow-up (typical/atypical/mixed)	–	3/16/4	4/8/4	Fisher's exact test, $p = 0.48$
Medication dose (HPD equivalent)				
Baseline (mg/day)	–	13.5 ± 11.4	10.7 ± 8.1	$F(1, 37) = 0.72$, $p = 0.402$
Cumulative dose during follow-up (mg)	–	9526.4 ± 8609.2	11,846.5 ± 11,411.3	$F(1, 37) = 0.52$ $p = 0.474$
Mean dose during follow-up (mg/day)	–	9.5 ± 7.2	15.2 ± 10.3	$F(1, 37) = 4.07$, $p = 0.051$
SAPS total score				
Baseline	–	29.0 ± 24.3 ($N = 20$)	31.1 ± 28.1 ($N = 15$)	$F(1, 33) = 0.06$, $p = 0.807$
Follow-up	–	17.0 ± 17.1 ($N = 22$)	34.9 ± 30.0 ($N = 16$)	$F(1, 36) = 5.43$, $p = 0.026$
SANS total score				
Baseline	–	52.1 ± 25.5 ($N = 20$)	51.2 ± 16.9 ($N = 16$)	$F(1, 33) = 0.01$, $p = 0.912$
Follow-up	–	38.0 ± 22.5 ($N = 22$)	57.3 ± 18.7 ($N = 16$)	$F(1, 36) = 7.85$, $p = 0.008$
Pineal gland volume (mm^3)				
Baseline	139.1 ± 64.8	105.0 ± 53.7	103.3 ± 43.5	$F(2, 55) = 2.50$, $p = 0.090$[a]
Follow-up	137.4 ± 62.5	103.7 ± 52.3	103.4 ± 42.8	$F(2, 55) = 2.34$, $p = 0.106$[a]
% change/year[b]	−0.3 ± 2.6	−0.2 ± 3.4	0.0 ± 4.2	$F(2, 54) = 0.66$, $p = 0.523$
Intracranial volume (cm^3)	1501 ± 158	1476 ± 140	1535 ± 197	$F(2, 56) = 0.08$, $p = 0.922$[c]

Values represent means ± SDs unless otherwise stated. Groups were matched for gender (Chi-square = 1.96, $p = 0.376$).
C, controls; FE. First-episode; HPD, haloperidol; SANS, scale for the assessment of negative symptoms; SAPS, scale for the assessment of positive symptoms. Sz, schizophrenia.
[a] The pineal volume was log-transformed for statistics because of skewed distribution ($p < 0.01$, Kolmogorov-Smirnov test).
[b] Negative value indicates a decrease in volume.
[c] Age was used as a covariate.

To assess pineal volume, the images were processed on a Linux PC (Fujitsu Limited, Tokyo, Japan) using Dr. View software (Infocom, 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. The signal intensity histogram distributions from the T1-weighted images across the whole cerebrum were then used to automatically segment the voxels into brain tissue component and cerebrospinal fluid (CSF). The intracranial volume (ICV) was measured to correct for differences in head size as described previously (Zhou et al., 2003); there were no significant group differences for ICV (Tables 1, 2).

2.3. Pineal gland measurements

Pineal gland volume was manually traced on consecutive 1-mm coronal slices with the corresponding sagittal and axial planes simultaneously presented for reference (Fig. 1). The pineal gland locates posterior to the habenula, a bright pyramidal-shaped structure protruding into the third ventricle on T1 images (Lawson et al., 2013), and can be delineated readily on the voxels of a brain tissue component as it is largely surrounded by CSF except for the attachment to the habenulae (Bumb et al., 2014; Carpenter et al., 2017; Matsuoka et al., 2018). According to the literature (Carpenter et al., 2017), the volume of cystic changes within the gland [pineal cysts (≥2 mm in diameter) or small cystic changes (<2 mm in diameter)], which were detected as circular areas of isointensity relative to CSF (Pu et al., 2007), were included in the pineal gland volume.

