Eur Arch Psychiatry Clin Neurosci (2002) 252 : 268 – 277 DOI 10.1007/s00406-002-0392-3

ORIGINAL PAPER

Tsutomu Takahashi · Michio Suzuki · Yasuhiro Kawasaki · Kenzo Kurokawa · Hirofumi Hagino · Ikiko Yamashita · Shi-Yu Zhou · Shigeru Nohara · Kazue Nakamura · Hikaru Seto · Masayoshi Kurachi

Volumetric magnetic resonance imaging study of the anterior cingulate gyrus in schizotypal disorder

Received: 28 May 2002 / Accepted: 30 October 2002

Abstract Lack of normal structural asymmetry of the anterior cingulate gyrus (ACG) in patients with schizophrenia has been reported in our previous study. However, to our knowledge, no morphological studies of the brain have examined changes in ACG volume in patients with schizotypal features. We investigated the volume of the gray matter and the white matter of the ACG by three-dimensional magnetic resonance imaging (MRI) in 24 patients who met the ICD-10 criteria for schizotypal disorder (12 males, 12 females) in comparison with 48 age- and gender-matched healthy control subjects (24 males, 24 females) and 40 patients with schizophrenia (20 males, 20 females). As we reported previously, right ACG gray matter volume was significantly reduced in the female patients with schizophrenia compared with the female controls. On the other hand, the gray and white matter volume of the ACG in the patients with schizotypal disorder did not differ significantly from the values in the healthy controls or the patients with schizophrenia. However, the female patients with schizotypal disorder showed a lack of right-greater-than-left asymmetry of the ACG gray and white matter found in the female controls. These results suggest that both schizotypal and schizophrenic subjects share, at least in part, the same cerebral asymmetry abnormalities.

T. Takahashi (✉) · M. Suzuki · Y. Kawasaki · H. Hagino · I. Yamashita · S-Y. Zhou · S. Nohara · K. Nakamura · M. Kurachi
Department of Neuropsychiatry
Toyama Medical and Pharmaceutical University
2630 Sugitani
Toyama 930–0194, Japan
Tel.: +81-76/434-2281
Fax: +81-76/434-5030
E-Mail: tsutomu@ms.toyama-mpu.ac.jp

K. Kurokawa
Neuropsychiatry Center
Fukui Prefectural Hospital

H. Seto
Department of Radiology
Toyama Medical and Pharmaceutical University

EAPCN 392

Key words anterior cingulate gyrus · magnetic resonance imaging · schizotypal disorder · schizophrenia · asymmetry

Introduction

Schizotypal disorder 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). It is thought to include the prodromal phase of schizophrenia as well as the schizotypal personality disorder (SPD) of the DSM-IV (American Psychiatric Association, 1994). Such patients with schizotypal features share genetic, biological, and psychological commonalities with patients with schizophrenia and are thought to be part of the schizophrenia spectrum (Siever et al. 1993). Although patients occasionally manifest transient quasi-psychotic episodes, schizotypal disorder is phenomenologically different from schizophrenia because of the absence of overt and sustained psychosis. Clarifying the differences and similarities of neurobiological abnormalities in schizotypal disorder and schizophrenia has implications for understanding the core pathophysiology of schizophrenia.

Several recent brain structural imaging studies have identified specific structural abnormalities in SPD patients similar to those seen in schizophrenia, although generally to a lesser degree and sparing some brain regions (reviewed by Siever et al. 2002). The abnormalities include large cerebrospinal fluid volume (Dickey et al. 2000), increased lateral ventricle size (Siever et al. 1995; Buchsbaum et al. 1997b; Silverman et al. 1998), volume reduction in temporal lobe structures (Dickey et al. 1999; Seidman et al. 1999; Downhill et al. 2001), and thalamic volume reduction (Hazlett et al. 1999; Seidman et al. 1999; Byne et al. 2001). The brain abnormalities shared by schizotypal patients and schizophrenic patients may represent a common denominator in schizo-

phrenia-spectrum disorders, whereas the differences may represent the prerequisites for overt psychotic symptoms. Therefore, assessing brain regions in schizotypal disorder that have previously been identified as impaired in schizophrenia is one possible strategy for advancing our understanding of the morphological characteristics of the brain underlying schizotypal disorder and schizophrenia.

