Potential contribution of pineal atrophy and pineal cysts toward vulnerability and clinical characteristics of psychosis

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ABSTRACT

Background: Magnetic resonance imaging (MRI) studies reported pineal gland atrophy in schizophrenia patients and individuals at a clinical high risk of developing psychosis, implicating abnormalities in melatonin secretion in the pathophysiology of psychosis. However, it currently remains unclear whether the morphology of the pineal gland contributes to symptomatology and sociocognitive functions.

Methods: This MRI study examined pineal gland volumes and the prevalence of pineal cysts as well as their relationship with clinical characteristics in 57 at risk mental state (ARMS) subjects, 63 patients with schizophrenia, and 61 healthy controls. The Social and Occupational Functioning Assessment Scale (SOFAS), the Schizophrenia Cognition Rating Scale (SCoRS), and the Brief Assessment of Cognition in Schizophrenia (BACS) were used to assess sociocognitive functions, while the Positive and Negative Syndrome Scale was employed to evaluate clinical symptoms in ARMS subjects and schizophrenia patients.

Results: Pineal gland volumes were significantly smaller in the ARMS and schizophrenia groups than in the controls, while no significant differences were observed in the prevalence of pineal cysts. Although BACS, SCoRS, and SOFAS scores were not associated with pineal morphology, patients with pineal cysts in the schizophrenia group exhibited severe positive psychotic symptoms with rather mild negative symptoms.

Conclusion: The present results indicate the potential of pineal atrophy as a vulnerability marker in various stages of psychosis and suggest that pineal cysts influence the clinical subtype of schizophrenia.

1. Introduction

The pineal gland is a neuroendocrine organ that secretes melatonin, which regulates circadian rhythms (Borjigin et al., 2012; Cajochen et al., 2003), and abnormalities in the secretion of melatonin in schizophrenia patients (reviewed by Bastos Jr. et al., 2019) support its involvement in the pathophysiology of this mental disorder. Magnetic resonance imaging (MRI) studies (Bersani et al., 2002; Fndikih et al., 2015; Takahashi et al., 2019a) showed smaller pineal volumes in schizophrenia patients regardless of the illness stage, such as clinical high-risk or at risk mental state (ARMS; Yung et al., 2005) and both first episode and chronic stage after onset (Takahashi et al., 2019a); however, conflicting findings have also been reported (Rajarethinam et al., 1995). One of the factors potentially contributing to impairments in neurodevelopment is low melatonin levels during pregnancy and/or in early life (Galván-Arrieta et al., 2017; Voiculescu et al., 2014), which have been implicated in the etiology of schizophrenia (Catts et al., 2013). Abnormalities in the function and/or structure of the pineal gland have been suggested to

Abbreviations: ARMS, At risk mental state; BACS, Brief Assessment of Cognition in Schizophrenia; JART, Japanese version of the National Adult Reading Test; PANSS, Positive and Negative Syndrome Scale; SCoRS, Schizophrenia Cognition Rating Scale; SOFAS, Social and Occupational Functioning Assessment Scale.

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reflect its role as a static model of vulnerability to the development of psychosis. Previous studies reported that melatonin levels (Bersani et al., 2003; Monteleone et al., 1997; Robinson et al., 1991) and pineal volumes (Bersani et al., 2002; Findlki et al., 2015; Takahashi et al., 2019a) in schizophrenia patients did not appear to be associated with symptom severity or antipsychotic medication. However, it currently remains unclear whether pineal abnormalities are associated with other core clinical features of schizophrenia, such as cognitive and social impairments.

