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ORIGINAL PAPER

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Lack of normal gender differences of the perigenual cingulate gyrus in schizophrenia spectrum disorders

A magnetic resonance imaging study

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Abstract We have previously reported a lack of normal gender differences of the perigenual cingulate gyrus in patients with schizophrenia. The purpose of this study was to examine the perigenual cingulate gyrus morphology in patients with schizotypal disorder. We investigated volume of the gray and white matter of the perigenual cingulate gyrus in 26 patients with schizotypal disorder (14 males, 12 females) in comparison with 61 age- and gender-matched healthy controls (30 males, 31 females) and 58 schizophrenia patients (31 males, 27 females) using magnetic resonance imaging. The volumetric measures of the perigenual cingulate gyrus were compared among the three groups that were entered into the same multiple analysis of variance model. The gray and white matter volume of the perigenual cingulate gyrus in the schizotypal patients did not differ significantly from the values in the healthy controls or the schizophrenia patients. Similar to schizophrenia, however, the schizotypal patients showed a lack of normal gender differences of the perigenual cingulate gray matter seen in the healthy controls (females > males). These results suggest that both schizotypal and schizophrenia patients may share the same disruption of the normal pattern of gender differences of the perigenual cingulate gyrus.

Key words perigenual cingulate gyrus · magnetic resonance imaging · schizotypal disorder · schizophrenia · gender differences

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Introduction

The rostral part of the anterior cingulate gyrus (i. e., perigenual cingulate gyrus) has been termed the affective subdivision of the anterior cingulate gyrus (Devinsky et al. 1995; Whalen et al. 1998). Both brain functional (Haznedar et al. 1997a; Yamasue et al. 2002; Laurens et al. 2003) and structural (Job et al. 2002; Suzuki et al. 2002; Takahashi et al. 2003) imaging studies have suggested the perigenual cingulate gyrus abnormalities to be involved in the pathophysiology of schizophrenia. In a previous magnetic resonance imaging (MRI) study, we reported that gender differences in the perigenual cingulate morphology among normal subjects (larger in females than in males) are reduced in patients with schizophrenia (Takahashi et al. 2003). It was also indicated that this reduction of the normal gender differences is attributable mainly to a significant volume reduction of the perigenual cingulate gyrus in the female patients. As demonstrated by Goldstein et al. (2002), disruption of the normal pattern of gender differences might be a common feature of the brain abnormalities in schizophrenia. To our knowledge, however, no brain morphological studies have examined changes in volume or gender differences of the perigenual cingulate gyrus in subjects with schizotypal features.

Schizotypal disorder of the ICD-10 is "a disorder characterized by eccentric behavior and anomalies of thinking and affect which resemble those seen in schizophrenia, though no definite and characteristic schizophrenic anomalies have occurred at any stage" (ICD-10; World Health Organization, 1992). This category is thought to include prodromal phase of schizophrenia as well as schizotypal personality disorder (SPD) of the DSM-IV (American Psychiatric Association 1994). Such subjects with schizotypal features share genetic, biological, and psychological commonalities with schizophrenia and are thought to be part of the schizophrenia spectrum (Siever et al. 1993).

In contrast to the large number of morphological

imaging studies in schizophrenia (Pearlson and Marsh 1999; Shenton et al. 2001), there is a relatively small but growing body of literature that examined brain morphology in schizotypal personality disorder or schizotypal disorder. Schizotypal subjects have been reported to show brain structural abnormalities similar to those seen in schizophrenia, although generally to a lesser degree and sparing some brain regions (Dickey et al. 2002a; Siever et al. 2002). The abnormalities include increased lateral ventricular size (Siever et al. 1995; Buchsbaum et al. 1997; Silverman et al. 1998), larger cerebrospinal fluid volume (Dickey et al. 2000), volume reduction in temporal lobe structures (Dickey et al. 1999, 2002b; Seidman et al. 1999; Downhill et al. 2001), volume reduction in the thalamus (Hazlett et al. 1999; Seidman et al. 1999; Byne et al. 2001) and basal ganglia (Shihabuddin et al. 2001; Levitt et al. 2002), shape and size differences in the corpus callosum (Downhill et al. 2000), and asymmetry anomaly in the parahippocampal gyrus (Dickey et al. 1999). In addition, we previously examined the volume of the caudal anterior cingulate gyrus in the schizotypal patients overlapping with subjects in the present study and found a lack of normal structural asymmetry of this region in schizotypal patients (Takahashi et al. 2002b). In that study, we suggested that both schizotypal and schizophrenia patients share, at least in part, the same cerebral asymmetry abnormalities. The shared brain abnormalities between schizotypal and schizophrenia patients might represent a common denominator in schizophrenia spectrum disorders, whereas the differences might account for the sparing of schizotypal patients from the development of overt psychotic symptoms. Therefore, assessing schizotypal patients on brain regions that have been identified previously as impaired in schizophrenia patients is one possible strategy for advancing our understanding of pathogenesis of schizophrenia.