The anterior cingulate gyrus (ACG) is part of the rostral limbic system and is involved in emotional and attentional functions (Devinsky et al. 1995). The gyrul and sulcal pattern in this region is extremely variable among individuals, and a right-greater-than-left structural asymmetry of the ACG has been reported, especially in female healthy subjects (Albanese et al. 1995; Paus et al. 1996; Pujol et al. 2002). In a previous volumetric magnetic resonance imaging (MRI) study, we reported finding structural abnormalities of the ACG in patients with schizophrenia (Takahashi et al. 2002). In that study, female patients with schizophrenia showed a lack of the right-greater-than-left ACG asymmetry found in female control subjects. The results also indicated that the reduction of the normal structural asymmetry is female-specific and mainly attributable to a significant reduction in the volume of the right ACG gray matter in female patients. As first recognized clearly by Crow et al. (Crow et al. 1989; Crow, 1990), a reversal or reduction of normal cerebral asymmetry is thought to be one of the most characteristic features of the brain in schizophrenia [as reviewed by DeLisi et al. (1997a) and Pearlson and Marsh (1999)]. To our knowledge, however, no morphological studies of the brain have examined changes in ACG volume or laterality in patients with schizotypal features.

Cognitive impairments that are similar to, but less pervasive than, those seen in schizophrenic patients have been observed in the schizophrenia-spectrum disorders (Condray and Steinhauer, 1992; Trestman et al. 1995; Voglmaier et al. 1997, 2000; Cadenhead et al. 1999; Diforio et al. 2000). Two of these previous neuropsychological studies in particular (Trestman et al. 1995; Cadenhead et al. 1999) have examined a wide-range of neuropsychological functions and reported SPD subjects to have possible widespread cognitive impairments that are lesser in magnitude than those observed in schizophrenic patients. The impairments include cognitive deficits in attention and executive functions, which are mediated, at least in part, by the anterior cingulate cortex (Devinsky et al. 1995).

Based on the previous structural imaging studies and the neuropsychological findings, it was hypothesized that patients with schizotypal disorder have structural abnormalities, such as volume reduction and/or lack of normal structural asymmetry of the ACG, and that the abnormalities are less severe than those seen in patients with schizophrenia. In the present study, we used three-dimensional (3-D) MRI to investigate the volume of the gray and white matter of the ACG in patients with schizotypal disorder and age- and gender-matched normal control subjects to test this hypothesis. Their ACG volume was also compared with our previously reported data of male and female patients with schizophrenia evaluated in an identical protocol (Takahashi et al. 2002).

Methods

Subjects

Twenty-four patients with schizotypal disorder (12 males and 12 females; mean age = 22.7 years, SD = 4.5) who met the ICD-10 diagnostic criteria for research (World Health Organization, 1993) were recruited from the inpatient and outpatient clinics of the Department of Neuropsychiatry, Toyama Medical and Pharmaceutical University Hospital. Candidates who had a previous history of overt psychotic episode or met the ICD-10 criteria for schizophrenia at the time of MRI scanning were excluded. 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; Andreasen et al. 1992) were stored in the database of the study. Whenever possible, the patient's family was interviewed by psychiatrists to provide additional information. All patients have consistently received adequate clinical follow-up to prevent serious psychotic problems as part of an early intervention program for psychoses (Sumiyoshi et al. 2000), and none of the patients' condition has evolved into overt schizophrenia to date (mean follow-up period = 2.4 years, SD = 1.8). Information about changes in mental condition during the follow-up period was also stored in the database and clinical records. Subjects were diagnosed by a consensus of at least two experienced psychiatrists based on these data. When necessary, the propriety of including cases in the study was discussed among clinical staff members involved in the program. At the time of the MRI scan 8 of the 24 patients with schizotypal disorder did not meet the diagnostic criterion that the typical feature be present for 2 years, but during the course of follow-up period all patients eventually fulfilled all of the criteria for schizotypal disorder. Twenty-two patients were on neuroleptic medication (mean haloperidol equivalent dose = 4.1 mg/day, SD = 1.0), with a mean duration of medication of 1.1 years (SD = 1.8). Twelve patients were treated with typical neuroleptics, 10 with atypical neuroleptics such as risperidone and perospirone, and 17 were also treated with anticholinergic drugs. 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 the 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 49.8 (SD = 21.5, range 11–84) and 16.5 (SD = 10.4, range 0–39), respectively.