Pineal cysts are commonly observed in human brains (detected in up to 40% of routine autopsies), but are generally asymptomatic and of no clinical significance (Atlas, 2002). Although the etiology of pineal cyst development has not yet been elucidated, cysts may arise from the incomplete fusion of the third ventricle diverticulum during fetal development (Taveras, 1996). Since the prevalence of midline brain abnormalities associated with early neurodevelopment, including a large cavum septi pellucidi (CSP) and the absence of the adhesio interthalamica (AI), may be elevated in patients with schizophrenia (Landin-Romero et al., 2016; Trzesniak et al., 2011a; Trzesniak et al., 2011b), pineal cysts may also be associated with its pathophysiology. We previously reported that the prevalence of pineal cysts did not significantly differ between healthy controls, ARMS subjects, and schizophrenia patients (23.1% of a total of 212 participants; Takahashi et al., 2019a); however, the relationships between pineal cysts and the clinical features of schizophrenia and associated conditions have not yet been clarified.

In the present study, we employed high-resolution MRI to assess the morphology of the pineal gland (volume and cyst prevalence) and to investigate its relationships with a broad range of clinical characteristics (e.g., symptomatology and sociocognitive functions) in ARMS subjects and schizophrenia patients. Based on our previous findings obtained from an independent cohort (Takahashi et al., 2019a), we predicted lower pineal volumes in both the ARMS and schizophrenia groups than in healthy controls and no significant group differences in the prevalence of pineal cysts. Since midline brain abnormalities during early neurodevelopment may contribute to the clinical subtypes of schizophrenia (Takahashi et al., 2017b), we specifically predicted the contribution of pineal cysts to the symptom profiles of schizophrenia.

2. Materials and methods

2.1. Study participants

Participants comprised 57 ARMS subjects, 63 schizophrenia patients, and 61 healthy controls. Sample characteristics (briefly summarized in Table 1) and inclusion/exclusion criteria were described in detail in our previous study (Takahashi et al., 2021; Takahashi et al., in press). Screening was performed for a history of severe obstetric complications, neurological illnesses, serious medical diseases (e.g., diabetes, thyroid disease, and steroid use), serious head trauma, or substance abuse. Screening for gross brain abnormalities was conducted by neuroradiologists; however, subjects with pineal cysts were not excluded. A clinical diagnosis was made by experienced psychiatrists based on the Comprehensive Assessment of At Risk Mental States (CAARMS) (Yung et al., 2005) for ARMS and the Structured Clinical Interview for DSM-IV Axis I Disorders Patient Edition (SCID-I/P) (First et al., 1997) for schizophrenia. Five ARMS subjects developed overt psychosis in the clinical follow-up at Toyama University Hospital (mean = 3.2 ± 2.9 years, median = 2.4), and were operationally diagnosed with schizophrenia. Based on illness duration, the schizophrenia group was divided into first-episode (≤1 year, 17 patients) and chronic (>3 years, 38 patients) subgroups. Eight patients with intermediate illness duration (greater than 1 year and lesser than 3 years) were excluded from the subgroup analysis (first-episode vs. chronic). Healthy controls were mainly recruited from the community and hospital staff with no personal or family history (among first-degree relatives) of psychiatric illnesses and were screened using the SCID-I Non-patient Edition (First

| Table 1 |
| Various and clinical data of ARMS subjects, schizophrenic patients, and healthy controls. |

| Group | C | ARMS | Sz |
|-------|---|------|----|
| Male/female (%) | 32/29 | 42/52 | 36/62 | Chi-squared = 2.23, p = 0.129 |
| Age (years) | 25.6 ± 18.6 ± 28.0 ± 3.2 | 40.6 ± 8.3 | 61.0 ± 5.9 | F(2, 178) = 34.93, p < 0.001; ARMS < C, Sz |
| Height (cm) | 160.0 ± 164.4 ± 163.2 ± 8.3 | 35.5/17 | 98.5 ± 5.9 | F(2, 178) = 1.68, p = 0.190 |
| Handedness (right/ left/mixed) | 30/1/2/5 | 52/2/9 | 9.7 ± 9.7 |
| JART-IQ | 110.2 ± 95.8 ± 99.5 ± 5.9 | 1459 ± 1436 ± 1419 ± 1456 |
| Duration of illness (years) | 2.9 ± 2.0 ± 2.8 ± 2.9 | 5.7 ± 2.5 | 7.4 ± 3.2 |
| Duration of antipsychotic medication (years) | – | 0.7 ± 1.2 ± 0.5 ± 1.2 | F(2, 178) = 8.78, p = 0.004; ARMS < Sz |
| Time between intake and onset (years) | – | 1.5 ± 2.6 ± 1.4 ± 2.5 | F(2, 178) = 7.45, p = 0.001; ARMS < Sz |
| BACS subdomain z-scores | – | 15.6 ± 13.9 ± 13.5 ± 3.2 | F(2, 178) = 17.32, p < 0.001; ARMS < Sz |
| Positive | – | 11.6 ± 13.9 ± 13.5 ± 3.2 | F(1, 118) = 7.45, p = 0.007; ARMS < Sz |
| Negative | – | 15.3 ± 16.3 ± 16.3 ± 6.6 | F(1, 118) = 6.3, p = 0.428 |
| General | – | 30.2 ± 31.0 ± 31.0 ± 7.9 | F(1, 118) = 0.25, p = 0.619 |
| Group-by-domain interaction, F(5, 590) = 0.629, p = 0.001 |