All measurements were carried out by one rater (TT) without knowledge of the subjects' identities or the times of the scans (baseline, follow-up). To determine the reliability of the measurement, a second rater (MN) measured the pineal gland in a subset of 10 randomly selected brains. Each pineal volume in these 10 brains was then remeasured after at least 4 weeks by the first rater. Inter- (TT and MN) and intra-rater intraclass correlation coefficients were > 0.92.

2.4. Statistical analysis

Clinical and demographic differences between groups were examined by one-way analysis of variance (ANOVA), χ^2 test, or Fisher's exact test (when >20% of cells had expected counts <5).

The relationships between baseline pineal volume and clinical variables [onset age, illness duration, medication (dose, duration), and total SAPS/SANS scores] in the cross-sectional sample were examined by Pearson's partial correlation coefficients, controlling for age and ICV with Bonferroni's correction. Pineal volume was log-transformed because of the skewed distribution (Table 1). In the longitudinal sample, we examined whether the annual change of pineal volume, which was calculated as [100 × (volume at follow-up - volume at baseline)/volume at baseline]/inter-scan interval (year), was associated with total SAPS/SANS scores (absolute score change between scans, score at follow-up) and cumulative dose of antipsychotics during scans using the same model. Annual volume change was normally distributed ($p = 0.211$, Shapiro-Wilk test).

For the cross-sectional comparison, pineal volume (log) was analyzed by analysis of covariance (ANCOVA), with age and ICV as covariates, and diagnosis and gender as between-subject factors. χ^2 tests were used to assess the frequency of the pineal cyst (≥2 mm) and small cystic change (<2 mm).

For the longitudinal comparison, annual change in pineal volume was analyzed by means of ANCOVA with age at first scan, ICV, and cumulative dose of antipsychotics during scans as covariates, and with diagnosis as a between-subject factor. Although gender was not used as a between-subject factor for the longitudinal analysis due to the small sample size, especially for females, none of the ANCOVA results reported herein changed when we included gender as a covariate. A post hoc