The control subjects consisted of a total of 48 healthy volunteers (24 males and 24 females) recruited from community volunteers, hospital staff, and medical or pharmaceutical students. The control subjects participating in this study included 40 subjects from a previous study (Takahashi et al. 2002) and an additional eight subjects (four males, four females). Their mean age was 24.2 ± 5.9 (SD) years. None of the control subjects were receiving pharmacological treatment for any medical disorders. Candidates were excluded if they had any personal or family history of psychiatric illness. In addition, all control candidates were interviewed and administered the Minnesota Multiphasic Personality Inventory (MMPI) by one experienced clinical psychologist (YI) in order to obtain a rather homogenous control group without eccentric profiles on the MMPI. Although the MMPI has not proved very sensitive for the detection of schizotypy (Walters, 1983), approximately 17 % of the candidates for normal control subjects were excluded for having an abnormal profile with a T-score exceeding 70. The schizophrenic comparison group comprised 40 patients with schizophrenia (20 males and 20 females; mean age = 26.1 years, SD = 5.0) in stable clinical conditions; they were identical with the schizophrenic group that was previously reported (Takahashi et

al. 2002). All patients fulfilled the ICD-10 diagnostic criteria for research (World Health Organization, 1993). All but two of the patients were on neuroleptic medication (mean haloperidol equivalent dose = 9.3 mg/day, SD = 9.4), with a mean duration of medication of 3.7 years (SD = 3.5). At the time of the MRI study, their mean scores on the SANS and the SAPS were 44.2 (SD = 21.0, range 8–84) and 23.5 (SD = 18.4, range 0–91.5), respectively. The clinical and demographic characteristics and ACG volume in the patients with schizophrenia and in 40 of the 48 normal control subjects have been reported previously (Takahashi et al. 2002).

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. The handedness of one female patient with schizotypal disorder was unknown; all of the other subjects were right-handed.

The 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 terms of gender, height, and parental education. As expected, however, there were significant differences in education across the three groups (control subjects, 15.4 ± 2.7 years; patients with schizophrenia, 13.6 ± 2.1 years; patients with schizotypal disorder, 12.5 ± 2.2 years; ANOVA, $F = 13.35$, $df = 2, 109$, $p < 0.001$). The post hoc Scheffé's test showed the control subjects to have attained a higher level of education than the patients with schizophrenia ($p = 0.003$) and the patients with schizotypal disorder ($p < 0.001$). There was a significant difference in age across the three groups (ANOVA, $F = 3.21$, $df = 2,109$, $p = 0.044$). The post hoc Scheffé's tests showed that the patients with schizophrenia were older than the patients with schizotypal disorder, but the difference was not statistically significant ($p = 0.053$). There were no significant differences between the patients with schizophrenia and the patients with schizotypal disorder in total score on the SANS and SAPS. However, there were significant differences in medication dosage (ANOVA, $F = 6.11$, $df = 1,62$, $p = 0.016$) and duration of neuroleptic medication (ANOVA, $F = 11.66$, $df = 1,62$, $p = 0.001$). 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. Each subject participated in the study after providing written informed consent. When subjects were less than 18 years old, informed consent was also obtained from their parents.