Values represent means ± SD unless otherwise stated.

ARMS, at risk mental state; BACS, Brief Assessment of Cognition in Schizophrenia; C, control subjects; JART, Japanese version of the National Adult Reading Test; HPD, haloperidol; PANSS, Positive and Negative Syndrome Scale; SCoRS, Schizophrenia Cognition Rating Scale; SOFAS, Social and Occupational Functioning Assessment Scale; Sz, schizophrenia.
et al., 1997). One female psychologist, who was familiar with the SCID, was included as a healthy subject, but the results of the study did not change even when we excluded this subject from the statistical analyses. The Committee on Medical Ethics of Toyama University approved the study protocol (No. I2013006). After a complete description of the study, all subjects provided their written informed consent in accordance with the principles of the Declaration of Helsinki. The parents/guardians of participants <20 years provided written consent. We recently reported pineal atrophy in various stages of psychosis using 1.5-tesla MRI data (Takahashi et al., 2019a), and none of the samples in the present study overlapped with those in the previous study.

2.2. Clinical assessment of ARMS subjects and schizophrenia patients

As previously described in detail (Takahashi et al., 2017a; Takahashi et al., 2018), clinical symptoms at the time of MRI scanning were rated by experienced psychiatrists using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). The sociocognitive functions of participants in the present study were assessed using the Brief Assessment of Cognition in Schizophrenia (BACS) (Keefe et al., 2004), Schizophrenia Cognition Rating Scale (SCoRS) (Keefe et al., 2006), and Occupational Functioning Assessment Scale (SOFAS) (Goldman et al., 1992).

2.3. Brain MRI procedures

All participants were scanned using the same 3-tesla Magnetom Verio (Siemens, Erlangen, Germany) at Toyama University Hospital; 176 contiguous 1.2-mm-thick T1-weighted slices were obtained in the sagittal plane using a 3-D MPRAGE sequence. Imaging parameters were previously described in detail (Takahashi et al., 2021). Brain images were reconstructed using the Dr. View software package (Infocom, Tokyo, Japan) into 1-mm-thick coronal images perpendicular to the anterior commissure-posterior commissure line. Voxels in entire T1-weighted images were semi-automatically segmented into brain tissue components and cerebrospinal fluid using their signal-intensity histogram distributions. SPM 12 (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) was used to assess intracranial volumes (ICV), and revealed no significant differences between the groups tested (Table 1).

2.4. Measurements of the pineal gland

As previously described in detail (Takahashi et al., 2019a; Takahashi et al., 2020), one rater (TT), who was blinded to the identities of subjects, manually traced the pineal gland on consecutive 1-mm coronal images (Fig. 1). Segmented brain tissue components (i.e., parenchymal volume) and internal pineal cysts (pineal cyst ≥2 mm or small changes in cyst diameters <2 mm; defined by Pu et al., 2007) were differentiated by the signal intensity of each image; therefore, total (cyst included) and parenchymal (non-cystic) pineal volumes were obtained. Intra- (TT) and inter-rater (TT and MN) reliabilities (intraclass correlation coefficients for pineal volume and Cronbach’s alpha for cyst type) in a subset of 10 randomly selected brains were all >0.92. These raters, who were experienced for the assessment of pineal morphology, showed high reliabilities (>0.9) also for independent MRI datasets (Takahashi et al., 2019a; Takahashi et al., in press).