Based on the previous structural imaging studies, it was hypothesized that patients with schizotypal disorder would have structural abnormalities that are qualitatively similar to those seen in overt schizophrenia such as volume reduction and/or lack of normal gender differences of the perigenual cingulate gyrus. In this study, we used three-dimensional (3-D) MRI to investigate the volume of the perigenual cingulate gray and white matter in patients with schizotypal disorder and age- and gender-matched healthy control subjects to test the hypothesis. Their perigenual cingulate gyrus volume was also compared with that of male and female patients with schizophrenia previously evaluated by us in an identical protocol (Takahashi et al. 2003).

Methods

Subjects

Twenty-six patients with schizotypal disorder (14 males and 12 females; mean age = 24.8 years, SD = 5.1, range = 18–37) who met the ICD-10 diagnostic criteria for research (World Health Organization 1993) were included in the present study. The patients were recruited from among the subjects who visited the clinics of the Department of Neuropsychiatry, Toyama Medical and Pharmaceutical University Hospital manifesting schizotypal features with distress or associated problems in their lives and needed to receive consistent clinical follow-up to prevent serious psychotic problems. Candidates who had a previous history of overt psychotic episode or met the ICD-10 criteria for schizophrenia during the follow-up period were excluded. None of the 26 patients has evolved into overt schizophrenia to date (mean follow-up period = 2.7 years, SD = 1.4). All available clinical information and data obtained from a detailed review of the clinical records and structured interviews by the Comprehensive Assessment of Symptoms and History (CASH) including the chapter of premorbid or intermorbid personality (Andreasen et al. 1992) were stored in the database of the study. Subjects were diagnosed by a consensus of at least two experienced psychiatrists based on these data. At the time of MRI scanning 7 of 26 patients with schizotypal disorder did not fulfill the diagnostic criterion that the typical feature is present for 2 years, but during the follow-up period all patients have fulfilled all of the criteria for schizotypal disorder. Twenty-one patients were outpatients, and other five patients underwent closer clinical and medical examinations including MRI during short-term admission. Twenty-four of the 26 patients were treated with low dose of antipsychotics; 10 patients were treated with typical neuroleptics and 14 patients were receiving atypical neuroleptics. The remaining two patients were neuroleptic naïve. The different typical and atypical neuroleptic dosages were converted into haloperidol equivalents using the guideline by Toru (2001). At the time of MRI study, their mean scores on the Scale for the Assessment of Negative Symptoms (SANS; Andreasen 1984a) and the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen 1984b) were 43.8 (SD = 25.0, range 5–84) and 14.7 (SD = 10.1, range 0–31), respectively.

The control subjects consisted of a total of 61 healthy volunteers (30 males and 31 females) recruited from the community, hospital staff, and medical or pharmaceutical students. The control subjects participating in this study included 39 subjects from a previous study (Takahashi et al. 2003) and an additional 22 subjects (10 males, 12 females). Their mean age was 24.5 ± 5.5 (SD) years (range, 18–38). None of the control subjects was receiving pharmacological treatment for any medical disorder. Subjects were excluded if they had any personal or family history of psychiatric illness. All control subjects were interviewed and administered the Minnesota Multiphasic Personality Inventory (MMPI) by one experienced clinical psychologist in order to obtain rather homogenous control subjects without eccentric profiles in MMPI. Approximately 17 % of the candidates for normal control subjects were excluded for having an abnormal profile with the T-score exceeding 70. The schizophrenic comparison group comprised 58 patients with schizophrenia (31 males and 27 females; mean age = 25.8, SD = 4.8, range = 18–36); this group overlapped 39 schizophrenia patients with our previous study investigating the perigenual cingulate gyrus morphology in schizophrenia patients (Takahashi et al. 2003). All patients fulfilled ICD-10 diagnostic criteria for research (World Health Organization 1993). All but one of the schizophrenia patients were on neuroleptic medication. At the time of MRI study, their mean scores on the SANS and the SAPS were 47.1 (SD = 23.6, range 8–99) and 25.1 (SD = 21.1, range 0–91.5), respectively.