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 = 10 ms; flip angle = 40°; field of view = 256 mm; and matrix size = 256 x 256 pixels. The voxel size was 1.0 x 1.0 x 1.0 mm^3. Magnetic field inhomogeneities in our scanner were monitored by weekly phantom scanning and daily basic quality control, and they were 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 with the software package Dr. View 5.0 (Asahi Kasei Joho System Co., Ltd., Tokyo, Japan) blind to subjects' gender and diagnosis.

Details of the data analyses have been described previously (Takahashi et al. 2002). Briefly, the scans were realigned in three dimensions on the workstation to standardize for differences in head tilt during image acquisition and were then reconstructed into entire contiguous coronal images, with a 1-mm thickness, perpendicular to the anterior commissure-posterior commissure (AC-PC) line. 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) according to the Alpert algorithm (Alpert et al. 1996). The histogram of gray levels was computed and used to select minimal intensity points between the gray matter and CSF peaks (lower intensity threshold) and between the gray and white matter peaks (upper intensity threshold). After first separating the CSF from the tissue by the lower intensity threshold, the resulting tissue compartment was separated into gray and white matter compartments by the upper intensity threshold. Although the images were not corrected for the magnetic field inhomogeneities, no visible effect on the quality of segmentation was detected in any of the cases. Prior to volumetric analysis of the ACG, 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.

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

Variable	control subjects		schizotypal patients		schizophrenic patients	
	male (n = 24)	female (n = 24)	male (n = 12)	female (n = 12)	male (n = 20)	female (n = 20)
Age (years)	24.5±5.9 (range, 14–38)	23.8±6.0 (range, 18–37)	22.2±4.9 (range, 18–32)	23.3±4.3 (range, 16–29)	26.4±5.1 (range, 19–36)	25.9±5.1 (range, 15–35)
Height (cm)	172.5±4.0[a]	159.3±3.8	171.6±7.3[a]	157.9±5.9	170.9±5.5[a]	159.0±3.9
Education (years)	16.6±3.3[b]	14.3±1.2	12.5±2.3	12.5±2.3	14.2±2.1	13.1±2.1
Parental education (years)	12.6±2.4	12.2±1.9	12.0±1.8	12.0±2.3	12.0±1.6	11.6±2.2
Age at onset (years)	–	–	–	–	21.6±4.7	21.2±3.9
Duration of illness (years)	–	–	–	–	4.8±4.3	5.2±4.6
Duration of medication (years)	–	–	1.7±2.3	0.6±0.9	3.3±3.1[c]	4.1±3.8[c]
Drug (mg/day, haloperidol equiv.)	–	–	6.0±6.4	2.2±1.6	7.7±5.2[d]	10.8±12.2[d]
Total SAPS score	–	–	15.6±9.8	17.4±11.4	19.5±18.0	27.5±18.4
Total SANS score	–	–	50.0±21.8	49.7±22.3	45.1±21.8	43.3±20.6

Values represent means ± SDs. *SANS* Scale for the Assessment of Negative Symptoms; *SAPS* Scale for the Assessment of Positive Symptoms.
Post hoc Scheffé's tests:
[a] Significantly different from the females ($p < 0.01$)
[b] Significantly different from the female controls ($p < 0.05$), the male schizophrenic patients ($p < 0.05$), the female schizophrenic patients ($p < 0.01$), and the male and female schizotypal patients ($p < 0.01$)
[c] Significantly different from the schizotypal patients ($p < 0.05$)
[d] Significantly different from the schizotypal patients ($p < 0.01$)

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 x 1 x 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. For insurance, ICV was measured using images of 5 randomly sampled subjects both on 1-mm thick sagittal slices and 5-mm thick sagittal slices, and the intraclass correlation coefficient (ICC) between these two strategies was 0.99.