2.5. Statistical analysis

Group differences in clinical and demographic data were examined...
by a one-way analysis of variance (ANOVA) or the $\chi^2$ test.

Pineal volumes (total, parenchymal) were compared between groups using an analysis of covariance (ANCOVA), with diagnosis and sex as between-subject factors and age and ICV as covariates. ANCOVA was also used to examine differences in the ARMS (with vs. without a later onset of psychosis) and schizophrenia (first-episode vs. chronic) subgroups. The prevalence of pineal cysts ($\geq 2$ mm) and small cystic changes ($< 2$ mm) were evaluated using the $\chi^2$ test.

The relationships between pineal parenchymal (non-cystic) volumes, which more accurately reflect melatonin secretion than total pineal volumes (Liebrich et al., 2014; Nolte et al., 2009), and clinical variables (onset age and illness duration for the schizophrenia group, the dose/duration of medication, PANSS positive/negative/general scores, and SOFAS, SCoRS, and BACS composite scores) were examined using Pearson’s partial correlation coefficients controlling for age and ICV. The potential effects of pineal cysts (cysts $\geq 2$ mm and small cystic changes) on these clinical variables were examined using ANOVA. Scheffe’s test was used to follow up any significant main effects or interactions for ANOVA/ANCOVA. Pineal volumes did not significantly differ between the schizophrenia group and in the schizophrenia group. Table 2

### 3.2. Pineal gland morphology (Table 2)

Total and parenchymal pineal volumes were significantly smaller in the ARMS and schizophrenia groups than in the control group (post-hoc tests, all $p < 0.01$; Fig. 2). Pineal volumes did not significantly differ in the ARMS (with vs. without a later onset of psychosis) and schizophrenia (first-episode vs. chronic) subgroups. There was no significant sex effect on pineal volumes.

No significant differences were observed in the prevalence of pineal cysts ($\geq 2$ mm and small cystic changes) on these clinical variables examined using ANOVA. Scheffe’s test was used to follow up any significant main effects or interactions for ANOVA/ANCOVA. Pineal volumes did not significantly differ in the ARMS and schizophrenia groups than in the control group (post-hoc tests, all $p < 0.01$; Fig. 2). Pineal volumes did not significantly differ in the ARMS (with vs. without a later onset of psychosis) and schizophrenia (first-episode vs. chronic) subgroups.

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### 3.3. Relationship between the morphology of the pineal gland and clinical variables

No correlations were observed between pineal parenchymal volumes and demographic (age and IQ) or clinical (onset age and illness duration for schizophrenia, medication, PANSS subscores, SOFAS, SCoRS, and BACS composite scores) variables in any group after Bonferroni’s correction for multiple comparisons.

Schizophrenia patients with any cystic changes ($\geq 2$ mm or small cystic changes) ($N = 33$) had more severe positive and milder negative symptoms than those without cystic changes ($N = 30$) (Table 3, Fig. 3). Furthermore, patients with cysts $\geq 2$ mm ($N = 16$) were characterized by a lower PANSS negative score than those without any cystic changes ($N = 30$) [$F(2, 60) = 3.60, p = 0.033$] or those without 2-mm cysts ($N = 47$) [$F(1, 61) = 6.09, p = 0.016$]. Other demographic and clinical variables did not significantly differ between schizophrenia patients with and without cysts (Table 3). We found no significant effect of cysts ($\geq 2$ mm and/or small cystic changes) on demographic or clinical variables in the ARMS group.