All subjects were physically healthy at the time of the study, and none had a lifetime history of serious head trauma, neurological illness, serious medical or surgical illness, or substance abuse disorder. The subjects were right-handed except one female patient with schizotypal disorder (unknown handedness). The subject overlap with our previous publication included 47/61 controls, 21/26 schizotypal patients, and 39/58 schizophrenia patients, where we reported an asymmetry anomaly of the caudal anterior cingulate gyrus in both schizotypal and schizophrenia patients (Takahashi et al. 2002b).

Demographic and clinical characteristics of the control subjects, patients with schizotypal disorder, and the patients with schizophrenia are summarized in Table 1. The three groups were matched in age, gender, height, and parental education. However, there were significant differences in education across the three groups (control subjects, 16.0 ± 2.5 years; patients with schizophrenia, 13.5 ± 1.9 years; patients with schizotypal disorder, 13.1 ± 2.0 years; ANOVA, F = 24.50,

Table 1 Clinical and demographic characteristics of normal control subjects, patients with schizotypal disorder, and patients with schizophrenia

Variable	Control Subjects		Schizotypal Patients		Schizophrenia Patients	
	Male (N = 30)	Female (N = 31)	Male (N = 14)	Female (N = 12)	Male (N = 31)	Female (N = 27)
Age (years)	24.9±5.1	24.2±5.9	23.6±5.4	26.3±4.6	25.5±4.9	26.2±4.8
Height (cm)	172.6±4.1[a]	159.6±4.3	170.0±7.3[a]	155.7±4.5	170.5±5.0[a]	157.8±4.2
Education (years)	17.1±2.7[b]	14.8±1.7	12.9±2.0	13.4±2.0	13.5±1.9	13.5±1.8
Parental education (years)	13.0±2.5	12.5±2.4	12.2±1.8	12.0±2.4	12.2±1.9	11.9±2.4
Age at onset (years)	–	–	–	–	22.0±4.5	22.3±4.1
Duration of illness (years)	–	–	–	–	3.6±4.0	4.3±4.3
Duration of medication (years)	–	–	1.6±2.1	1.0±1.5	2.4±2.9[c]	3.2±3.7[c]
Drug (mg/day, haloperidol equiv.)	–	–	5.2±5.4	2.4±1.7	11.9±8.6[d]	10.8±10.8[d]
Total SAPS score	–	–	13.7±10.1	16.0±10.6 (N=11)	23.1±21.4[e]	27.5±20.8[e]
Total SANS score	–	–	42.0±26.2	46.0±24.5 (N=11)	49.8±22.8	43.9±24.5

Values represent means±SDs. *SANS*, Scale for the Assessment of Negative Symptoms; *SAPS*, Scale for the Assessment of Positive Symptoms.
[a]$p < 0.01$: compared to the females; [b]$p < 0.01$: compared to the female controls, the male and female schizotypal patients, and the male and female schizophrenia patients; [c]$p = 0.03$: compared to the schizotypal patients; [d]$p < 0.01$: compared to the schizotypal patients; [e]$p = 0.02$: compared to the schizotypal patients.
ANOVA followed by Scheffé's test was used

df = 2, 142, $p < 0.001$). The post hoc Scheffé's test showed the control subjects to have attained a higher level of education than the patients with either disorder ($p < 0.001$). Total SAPS score of the schizophrenia patients was significantly higher than that of the schizotypal patients (ANOVA, F = 5.53, df = 1, 81, $p = 0.021$) although there were no significant differences between the patients with schizophrenia and schizotypal disorder in the total score for SANS. There were significant differences in medication dosage (ANOVA, F = 14.33, df = 1.82, $p < 0.001$) and duration of neuroleptic medication (ANOVA, F = 4.48, df = 1, 81, $p = 0.037$). The patients with schizotypal disorder received significantly smaller amounts of neuroleptic than the patients with schizophrenia. This study was approved by the Committee on Medical Ethics of Toyama Medical and Pharmaceutical University. All subjects participated in the study after providing written informed consent.

