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Letter to the Editor

Reduced pineal gland volume in schizotypal disorder

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Dear Editors,

Neuroimaging has generally demonstrated a smaller pineal volume, which probably relates to abnormal melatonin secretion and consequent circadian dysregulation, in schizophrenia regardless of the stage, medications, and symptoms (Bastos Jr. et al., 2019; Takahashi et al., 2019). Accordingly, structural and/or functional pineal gland abnormalities may be a trait marker of schizophrenia. However, it is unknown whether pineal abnormalities also occur in schizotypal (personality) disorder, which is genetically related to schizophrenia (Siever and Davis, 2004) and characterized by milder schizophrenic features without overt/sustained psychosis (World Health Organization, 1993), as a possible indicator of common vulnerability with schizophrenia. In this study, magnetic resonance imaging (MRI) was performed to measure the pineal gland volume in patients with schizotypal disorder and the results were compared with data obtained in patients with schizophrenia and healthy controls.

The subjects were 47 patients with schizotypal disorder, 111 patients with schizophrenia, and 88 control subjects (Table 1). This was the first MRI investigation of the pineal gland in our schizotypal disorder patients, while the pineal volume has been reported previously for most subjects in the schizophrenia group (104/111) and the healthy control group (84/88) (Takahashi et al., 2019). Patients with schizotypal disorder fulfilling the ICD-10 research criteria (World Health Organization, 1993) were recruited at the outpatient clinic of the Department of Neuropsychiatry of Toyama University Hospital. Their characteristics have been detailed previously (Suzuki et al., 2005). All patients met the DSM Axis II diagnosis of schizotypal personality disorder, and 13 subjects had a history of transient quasi-psychotic episodes fulfilling the DSM Axis I diagnosis of brief psychotic disorder (American Psychiatric Association, 1994). The remaining 34 patients had no Axis I diagnosis. None of them had developed schizophrenia during follow-up for at least 2 years. Recruitment of the schizophrenia patients and healthy controls, as well as inclusion/exclusion criteria for the study participants, have been reported elsewhere (Takahashi et al., in press). Symptoms of the patients were assessed at the time of scanning by using the Scale for the Assessment of Negative Symptoms and the Scale for the Assessment of Positive Symptoms (SANS/SAPS; Andreasen, 1984), but their sleep disturbance was not systematically evaluated. This study was approved by the Toyama University Committee on Medical Ethics. All participants provided written informed consent.

The study participants underwent brain MRI with a 1.5 T Magnetom Vision (Siemens Medical System, Inc., Erlangen, Germany) at Toyama University Hospital. A three-dimensional gradient-echo fast low-angle shots (FLASH) sequence was employed for T1-weighted imaging to obtain 160–180 contiguous sagittal slices with a thickness of 1.0 mm. Details of the imaging parameters were reported elsewhere (Takahashi et al., 2019). Dr. View software (Infocom, Tokyo, Japan) was employed to manually trace the pineal gland on reconstructed coronal images with a slice thickness of 1 mm and no slice gap (Takahashi et al., 2019). Areas of cystic change within the pineal gland (definite cysts ≥2 mm in diameter or small cysts <2 mm in diameter) were included in the pineal volume (Supplementary Fig. 1). The intraclass correlation coefficients for intra-rater (TT) and inter-rater (TT and MN) variability ($N = 10$) were all >0.92.

Analysis of covariance (ANCOVA) was performed on the pineal volume data with age and ICV as covariates, and with diagnosis and gender as between-subject factors. A post hoc Scheffé's test was done to assess any significant main effects or interactions. The χ^2 test was used to compare the prevalence of pineal cysts among the groups. Relations between pineal volume (log) and clinical variables were examined by Pearson's partial correlation coefficient analysis with adjustment for age and ICV. In all analyses, significance was accepted at $p < 0.05$.

ANCOVA showed a significant main effect of diagnosis on the pineal volume, since patients with schizophrenia (post-hoc test, $p = 0.001$)

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Table 1
Sample characteristics and brain measures of the study participants.