Whole brain measurements

The whole brain was separated from the brainstem and cerebellum by manual editing on each coronal slice. The brainstem was excluded by the plane that was parallel to the AC-PC plane and passing through the sulcus pontinus superior. The total (whole brain) volumes for the gray and white matter were then calculated by summing the voxels for each tissue compartment across all brain slices and included both hemispheres from the frontal to the occipital poles.

Anterior cingulate gyrus measurements

The anatomical boundaries of the ACG were based on detailed guidelines described elsewhere (Takahashi et al. 2002). The left and right ACGs were separately traced in consecutive coronal 1-mm slices from posterior to anterior, beginning with the plane on which the anterior commissure first appeared and ending anteriorly with the first plane on which there was no evidence of the corpus callosum. On each coronal slice, the ACG was bounded superiorly by the cingulate sulcus, and inferiorly by the callosal sulcus. The above-described tissue segmentation procedure was used to calculate the volume of the gray matter and white matter of the ACG by summing the voxels for each of these tissue compartments (Fig. 1).

All measurements were carried out by one rater (TT), blinded to subject gender and diagnosis. To determine the reliability of the ACG measurements, five subjects were randomly selected, for a total of approximately 150 slices. The ACGs in a subset of these five subjects were measured independently by two raters (TT, KY) and intraclass correlation coefficients (ICCs) were calculated. The inter-rater ICCs of the gray and white matter of the ACG were greater than 0.96. Each volume was then remeasured after at least four weeks by the first rater; the intra-rater ICCs of the gray and white matter of the ACG were greater than 0.98, indicating excellent reliability.

Statistical analysis

Statistical analysis was carried out using the software package STATISTICA 4.1J for Macintosh (StatSoft, Tulsa, OK, USA). The ICV data were analyzed by analysis of variance with age as a covariate (ANCOVA) and group (control subjects, patients with schizotypal disorder, and patients with schizophrenia) and gender (male, female) as between-subject factors. Relative ACG volume, used to control for differences in head size, was obtained by dividing the absolute volume of the ACG by ICV and multiplying the result by 100. The relative ACG 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. Hemispheric differences across the three groups for the total (whole brain) volumes of the gray and white matter were tested using the same model but with age and ICV as covariates. Age was used as a covariate in these analyses to correct for the differences in age between the patients with schizophrenia and the patients with schizotypal disorder. Post hoc Spjotvoll and Stoline tests, modified Tukey's tests for unequal sample size, were conducted to follow up the significant main effects or interactions.

Correlations between the relative ACG volume and age, education, medication dosage, and duration of medication were analyzed by using Spearman's rank correlation coefficients. In the patients with schizophrenia, correlation between illness duration and the relative ACG volume was also analyzed. 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, $F = 50.77$; $df = 1,105$; $p < 0.001$). Post hoc analysis revealed that the ICV was significantly larger in males than in females ($p < 0.001$).