Magnetic resonance imaging procedures

Magnetic resonance images were obtained utilizing 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. Imaging parameters were: 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 x 1.0 mm^3. Magnetic field inhomogeneities in our scanner were monitored with weekly phantom scanning and daily basic quality control, and had been stable over the MR acquisition time for this study.

The images were transferred to a Unix workstation (Silicon Graphics, Inc., Mountain View, CA, USA). The data were coded randomly and analyzed blind to subjects' gender and diagnosis using the software package Dr. View 5.2 (Asahi Kasei Joho System Co., Ltd., Tokyo, Japan). Details of the data analyses have been described previously (Takahashi et al. 2002a, 2003). Briefly, brain images were realigned in three dimensions to standardize the differences in head tilt during image acquisition. Standardized scans were then reconstructed into entire contiguous axial images, with a 1-mm thickness, parallel to the anterior commissure-posterior commissure (AC-PC) line on the workstation. Prior to volumetric analysis, masks were semi-automatically created to demarcate the outer extent of the intracranial contents, with the skull, scalp, and neck tissue removed. Minimal manual editing of the masks was required. Then, according to the Alpert algorithm (Alpert et al. 1996), the signal-intensity histogram distributions from the T1-weighted images across the whole brain for each subject were used to segment the voxels semi-automatically into gray matter, white matter, and cerebrospinal fluid (CSF). Although the images were not corrected for the magnetic field inhomogeneities, no visible effects on quality of segmentation were observed in any of the cases.

Intracranial volume (ICV) measurements

Before creating the mask images, the 1 mm-thick coronal slices which had been corrected for head tilt were reformatted into consecutive 5 mm-thick sagittal slices with each voxel as 1 × 1 × 5 mm^3. The intracranial cavity was manually traced in each slice, using the anatomical landmarks according to a study by Eritaia et al. (2000). ICV was calculated by summing the measured volumes of all slices.

Whole brain measurements

The whole brain was separated from the brainstem and cerebellum by manual editing on coronal 1-mm slices. The brainstem was excluded by the plane that was parallel to the AC-PC plane and passing through the sulcus pontinus superior. The whole brain volume was then calculated by summing the voxels for tissue compartments across all brain slices and included both hemispheres from the frontal to the occipital poles.

Perigenual cingulate gyrus measurements

Boundaries for the perigenual cingulate gyrus are illustrated in Fig. 1. The perigenual cingulate gyrus was bounded anteriorly by the cingulate sulcus, and posteriorly by the plane that was perpendicular to the AC-PC line and passing through the genu of the anterior margin of the corpus callosum. The left and right perigenual cingulate gyri were separately traced in consecutive axial 1-mm slices from ventral to dorsal, beginning with the plane showing the appearance of the cingulate sulcus and ending dorsally with that showing the disappearance of the corpus callosum, following the methods of Haznedar et al. (1997b). Using the above-mentioned tissue segmentation procedure, the perigenual cingulate gray and white matter volumes were calculated by summing the voxels for each of these tissue compartments.