	C	SzTypal	Sz	Group comparisons
Male/female	49/39	29/18	59/52	Chi-square = 0.98, $p = 0.613$
Age (years)	24.1 ± 6.0	25.0 ± 5.4	25.8 ± 5.4	F (2, 243) = 2.38, $p = 0.095$
Height (cm)	166.3 ± 7.8	165.9 ± 8.7	164.5 ± 8.0	F (2, 243) = 1.34, $p = 0.264$
Education (years)	15.7 ± 3.0	13.1 ± 2.0	13.5 ± 2.0	F (2, 243) = 26.23, $p < 0.001$; Sz, SzTypal < C
Onset age (years)	–	–	22.2 ± 4.7	–
Illness duration (years)	–	–	3.6 ± 4.1	–
Antipsychotic medication				
Dose (haloperidol equivalent, mg/day)	–	4.8 ± 5.7	10.1 ± 8.8	F (1, 156) = 14.64, $p < 0.001$; SzTypal < Sz
Duration (years)	–	1.5 ± 3.0	2.7 ± 3.6	F (1, 156) = 3.70, $p = 0.056$
Type (atypical/mixed/typical)	–	26/0/14	65/4/40	Fisher's exact test, $p = 0.636$
Hypnotic medication				
Use (yes/no)	–	24/23	50/61	Chi-square = 0.48, $p = 0.488$
Dose (diazepam equivalent, mg/day)	–	9.0 ± 5.3 ($N = 24$)	10.3 ± 6.7 ($N = 50$)	F (1, 156) = 0.01, $p = 0.937$
Total SAPS scores[a]	–	16.0 ± 9.2	27.2 ± 20.9	F (1, 147) = 11.86, $p < 0.001$; SzTypal < Sz
Total SANS scores[a]	–	41.9 ± 21.7	49.8 ± 22.8	F (1, 147) = 3.93, $p = 0.049$; SzTypal < Sz
Pineal gland volume (mm^3)[b]	130.1 ± 59.8	102.0 ± 52.2	104.2 ± 47.3	F (2, 238) = 9.06, $p < 0.001$; Sz, SzTypal < C
Cyst (≥ 2 mm) [N(%)]	26 (29.5%)	9 (19.1%)	24 (21.6%)	Chi-square = 2.44, $p = 0.296$
Small cystic change (<2 mm) [N(%)]	13 (14.8%)	11 (23.4%)	25 (22.5%)	Chi-square = 2.29, $p = 0.318$
Intracranial volume (cm^3)	1500 ± 148	1524 ± 148	1501 ± 158	F (2, 242) = 0.47, $p = 0.629$

Values are means ± SDs unless otherwise stated.
C, controls; SANS, scale for the assessment of negative symptoms; SAPS, scale for the assessment of positive symptoms; Sz, schizophrenia; SzTypal, schizotypal disorder.
[a] Data are not available for two SzTypal and seven Sz subjects.
[b] Log-transformed for group comparison due to its skewed distribution ($p < 0.01$, Shapiro-Wilk test).

and schizotypal disorder (post-hoc test, $p = 0.002$) had significantly smaller pineal volumes than the controls (Table 1, Supplementary Fig. 2). No gender difference of pineal volume was noted. Both pineal cysts and small cystic changes did not differ in prevalence among the groups (Table 1). Pineal volume was not correlated with clinical variables, including the age of onset and duration (schizophrenia) or the dose/duration of medication and total SAPS/SANS scores (schizophrenia and schizotypal disorder) after Bonferroni's correction. These clinical variables did not differ between the subjects with and without cystic changes of the pineal gland.

The present study demonstrated similar reduction of pineal volume in a relatively large group of patients with schizotypal disorder and schizophrenia. We found no significant relation between morphologic features of the pineal gland (such as its volume and cystic change) and clinical variables in either patient group. While we were unable to directly assess the mechanism underlying changes of pineal volume, low melatonin levels in utero and/or during early life may influence neurodevelopment by inhibiting neuronal differentiation and axogenesis (Galván-Arrieta et al., 2017). It was also reported that the pineal volume normally increases during infancy, and then remains stable (Sumida et al., 1996). Taken together with our previous finding of a stable pineal volume in various stages of schizophrenia (Takahashi et al., 2019), it is possible that the pineal volume indicates a common vulnerability to neurodevelopmental pathology in schizophrenia spectrum disorders (Takahashi and Suzuki, 2018). While little is known about the pattern of melatonin secretion in schizotypal disorder, our findings are in line with reports of altered sleep architecture in individuals with schizotypal traits (Kuula et al., 2018), as well as a case report of patient with sleep-wake schedule disorder whose schizotypal symptoms improved after oral melatonin treatment (Dagan and Ayalon, 2005). However, further assessment of both pineal volume and melatonin levels will be needed to clarify the position of the pineal gland in schizophrenia spectrum pathophysiology. Because a substantial number of patients took hypnotics at the time of scanning (Table 1), the reduced pineal size might be a general marker of sleep disturbance (i.e., not specific to schizophrenia spectrum). However, the pineal volume did not differ between the patients with [108.3 ± 43.7 mm^3($N = 74$)] and without [99.4 ± 52.5 mm^3($N = 84$)] hypnotic use (data not shown). It should be also noted that the cyst volume within the pineal gland could not be reliably measured in our study or other MRI studies (e.g., Carpenter et al., 2017), especially for small cystic changes. Thus, further investigation using higher resolution imaging will be needed to separately assess the volume of the pineal parenchyma, which more closely reflects melatonin secretion (Liebrich et al., 2014), and the pineal cyst volume.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2019.05.004.

Contributors

MS and TT conceived the idea and methodology of the study. TT conducted the statistical analyses and wrote the manuscript. 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 and data processing. AF, MK, YN, and MN managed the MRI and clinical data. MS and YT contributed to writing and editing of the manuscript. All authors contributed to and approved the final manuscript.

Conflict of interest

All authors declare that they have no conflicts of interest.

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