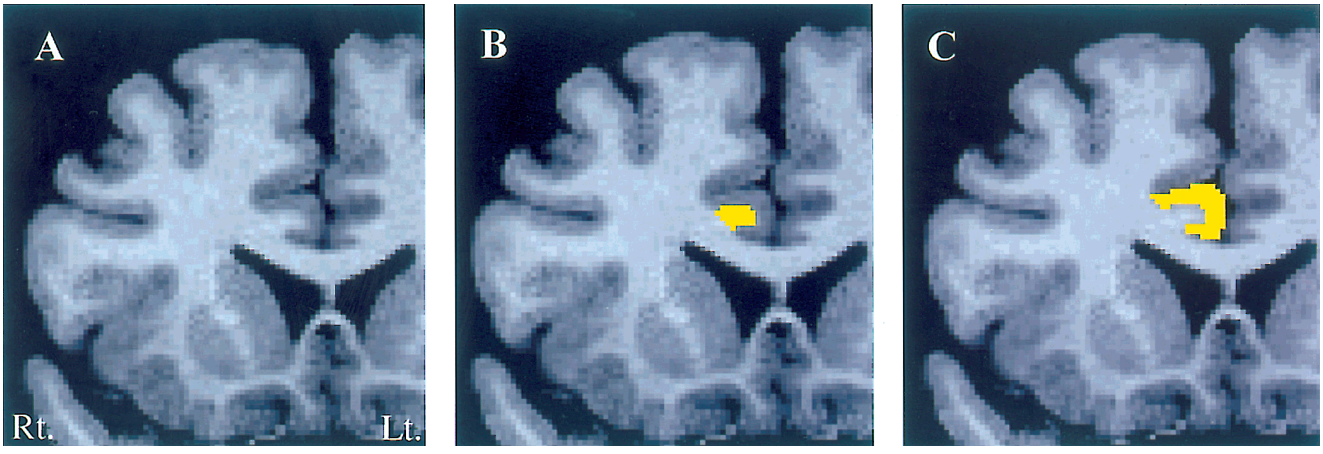

Fig. 1 An example of gray and white matter measurements of the anterior cingulate gyrus (ACG). A reconstructed T1-weighted coronal image with 1.0-mm thickness (**A**), a bitmap image of the ACG white matter (yellow) superimposed onto the T1-weighted image (**B**), and a bitmap image of the ACG gray matter (yellow) superimposed onto the T1- weighted image (**C**) are shown

Table 2 Intracranial volume (ICV) and relative volume of the gray and white matter of the anterior cingulate gyrus (ACG) in control subjects, patients with schizotypal disorder, and patients with schizophrenia

	Control Subjects				Schizotypal Patients				Schizophrenic Patients			
	Male (N = 24)		Female (N = 24)		Male (N = 12)		Female (N = 12)		Male (N = 20)		Female (N = 20)	
Brain region	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
ICV (cm^3)	1591[b]	90	1405	90	1547[b]	115 (–2.8)	1468	169 (+4.3)	1593[b]	138 (+0.1)	1377	98 (–2.0)
ACG Gray Matter												
Left	0.132	0.036	0.140	0.031	0.133	0.044 (+0.8)	0.150	0.052 (+6.7)	0.128	0.021 (–3.0)	0.127	(0.028 (–9.3)
Right	0.157	0.042	0.200[a, b, c]	0.041	0.165	0.025 (+4.9)	0.174	0.035 (–13.0)	0.153	0.035 (–2.5)	0.156	0.031 (–22.0)
ACG White Matter												
Left	0.038	0.013	0.037	0.013	0.040	0.016 (+5.3)	0.039	0.016 (+5.1)	0.042	0.011 (+9.5)	0.037	0.011 (±0.0)
Right	0.040	0.016	0.052[c]	0.012	0.043	0.009 (+7.5)	0.041	0.018 (–21.2)	0.049	0.015 (+18.4)	0.044	0.016 (–15.4)

Relative ACG volume was calculated using the formula: (absolute ACG volume/ICV) x 100.
Numbers in parentheses indicate % difference between the controls and the patients.
Post hoc Spjotvoll and Stoline tests: [a] $p < 0.01$ (Control vs Schizophrenia); [b] $p < 0.01$ (Male vs Female); [c] $p < 0.01$ (Left vs Right)

Hemispheric differences in total gray and white matter

As for the laterality effects, repeated measures MANCOVA revealed significant group x hemisphere ($F = 4.96$; $df = 2,106$; $p = 0.009$) and group x gender x hemisphere ($F = 3.14$; $df = 2,106$; $p = 0.047$) interactions for the total gray matter volume, and a significant group x gender x hemisphere interaction ($F = 3.78$; $df = 2,106$; $p = 0.026$) for the total white matter volume. Post hoc analyses showed the gray matter volume to be significantly larger on the left than on the right hemisphere in the male controls ($p < 0.001$) and in the male patients with schizophrenia ($p < 0.001$). However, this asymmetry was not significant in the male patients with schizotypal disorder or in the female subjects. The total white matter volume was larger on the right than on the left hemisphere in all the groups.