### 4. Discussion

This MRI study examined the relationships between the morphology of the pineal gland (total and parenchymal volumes, prevalence of cysts and small cystic changes) and a wide range of clinical characteristics in the ARMS and schizophrenia groups. The results obtained revealed reductions in pineal volumes in the ARMS and schizophrenia groups irrespective of ARMS outcomes (a later onset of psychosis), the illness stages of schizophrenia, and the medication status. Although no correlations were observed between pineal volumes and clinical symptoms or sociocognitive functions, pineal cysts may contribute to the clinical subtypes of schizophrenia based on symptom profiles.

The present results on pineal volumes are consistent with previous MRI findings showing the presence of pineal atrophy before the onset of psychosis as a vulnerability factor and no changes in pineal volumes during the course of schizophrenia (Takahashi et al., 2019a), with symptom severity and antipsychotic medication having no significant effect on pineal volumes (Bersani et al., 2002; Findlaki et al., 2015;
and Occupational Functioning Assessment Scale.

Values represent means with and without cysts.

Table 3

Demographic clinical data and brain measurements in schizophrenic patients with and without cysts.

| Cyst | No cyst | Group difference |
|------|--------|------------------|
| (N = 33) | (N = 30) |                  |
| Male/female (% male) | 16/17 | 13/17 | Chi-squared = 0.17, p = 0.682 |
| Age (48.9%) | 29.1 ± 9.6 | 26.8 ± 7.9 | F(1, 61) = 0.97, p = 0.329 |
| Height (cm) | 164.2 ± 8.9 | 162.0 ± 7.9 | F(1, 61) = 1.08, p = 0.304 |
| Handedness (right/left/mixed) | 27/1/5 | 25/1/4 | Fisher’s exact test, p = 1.00 |
| JART-IQ | 100.7 ± 9.0 | 98.3 ± 10.4 | F(1, 61) = 0.94, p = 0.337 |
| First episode/chronic | 9/20 | 8/14 | Chi-squared = 0.00, p = 0.983 |
| Age at onset (years) | 22.8 ± 7.0 | 21.9 ± 7.0 | F(1, 61) = 0.19, p = 0.664 |
| Duration of illness (years) | 6.2 ± 7.0 | 4.8 ± 4.6 | F(1, 61) = 0.00, p = 0.966 |
| Dose of antipsychotics (HPD equiv., mg/day) | 9.6 ± 9.2 | 8.6 ± 7.3 | F(1, 61) = 0.04, p = 0.846 |
| Type of antipsychotics (typical/atypical/mixed) | 1/22/4 | 0/23/1 | Fisher’s exact test, p = 0.354 |
| Duration of antipsychotic medication (years) | 5.0 ± 7.1 | 3.6 ± 4.4 | F(1, 61) = 0.03, p = 0.857 |
| PANSS | | | |
| Positive | 15.2 ± 5.6 | 12.4 ± 5.3 | F(1, 61) = 4.17, p = 0.045; Cyst > Non-cyst |
| Negative | 14.7 ± 5.4 | 18.0 ± 6.4 | F(1, 61) = 4.97, p = 0.029; Non-cyst > Cyst |
| General | 31.1 ± 9.9 | 30.8 ± 9.7 | F(1, 61) = 0.02, p = 0.897 |
| BACS subdomain z-scores | | | |
| Verbal memory | -1.2 ± 1.6 | -1.5 ± 1.3 | Group-by-domain interaction, F(5, 305) = 0.65, p = 0.663 |
| Working memory | -1.2 ± 1.4 | -0.8 ± 1.2 | |
| Motor function | -1.9 ± 1.5 | -1.9 ± 1.5 | |
| Verbal fluency | -0.7 ± 1.1 | -0.9 ± 1.1 | |
| Attention and processing speed | -1.4 ± 1.5 | -1.4 ± 1.5 | |
| Executive function | -0.8 ± 1.5 | -0.8 ± 1.5 | |
| BACS composite z-score | -1.2 ± 1.0 | -1.2 ± 0.9 | F(1, 60) = 0.00, p = 0.983 |
| SOFAS | 48.7 ± 14.6 | 47.5 ± 13.2 | F(1, 60) = 0.06, p = 0.804 |
| SCQs global rating score | 5.3 ± 2.6 | 5.2 ± 2.4 | F(1, 60) = 0.00, p = 0.960 |
| Intracranial volume | 1430 ± 173 | 1453 ± 163 | F(1, 60) = 0.27, p = 0.609 |
| Total pineal volume (mm$^3$) | 134.2 ± 44.5 | 75.2 ± 24.9 | Cyst > Non-cyst |
| Pinenal parenchymal volume (mm$^3$) | 128.0 ± 43.5 | 75.2 ± 24.9 | F(1, 59) = 0.37, p < 0.001; Cyst > Non-cyst |