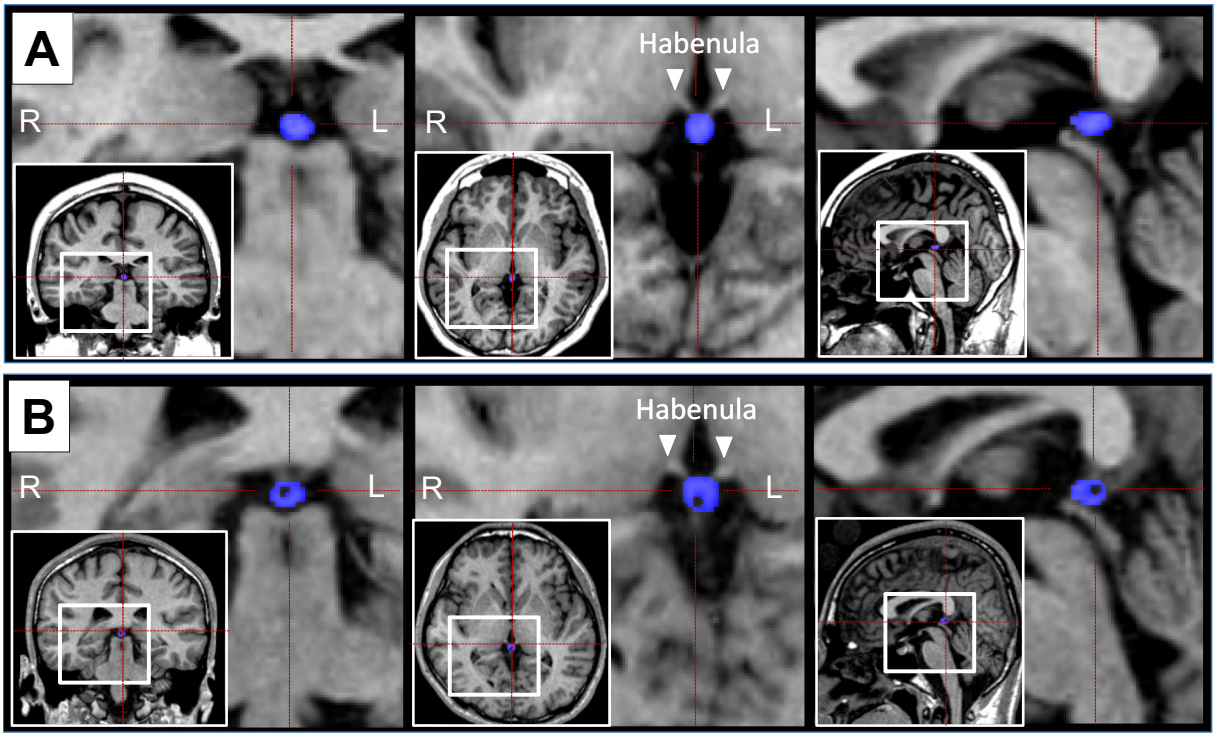

Fig. 1. Coronal (left), axial (middle), and sagittal (right) views of sample MR images of the pineal gland (colored in blue) in subjects without (A) and with (B) a pineal cyst. The pineal gland was automatically delineated from surrounding cerebrospinal fluid space by using the signal intensity histogram, except for the attachment to the habenulae (i.e., the pineal stalk) that was excluded from the measurement of the pineal gland. L, left; R, right.

Duncan test was used to follow-up the analyses. Statistical significance was defined as $p < 0.05$.

3. Results

3.1. Demographic characteristics

Demographic and clinical characteristics of the entire cross-sectional sample are summarized in Table 1. Groups were matched for gender and height, but there were significant differences in age and personal/parental education. The chronic Sz patients had a younger onset age and longer illness duration compared to FESz patients. As predicted, the dose and duration of antipsychotic medication differed between the groups (ARMS < FESZ < chronic Sz). The ARMS subjects were generally characterized by less severe positive and negative symptoms compared with the Sz patients. The characteristics of the longitudinal subsample (Table 2) were comparable to those of the entire study sample.

3.2. Relationship between the pineal gland and demographic/clinical variables

Pineal volume did not correlate with age or personal/parental education in any group. In the cross-sectional sample, pineal volume did not significantly correlate with clinical variables [onset age and illness duration (for the Sz groups), dose and duration of antipsychotic medication, and total SAPS/SANS scores (for the ARMS and Sz groups)] (Supplementary table 1). The subjects with and without cystic change [cyst (≥2 mm) or cystic change of any size] did not differ in these demographic/clinical variables. In the longitudinal sample of Sz, the annual pineal gland volume change did not significantly correlate with total SAPS/SANS scores (change between scans, score at follow-up), and cumulative dose of antipsychotics during scans (Supplementary table 1).

3.3. Cross-sectional analyses of the pineal gland in the control, ARMS, FESz, and chronic Sz subjects

There was a significant group difference in pineal gland volume (Table 1, Fig. 2); the ARMS (post-hoc test, $p = 0.015$), FESz (post-hoc test, $p = 0.020$), and chronic Sz (post-hoc test, $p = 0.020$) groups had a significantly smaller volume compared with controls. There was no significant effect or interaction involving gender. These results did not change when we included only patients with illness duration ≤1 year ($N = 48$) as FESz patients (mean pineal volume = 105.1 ± 47.9 mm^3). There was no difference in pineal volume between Sz patients treated with typical (18 FE and 19 chronic patients) and atypical (43 FE and 18 chronic patients) antipsychotics [$F(1, 94) = 1.31$, $p = 0.255$].

The prevalence of pineal cysts [23.1% (49/212) in all participants] and small cystic changes [20.3% (43/212) in all participants] did not differ between groups (Table 1). When we examined only the subjects without cystic change, the FESz group ($N = 36$; post-hoc test, $p = 0.032$), but not ARMS ($N = 12$; post-hoc test, $p = 0.160$) and chronic Sz ($N = 23$; post-hoc test, $p = 0.133$) groups, had a significantly smaller pineal volume compared with controls (Table 1), potentially due to reduced statistical power. Nevertheless, the ARMS and chronic Sz groups had a smaller pineal volume compared to controls with medium to large effect sizes (Cohen's $d = -0.38$ to -0.54).