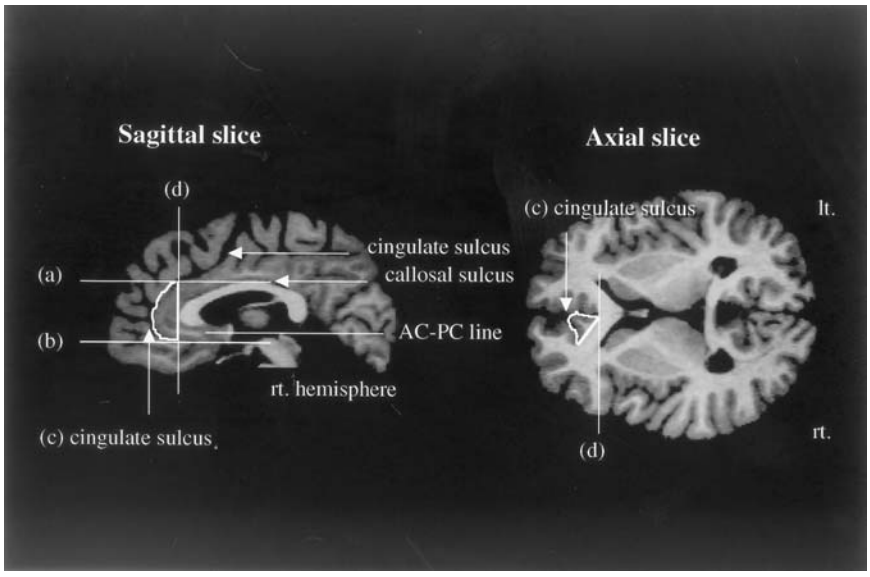

Fig. 1 Boundaries for the perigenual cingulate gyrus. The perigenual cingulate gyrus was traced bilaterally in consecutive axial 1-mm slices parallel to the anterior commissure-posterior commissure (AC-PC) line. The most dorsal axial plane showing the corpus callosum (**a**) and the most ventral axial plane showing the cingulate sulcus (**b**) were chosen as the superior and inferior boundaries, respectively. On each axial slice, the perigenual cingulate gyrus was bounded anteriorly by the cingulate sulcus (**c**), and posteriorly by the plane that was perpendicular to the AC-PC line and passing through the anterior margin of the genu of the corpus callosum (**d**)

All measurements were carried out by one rater (TT), who was blinded to subjects' identity, gender, and diagnosis. Inter- and intra-rater intraclass correlation coefficients of the perigenual cingulate gyrus gray and white matter calculated in a random sample of five brains were over 0.92.

Statistical analysis

Statistical analysis was carried out using the software package STATISTICA 4.1J for Macintosh (StatSoft, Tulsa, OK, USA). The absolute intracranial volume (ICV) was analyzed using analysis of variance with age and height as covariates (ANCOVA), and group (control subjects, patients with schizotypal disorder, and patients with schizophrenia) and gender (male, female) as between-subject factors. Gender differences across the three groups for the total (whole brain) volumes of the gray and white matter were analyzed using the same model but with age and ICV as covariates. The relative perigenual cingulate gyrus volume, used to control for the difference in the head size, was obtained by dividing the absolute volume of the perigenual cingulate gyrus by ICV and multiplying the result by 100. The relative perigenual cingulate gyrus gray and white matter volumes were analyzed by repeated measures multivariate analysis of variance with age as a covariate (MANCOVA), group and gender as between-subject factors, and hemisphere (left, right) as a within-subject variable. Post hoc Scheffé's tests were conducted to follow up the significant main effects or interactions yielded by these analyses.

Correlations between the relative perigenual cingulate gyrus volume and age, medication dosage, and duration of medication were analyzed using Spearman's rank correlation coefficients. Statistical significance was defined as $p < 0.05$.

Results

Intracranial volume (ICV) measurements

The absolute ICV of the control subjects, patients with schizotypal disorder, and patients with schizophrenia are shown in Table 2. There was a significant main effect for gender (ANCOVA, $F = 5.70$; $df = 1,137$; $p = 0.018$). Post hoc Scheffé's test revealed that the ICV was significantly larger in males than in females ($p < 0.001$).

Gender differences in total gray and white matter

ANCOVA of the total gray or white matter revealed no main effect for gender or gender x group interaction. However, ANCOVA of the total gray matter revealed significant main effect for group ($F = 4.49$; $df = 2,137$; $p = 0.013$); the patients with schizophrenia had significantly smaller gray matter than the control subjects (post hoc Scheffé's test, $p < 0.001$) and the patients with schizotypal disorder (post hoc Scheffé's test, $p = 0.015$).

Perigenual cingulate gyrus volume measurements

The relative perigenual cingulate gyrus volumes in the control subjects, patients with schizotypal disorder, and patients with schizophrenia are shown in Table 2. Repeated measures MANCOVA of the perigenual cingulate gray matter revealed significant main effects for group ($F = 9.48$; $df = 2,138$; $p < 0.001$) and gender ($F = 10.44$; $df = 1,138$; $p = 0.002$) and a significant group x gender interaction ($F = 3.93$; $df = 2,138$; $p = 0.022$). Repeated measures MANCOVA of the perigenual cingulate white matter revealed a significant main effect for hemisphere ($F = 15.82$; $df = 1,139$; $p < 0.001$).