Values represent means ± SD unless otherwise stated.

BACS, Brief Assessment of Cognition in Schizophrenia; JART, Japanese version of National Adult Reading Test; HPD, haloperidol; PANSS, Positive and Negative Syndrome Scale; SCoRS, Schizophrenia Cognition Rating Scale; SOFAS, Social and Occupational Functioning Assessment Scale.

* Age was used as a covariate.

** Age and intracranial volume were used as covariates.

Takahashi et al., 2019a). The findings of a previous MRI study (Rajarathinam et al., 1995) demonstrated that pineal volumes were normal ranges in schizophrenia patients; however, these findings may have been partly limited by the lack of information on pineal cysts, as discussed elsewhere (Rastos Jr. et al., 2019). These structural MRI studies could not address the functional significance (e.g., hormonal dysregulation) underlying changes in pineal volumes in schizophrenia patients. Nevertheless, the findings obtained support the risk of vulnerability to psychopathology being increased by abnormalities in melatonin secretion from the pineal gland in early life because, in addition to its antioxidant and anti-inflammatory effects, melatonin has been suggested to exert neuroprotective effects in the brains of neonates (Biran et al., 2014; Voiculescu et al., 2014) and adults (Anderson and Maes, 2012) through its regulation of myelination during maturation.

In the present study, the prevalence of pineal cysts in the control group (18.0% for cysts ≥2 mm, 29.5% for small cystic changes <2 mm) was consistent with that in high-resolution MRI studies that differentiated a cyst ≥2 mm (16.1 to 29.1%) and small cystic changes (8.9 to 21.2%) (Pu et al., 2007; Sun et al., 2009; Takahashi et al., 2019a; Takahashi et al., 2020). The prevalence of pineal cysts or small cystic changes did not significantly differ between the groups examined herein; however, schizophrenia patients with pineal cysts, particularly large cysts (≥2 mm), exhibited severe positive and mild negative symptoms. Pineal cysts are regarded as normal anatomical variants, except for extremely large cysts (≥15 mm in diameter) (Atlas, 2002; Pu et al., 2007), because they rarely change in size for long periods (Al-Holou et al., 2011; Barbioriak et al., 2001) and may not contribute to the secretion of melatonin (Liebrich et al., 2014; Nölle et al., 2009). However, these cysts (i.e., incomplete obliteration of the cavum pineale) may reflect early neurodevelopmental anomalies in the epithalamus because they may be a consequence of incomplete fusion of the third ventricle diverticulum during early gestation (Taveras, 1996). Dysfunction of the epithalamus (e.g., the habenula) may lead to the disconnection of the limbic circuitry (Grod et al., 2020; Zahn and Root, 2017), which has been implicated in a range of clinical symptoms in schizophrenia patients (Canu et al., 2014; Vitolo et al., 2017). As demonstrated for other midline brain structures (CSP and AI) (Landin-Romero et al., 2016; Trzesniak et al., 2011a; Trzesniak et al., 2011b), pineal cysts may be an early neurodevelopmental marker associated with the clinical subtype of schizophrenia. Since the prevalence of cysts ≥2 mm was slightly higher in the schizophrenia group (25.4%) than in the control group (18.0%) in the present study, it needs to be examined in more detail in a larger sample size, ideally in combination with a functional/connectivity whole brain analysis.