3.4. Longitudinal analyses of the pineal gland in the control, FESz, and chronic Sz subjects

ANCOVA of the annual pineal gland volume change showed no significant main effect of diagnosis (Table 2). When we used repeated measures ANCOVA with time (baseline, follow-up) as a within-subject variable, with age, ICV, inter-scan interval, and cumulative medication dose as covariates, and with diagnosis as a between-subject factor, pineal volume revealed no significant effect of time [$F(1, 57) = 1.02$, $p = 0.317$], diagnosis [$F(2, 53) = 1.20$, $p = 0.309$], or their interaction [$F(2, 57) = 0.34$, $p = 0.710$], indicating that the pineal gland exhibited no significant volume changes over time in any group (Fig. 3). These results did not change even when we examined only the subjects without cystic change.

4. Discussion

To our knowledge, this is the first MRI study to report pineal gland morphology in both cross-sectional and longitudinal designs at various stages of Sz. In the baseline comparison, the ARMS, FESz, and chronic Sz groups had a significantly smaller volume as compared with healthy controls to the same degree, while the prevalence of pineal cysts did not differ between groups. In the longitudinal comparison, pineal volume did not change over time in healthy controls, or in FE and chronic Sz patients. We did not find any significant relation between pineal gland morphology and clinical variables (onset age, illness duration, medication, and symptom ratings). These findings may support the notion that pineal volume is a static vulnerability marker of Sz related to neurodevelopmental pathology.

Our baseline findings replicated and expanded previous findings in chronic Sz (Bersani et al., 2002; Fındıklı et al., 2015) in finding that Sz patients had a smaller pineal gland, which implicates the involvement of melatonin (Liebrich et al., 2014), even at early illness stages and

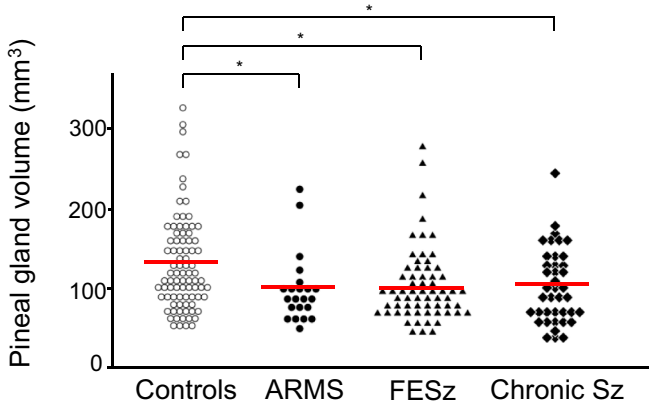

Fig. 2. Pineal gland volume in the cross-sectional sample of healthy controls, subjects with at-risk mental state (ARMS), patients with first-episode schizophrenia (FESz), and patients with chronic Sz. Horizontal lines indicate mean values. Post hoc test: *$p < 0.05$.

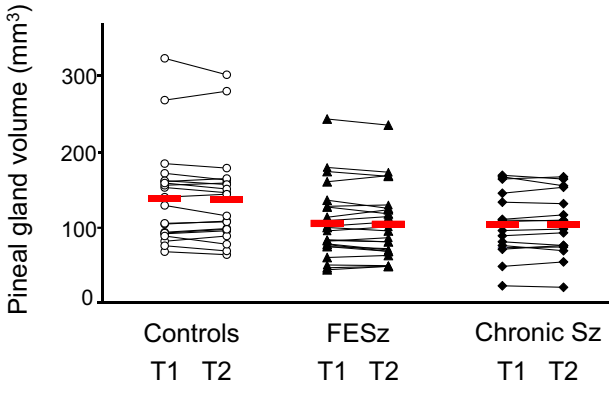

Fig. 3. Progressive volume changes of the pineal gland in healthy controls, patients with first-episode schizophrenia (FESz), and patients with chronic Sz. Values of baseline (T1) and follow-up (T2) scans in each subject are connected with a straight line. Horizontal bars indicate the means of each group.