Post hoc analysis showed the relative volume of the perigenual cingulate gyrus gray matter to be significantly larger in female controls than in male controls ($p = 0.001$), while this gender difference was not significant in patients with schizotypal disorder ($p = 0.972$) or patients with schizophrenia ($p = 0.999$) (Fig. 2). Consistent with our previous study (Takahashi et al. 2003), the relative volume of the perigenual cingulate gray matter was significantly smaller in the female patients with schizophrenia compared to the female controls ($p < 0.001$). The relative volume of the perigenual cingulate gray matter in the schizotypal patients did not differ significantly from the values in the healthy controls

Table 2 Results of intracranial volume (ICV) and perigenual cingulate gyrus measures

	Control Subjects				Schizotypal Patients				Schizophrenia Patients			
	Male (N = 30)		Female (N = 31)		Male (N = 14)		Female (N = 12)		Male (N = 31)		Female (N = 27)	
Brain region	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
ICV (cm^3)	1590[a]	96	1400	94	1541[a]	107	1431	155	1568[a]	138	1390	104
Perigenual cingulate GM												
Left	0.120	0.033	0.160[b]	0.049	0.127	0.055	0.136	0.048	0.111	0.032	0.117	0.044
Right	0.134	0.039	0.161[b]	0.044	0.130	0.029	0.142	0.039	0.125	0.035	0.126	0.036
Perigenual cingulate WM												
Left	0.012	0.006	0.018	0.011	0.013	0.008	0.013	0.008	0.010	0.008	0.011	0.006
Right	0.017[c]	0.011	0.019[c]	0.010	0.019[c]	0.011	0.017[c]	0.012	0.016[c]	0.013	0.016[c]	0.009

GM, gray matter *WM*, white matter

Perigenual cingulate gyrus volume was calculated as a percentage of the absolute perigenual cingulate gyrus volume to the ICV.

[a]$p < 0.01$, compared to the ICV in the females; [b]$p < 0.01$, compared to the perigenual cingulate GM in the male controls; $p < 0.01$, compared to the perigenual cingulate GM in the male and female schizophrenia patients; $p < 0.05$, compared to the perigenual cingulate GM in the male schizotypal patients; [c]$p < 0.01$, compared to the left perigenual cingulate WM.

ANCOVA or repeated measures MANCOVA followed by Scheffé's tests was used

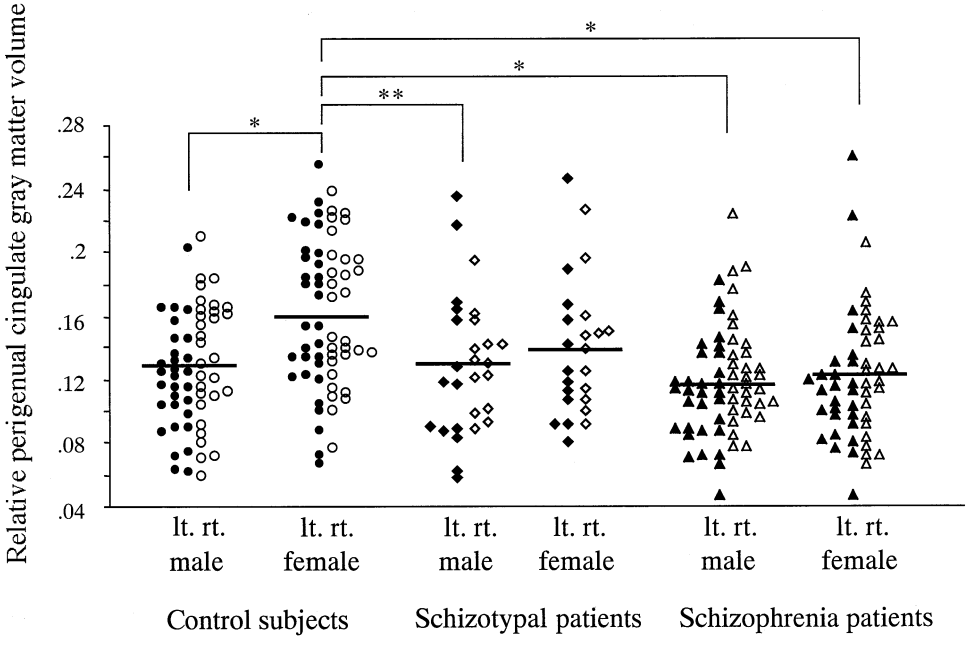

Fig. 2 Relative volume of the perigenual cingulate gray matter in the normal control subjects, patients with schizotypal disorder, and patients with schizophrenia. Horizontal lines indicate mean values. Post hoc Scheffé's test: * $p < 0.01$, ** $p < 0.05$

or the schizophrenia patients. As for white matter, the relative white matter volume of the perigenual cingulate gyrus was significantly larger on the right than on the left hemisphere ($p < 0.001$). However, there were no significant differences in the relative white matter volume among the three groups.