Anterior cingulate gyrus volume measurements

The relative ACG volumes in the control subjects, patients with schizotypal disorder, and patients with schizophrenia are shown in Table 2, Fig. 2, and Fig. 3. Repeated measures MANCOVA of the ACG gray matter revealed significant main effects for group ($F = 3.74$; $df = 2,105$; $p = 0.027$), gender ($F = 6.87$; $df = 1,105$; $p = 0.010$), and hemisphere ($F = 44.85$; $df = 1,106$; $p < 0.001$). Repeated measures MANCOVA of the ACG white matter revealed a significant main effect for hemisphere ($F = 10.64$; $df = 1,106$; $p = 0.001$) and a significant group x gender interaction ($F = 3.18$; $df = 2,105$; $p = 0.046$).

Post hoc analyses showed that the ACG gray and white matter volumes of the patients with schizotypal disorder did not differ significantly from those of the normal control subjects or the patients with schizophrenia. The volumes of the ACG gray and white matter were significantly larger on the right than on the left in the female controls (gray matter, $p < 0.001$; white matter, $p = 0.006$), whereas this asymmetry was not significant in the female patients with schizotypal disorder (gray matter, $p = 0.847$; white matter, $p = 1.000$) or the female patients with schizophrenia (gray matter, $p = 0.253$; white matter, $p = 0.878$). As we reported previously (Takahashi et al. 2002), the volume of the right ACG gray matter was significantly smaller in the female patients with schizophrenia compared to the female controls ($p = 0.008$). The volume of the right ACG gray matter in

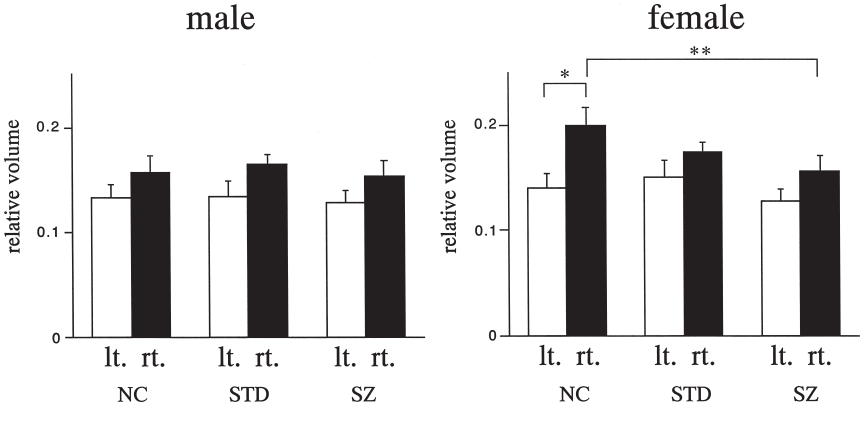

Fig. 2 ACG gray matter volume in the normal control subjects, patients with schizotypal disorder, and patients with schizophrenia. The white and black columns indicate mean relative gray matter volumes of the left and right anterior cingulate gyrus, respectively. Error bars indicate SDs. *NC* normal controls; *STD* schizotypal disorder; *SZ* schizophrenia. Post hoc Spjotvoll and Stoline tests: * $p < 0.001$, ** $p = 0.008$