that potential confounding factors after illness onset such as medication and disease chronicity do not affect pineal volume. Further, our findings suggested that clinical high-risk subjects for psychosis share a pineal abnormality with patients with established Sz as a possible indicator of common vulnerability. However, there is also an early MRI study by Rajarethinam et al. (1995) that found normal pineal volume in chronic Sz. Other previous studies (Bersani et al., 2002; Fındıklı et al., 2015) estimated pineal volume by an approximation formula (1/2 × length × width × height), which shows a rather weak correlation with true volumetric value (Sun et al., 2009), in a relatively small sample ($n = 15$ to 17), but Rajarethinam et al. (1995) manually measured true gland volume in a larger cohort of chronic Sz ($N = 45$). As discussed by Fındıklı et al. (2015), a different approach to pineal cyst, which influences pineal gland volume (Sun et al., 2009), may partly explain the discrepancy between the studies; Fındıklı et al. (2015) excluded subjects with pineal cyst from their study, and there was no information regarding cyst in the studies by Rajarethinam et al. (1995) and Bersani et al. (2002). However, we found no group difference in the prevalence of pineal cysts or small cystic changes, which was comparable to those reported in an autopsy (Tapp and Huxley, 1972) and high-resolution MRI (Carpenter et al., 2017; Pu et al., 2007) studies in healthy subjects, suggesting that pineal cyst may not play a major role in the pathophysiology of Sz. On the other hand, it should be noted that the absolute pineal volume in healthy controls reported by Rajarethinam et al., 1995 (mean = 213 mm^3) was almost twice as large as that in this (Table 1) and other MRI studies of true pineal volume (Acer et al., 2012; Bumb et al., 2014; Matsuoka et al., 2018; Sun et al., 2009), suggesting some methodological differences between the studies. Nevertheless, given that this is probably the first MRI study showing reduced pineal volume in ARMS and that no studies to date reported abnormal melatonin secretion in high-risk subjects for developing psychosis, further studies are needed to examine the potential role of functional/structural abnormalities of the pineal gland as a vulnerability marker of Sz.

In sharp contrast to active cortical atrophy (Takahashi et al., 2010, 2011a) and progressive expansion of the pituitary gland (Takahashi et al., 2011b), another endocrine origin situated in the midline brain region (Phillips et al., 2006), in the largely overlapping FESz subjects, the present longitudinal analyses demonstrated no progressive pineal gland volume changes in both FE and chronic phases of Sz. While the extent of the ongoing active pathological process in the early stages was implicated in the severity and early course of clinical symptoms in Sz (Takahashi and Suzuki, 2018), the present results did not support such a role for the pineal gland. Antipsychotic medication can significantly affect brain morphology (Moncrieff and Leo, 2010), especially regarding progressive brain changes in Sz (Takahashi et al., 2010, 2011b; van Haren et al., 2011), but we did not find any medication effect on pineal volume in this study. It was also reported that pineal melatonin rhythms and production decrease in the aging process (Wu and Swaab, 2005). However, in combination with the present cross-sectional findings, especially for reduced pineal volume in ARMS and no relation between pineal volume and illness duration in Sz, our longitudinal analyses revealed that reduced pineal volume may be a static marker from the earliest stages of Sz.