The relative volume of perigenual cingulate gray or white matter did not correlate with age, medication dosage, or duration of neuroleptic medication.

Discussion

In the present study, the perigenual cingulate gray and white matter volumes of the patients with schizotypal disorder did not differ significantly from those of the healthy control subjects or the patients with schizophrenia. Similar to the patients with schizophrenia, however, the patients with schizotypal disorder showed a lack of gender differences of the perigenual cingulate gray matter (larger in females than in males) seen in the healthy controls. Because there were no effects of gender on the total (whole brain) gray matter volume, it is strongly suggested that the lack of normal gender differences we found in the present study represent morphologic changes unique to the perigenual cingulate gyrus. Thus, the patients with schizotypal disorder were found to have structural abnormalities of the perigenual cingulate gyrus qualitatively similar to those seen in patients with schizophrenia, generally supporting our hypothesis.

As supported by previous brain morphological studies (Siever et al. 1995; Buchsbaum et al. 1997; Kwon et al.

1998; Silverman et al. 1998), schizotypal and schizophrenia patients may have a common neurobiological basis for vulnerability factors as part of the schizophrenia spectrum. On the other hand, several recent MRI studies have reported specific differences in brain morphological abnormalities between schizotypal and schizophrenia patients (Dickey et al. 1999; Byne et al. 2001; Downhill et al. 2001). For example, Byne et al. (2001) reported both the patients with schizophrenia and SPD patients to have volume reduction in the thalamic pulvinar nucleus, but only patients with schizophrenia to have volume reduction in the thalamic mediodorsal nucleus. In a recent review of morphological brain abnormalities in SPD, Siever et al. (2002) hypothesized that both schizotypal and schizophrenia patients appear to show abnormalities in temporal lobe volume, but SPD patients do not appear to show the volumetric decrease in the prefrontal cortex that schizophrenia patients show. Dickey et al. (2003) hypothesized from their MRI observations that brain areas involved in emotional processing are spared in SPD subjects. Our results showing that the perigenual cingulate gray matter volume is relatively preserved in schizotypal disorder compared to schizophrenia may be partly consistent with these hypotheses, since the perigenual cingulate gray matter has extensive connections with the prefrontal region (Baleydier and Mauguiere 1980; Devinsky et al. 1995) and is activated in response to emotional manipulations in healthy subjects (George et al. 1993, 1995; Whalen et al. 1998; Ploghaus et al. 2001). However, the characteristics of the brain structures in subjects with schizotypal features have been less extensively studied than those of schizophrenia and the findings are not always consistent. Additional comprehensive assessment of multiple brain regions in the same group of subjects would be essential for our understanding of the brain morphological characteristics underlying schizotypal disorder and schizophrenia.

The rostral and caudal parts of the anterior cingulate gyrus (ACG) have been reported to have cytoarchitectural, connectional, and functional differences (Devinsky et al. 1995; Whalen et al. 1998). The rostral part of the ACG (i. e., perigenual cingulate gyrus) has been termed the affective subdivision; in contrast, the caudal part is considered to be the cognitive division. In a previous MRI study, we examined the volume of the caudal ACG in the largely overlapping schizotypal patients discussed here and reported the right-greater-than-left asymmetry seen in the female controls to be significantly reduced in female schizotypal patients (Takahashi et al. 2002b). On the other hand, in the present study, we found no laterality abnormalities of the perigenual cingulate morphology in schizotypal disorder. These findings suggest that the rostral and the caudal parts of the ACG have, at least in part, different patterns of morphological changes in schizotypal patients, possibly related to different involvements of affective versus cognitive divisions of the ACG in the pathophysiology of schizophrenia spectrum disorders.