Pineal morphology (volume and cyst prevalence) did not correlate with sociocognitive functions in the schizophrenia and ARMS groups in the present study. Based on the role of the pineal morphology as an early neurodevelopmental marker related to general vulnerability to psychopathology (discussed above), this result appears to be inconsistent with our previous findings that brain neurodevelopmental markers (e.g., sulcogyrall pattern) are associated with cognitive impairments in schizophrenia and clinical high-risk groups (Takahashi et al., 2019b; Takahashi et al., 2021); these findings may support the notion that the presence of cognitive impairments, particularly in verbal fluency (Fusar-Poli et al., 2012) and social function (Lee et al., 2015), prior to the onset may be a trait vulnerability marker of psychosis. Furthermore, the relationship between reduced serum melatonin concentrations (Salhab et al., 2019) or disturbed circadian rhythms (Bromundt et al., 2011) and cognitive impairments in schizophrenia implicates core role of pineal abnormalities. However, Carpenter et al. (2017) demonstrated that SOFAS score was associated with melatonin level but not with pineal volume in patients with affective disorders, suggesting a discrepancy between pineal morphology and function. Since the present study was partly limited by the lack of endocrine data (particularly melatonin secretion patterns) and a clinical evaluation of sleep patterns, additional assessments of these variables with pineal measurements are needed to clarify the role of the pineal gland in the pathophysiology of schizophrenia.

Some limitations in the present study need to be addressed. Technical difficulties were associated with pineal measurements using MRI. Computed tomography studies reported that the incidence of abnormally enlarged pineal calcifications was higher in schizophrenia...
patients (Sandyk, 1990) and was associated with clinical characteristics, such as age of onset (Sandyk, 1992), symptomatology, and cortical atrophy (Sandyk and Kay, 1991). However, calcifications were not visualized using common MRI sequences. Another limitation is the small ARMS sample size, particularly those with a later onset of psychosis (N = 5); therefore, the relationship between the morphology of the pineal gland and ARMS outcomes needs to be investigated in a larger cohort. Moreover, alterations have been reported in melatonin secretory patterns in various neuropsychiatric disorders, including affective disorders (Pacchierotti et al., 2001), autism spectrum disorders (Rossignol and Frye, 2014), and Alzheimer’s disease (Wu and Swaab, 2005). In addition, patients with major depression, particularly the non-melancholic subtype (Takahashi et al., 2020), may have smaller pineal volumes and a higher prevalence of pineal cysts than controls (Zhao et al., 2019). Therefore, further studies on the disease specificity of pineal abnormalities are warranted.

5. Conclusions

The present MRI study suggests the role of pineal atrophy as a stable vulnerability marker of psychosis, implicating that melatonin dysregulation during early life may contribute to early neurodevelopmental pathology of psychosis. Further, our results of significant relationship between pineal cysts (particularly cysts ≥2 mm) and symptom profiles of schizophrenia support that fetal development of the epithalamus may influence the clinical subtypes of schizophrenia. However, further studies in combination with hormonal investigation of melatonin levels and functional/connectivity whole brain analysis would be required to clarify the role of pineal morphology in the pathophysiology of psychosis.

CRediT authorship contribution statement

Tsutomu Takahashi: Conceptualization, Methodology, Software, Formal analysis, Investigation, Writing – original draft, Visualization, Funding acquisition. Daiki Sasabayashi: Validation, Resources, Funding acquisition. Yoichiro Takayanagi: Writing – review & editing. Yuko Higuchi: Resources, Data curation. Yuko Mizukami: Resources, Data curation. Yukiko Akasaki: Resources, Data curation. Shimako Nishiyama: Resources, Data curation. Atsushi Furuichi: Resources, Data curation. Tien Viet Pham: Resources. Haruko Kobayashi: Resources. Kyo Noguchi: Methodology, Software, Resources. Michio Suzuki: Conceptualization, Writing - review & editing, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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T. Takahashi et al.

NeuroImage: Clinical 32 (2021) 102805

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