The present structural MRI study could not address the underlying mechanism for pineal volume change, but our findings in various stages of Sz support the notion of its neurodevelopmental origin (Bersani et al., 2002; Fındıklı et al., 2015) as well as neuroendocrine findings that implicate the crucial role of altered melatonin levels in the pathophysiology of Sz (Anderson and Maes, 2012; Morera-Fumero and Abreu-Gonzalez, 2013; Pacchierotti et al., 2001). In normal development, the pineal gland develops during gestation to infancy and its size remains stationary between the ages of 2 and 20 years (Cooper, 1932; Sumida et al., 1996). As demonstrated in an in vitro study using human olfactory neuronal precursors (Galván-Arrieta et al., 2017), low levels of melatonin during gestation can cause abnormalities in neuronal differentiation leading to impaired connectivity and functionality of neuronal circuitries, which were reported in schizophrenia (Canu et al., 2015; Schmitt et al., 2011). However, in human brains, the embryo and fetus pineal gland does not produce significant amounts of melatonin and brain development at this stage is largely dependent on maternal melatonin (Biran et al., 2014; Voiculescu et al., 2014). Nevertheless, it may be possible that disturbance of pineal melatonin functions in early life is associated with general vulnerability to psychopathology, because melatonin has a neuroprotective effect both in neonatal and adult brain by regulating myelination during the maturation process as well as through its anti-inflammatory and antioxidative effects (Anderson and Maes, 2012; Biran et al., 2014; Voiculescu et al., 2014).

A few limitations to the current study should be described. First, only cross-sectional data were available for the ARMS group and its sample size was relatively small, especially for those who later developed Sz ($N = 5$). In addition, the ARMS is a heterogeneous concept at risk not only for Sz (e.g., affective psychosis) (Fusar-Poli et al., 2013). Thus, pineal gland morphology prior to the onset of Sz and other psychoses, as well as possible volume changes during transition period, should be tested longitudinally in a larger, well-defined high-risk cohort. Second, we did not assess the function (e.g., melatonin levels) and abnormal calcification of the pineal gland. Previous computed tomography studies in Sz reported a higher incidence of pathologically enlarged pineal calcification (Sandyk, 1990), with the association between the calcification and clinical features [e.g., onset age (Sandyk, 1992), prefrontal atrophy and symptom severity (Sandyk and Kay, 1991)], but T1-weighted MR images used in this study were not appropriate for assessing calcification. Third, pineal gland volume in this study included the volume of the cyst within the gland, because exact cyst volume could not be reliably measured especially for small cystic changes (<2 mm). However, as pineal parenchyma volume (i.e., non-cystic volume) may better reflect melatonin secretion levels than total pineal volume (Liebrich et al., 2014; Nölte et al., 2009), future studies using higher resolution images should separately assess the volume of the pineal parenchyma and cystic volumes. Finally, while Fındıklı et al. (2015) found normal pineal volume in mood disorders (bipolar disorder and unipolar depression), the alteration of the melatonin secretary pattern [e.g., affective disorders (Pacchierotti et al., 2001), autism spectrum disorders (Rossignol and Frye, 2014)] as well as reduced pineal volume [e.g., attention deficit hyperactivity disorder (Bumb et al., 2016), primary insomnia (Bumb et al., 2014), and Alzheimer's disease (Matsuoka et al., 2018)] was found in various neuropsychiatric disorders. Thus, the disease specificity of our findings should be further examined. In addition, although we excluded the control subjects with a family history of neuropsychiatric illness from the study, possible genetic effects of various neuropsychiatric disorders on the pineal volume should be also tested in future.

In conclusion, the present MRI study demonstrated a smaller pineal volume in Sz, which already existed in first-episode patients, and this showed no active progressive changes after illness onset and did not correlate with clinical variables (e.g., illness duration, symptom severity, and medication). Further, clinical high-risk subjects for psychosis shared a pineal volume reduction with patients with Sz. Our results thus suggest the role of the pineal gland volume as a static vulnerability marker of Sz, while future studies are needed to clarify the disease specificity of our findings.

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Conflict of interest

All authors declare that they have no conflicts of interest.

Contributors

In this study, MS and TT conceived the idea and methodology of the study. TT conducted the statistical analyses and wrote the manuscript. SN, YH, DS, MN, and YN recruited subjects and were involved in clinical and diagnostic assessments. TT and MN analyzed the MRI data. KN provided technical support for MRI scanning and data processing. AF, MK, YN, and MN managed the MRI and clinical data. MS, YH, and YT contributed to the writing

and editing of the manuscript. All authors contributed to and have approved the final manuscript.

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