As described above, the perigenual cingulate gyrus is involved in emotional function, where females were reported to have relatively higher glucose metabolism during the resting state than males among healthy subjects (Gur et al. 1995). In a previous MRI study, Paus et al. (1996) reported the intrasulcus gray matter volume of the anterior part of the cingulate sulcus to be significantly larger in female controls than in male controls. The present finding of normal gender differences in the perigenual cingulate gyrus volume is in agreement with these previous observations. These normal gender differences of the perigenual cingulate gyrus were not significant in patients with schizotypal disorder. This disruption of the normal patterns of gender differences is similar to those seen in schizophrenia (Takahashi et al. 2003). In healthy subjects, gender differences in brain morphology that occur during fetal development, such as differences in cortical asymmetries (De Lacoste 1991) or in shape of the corpus callosum (De Lacoste 1986), have been reported. Given that the gender differences of the perigenual cingulate gyrus are also regulated prenatally, our finding of a lack of the normal gender differences in patients with both schizophrenia and schizotypal disorder may suggest a common process involving abnormal neurodevelopment in schizophrenia spectrum disorders. These findings suggest that schizotypal disorder may be a milder form on a continuum of schizophrenia spectrum disorders.

On the other hand, since schizotypal disorder "occasionally evolves into overt schizophrenia" (ICD-10; World Health Organization, 1992), the present cross-sectional finding of possibly less severe structural abnormalities of the perigenual cingulate gyrus in patients with schizotypal disorder may suggest a progressive change in neuroanatomy of the perigenual cingulate gyrus that occurs during the prodromal phase and/or after the onset of schizophrenia in individuals predisposed to this illness. Indeed, Pantelis et al. (2003) have examined the brain morphology before and after the onset of psychosis in ultra high-risk individuals using voxel-based analysis of MRI and reported a longitudinal gray matter volume reduction of the cingulate gyrus between the prodromal phase and first expression of psychotic symptoms. They also found that individuals who subsequently developed overt psychosis had significantly smaller volumes of the gray matter in several brain regions such as the prefrontal cortex and cingulate cortex at baseline than those who did not develop psychosis. The latter finding seems especially important in view of the early intervention of psychosis and should be confirmed in further studies. For example, the volumetric method as in this study might endow their results with greater validity and provide more detailed information on brain morphological features in the prodromal phase of schizophrenia. However, the follow-up periods of schizotypal patients in this study were relatively short and we cannot answer at present how many patients develop overt schizophrenia later. An even longer follow up to assess progressive changes over time will be required to differentiate brain morphology between

schizotypal patients who do or do not later develop schizophrenia.

Some limitations of the present study need to be addressed. First, the relatively small sample number of the patients with schizotypal disorder limits the ability to generalize the findings from the present study. An additional study with a large number of subjects should be performed to confirm our findings concerning the perigenual cingulate gyrus volume in the patients with schizotypal disorder. A second limitation is that the patients with schizotypal disorder in the present study were recruited from a clinical population and most patients were on neuroleptic medication. The relationship between brain morphological features and neuroleptic medication has been reported in schizophrenia (Chakos et al. 1995; Keshavan et al. 1994, 1998; Gur et al. 1998) and possible effects of neuroleptic medications could not be eliminated from our findings. To our knowledge, however, no specific effect of neuroleptic medication on the perigenual cingulate morphology has been reported. In addition, the perigenual cingulate gyrus volume did not correlate with medication dosage or duration of neuroleptic medication in either patient group in the present study. With regard to the types of neuroleptics, functional brain imaging studies have suggested that atypical neuroleptics have greater effects on the function of anterior cingulate neurons than typical neuroleptics (Braus et al. 2002; Lahti et al. 2003). However, the type of neuroleptic medication (typical versus atypical) did not influence the perigenual cingulate gyrus volume in the present study (data not shown). A third limitation is that we used the corpus callosum as an anatomical landmark for definition of the perigenual cingulate gyrus. The corpus callosum is one of several brain regions reported to be abnormal in schizophrenic brains (Woodruf et al. 1993, 1995; Tibbo et al. 1998; Downhill et al. 2000). We are not excluding the possibility that differences in size or shape of the corpus callosum among the three groups (normal controls, patients with schizotypal disorder, and patients with schizophrenia) biased the results.

In conclusion, the present findings suggest that both schizotypal and schizophrenia patients share the same disruption of normal patterns of gender differences of the perigenual cingulate gyrus, possibly reflecting a pathophysiologic process common to both disorders.

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