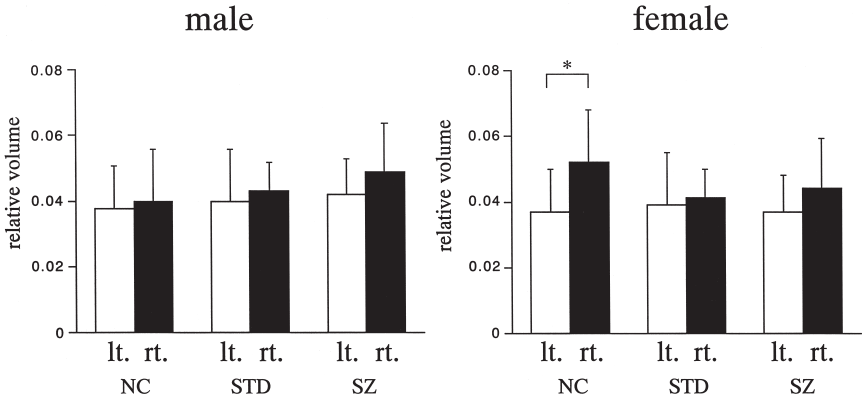

Fig. 3 ACG white matter volume in the normal control subjects, patients with schizotypal disorder, and patients with schizophrenia. The white and black columns indicate mean relative white matter volumes of the left and right anterior cingulate gyrus, respectively. Error bars indicate SDs. *NC* normal controls; *STD* schizotypal disorder; *SZ* schizophrenia. Post hoc Spjotvoll and Stoline tests: * $p = 0.006$

the female patients with schizotypal disorder was intermediate between that of the female controls and the female patients with schizophrenia, and did not differ significantly from either of these two groups (versus female controls, p = 0.829; versus female patients with schizophrenia, p = 0.980). There were no significant differences in ACG volume across the three groups among the male subjects.

There was no significant correlation between relative ACG volume and age, education, medication dosage, or duration of neuroleptic medication in both the patients groups. In the patients with schizophrenia, illness duration did not correlate with relative ACG volume.

Discussion

In the present study, we used 3-D MRI to investigate the volume of the gray and white matter of the ACG of patients with schizotypal disorder in comparison with healthy control subjects and patients with schizophrenia. The gray and white matter volume of the ACG of the patients with schizotypal disorder did not differ significantly from the values in the healthy control subjects or the patients with schizophrenia. Similar to the patients with schizophrenia, however, the female patients with schizotypal disorder showed a lack of the normal structural asymmetry of the ACG gray and white matter seen in the female controls (larger on the right than on the left hemisphere). Since the total volumes of the gray and white matter did not alter in the same way, it is strongly suggested that asymmetry anomalies seen in our study represent morphological changes unique to the ACG.

The diagnostic criteria of schizotypal disorder of ICD-10 are almost identical to those of SPD of DSM-IV (American Psychiatric Association, 1994). However, there are subtle differences between the two categories. SPD is a stable personality, in contrast, schizotypal disorder of the ICD-10 requires a period of at least two years and the criteria include poor rapport with others and a tendency of social withdrawal, and occasional transient quasi-psychotic episodes in addition to the items of SPD. In addition, schizotypal disorder "occasionally evolves into overt schizophrenia." Thus, the schizotypal disorder of ICD-10 includes prodromal schizophrenia in addition to SPD of the DSM-IV. However, prior to the onset of psychosis, the clinical manifestations of two groups of patients who later develop schizophrenia or not are indistinguishable. Some of the patients with schizotypal disorder in this study could be at risk for developing psychosis later; they can be diagnosed as the prodromal phase of schizophrenia but not as the SPD according to the concept of the DSM-IV. We, therefore, adopted the ICD-10 criteria for schizotypal disorder in the present study.

With regard to the subject selection, the schizotypal patients in this study were recruited from a clinical population. Twenty-one of the 24 patients with schizotypal disorder were also assessed using Brief Psychiatric Rating Scale (BPRS; Overall et al. 1962) at the time of scanning. Their total BPRS score (mean = 38.9, SD = 11.3) was comparable with those in previous clinical-based studies of SPD (mean = 37.5, SD = 6.2) (Hazlett et al. 1999; Byne et al. 2001). With regard to the schizophrenia group, early phase schizophrenia and partially remitted patients were consecutively recruited, and as a result, there were no significant differences in the SANS and SAPS scores between the patients with schizophrenia and schizotypal disorder.

The ACG is involved in emotional and attentional functions, for which the right hemisphere is considered to be dominant among normal subjects (Perlmutter et al. 1987). In a positron emission tomography (PET) study, Gur et al. (1995) reported that females have relatively higher glucose metabolism of the ACG during the resting state than males among healthy subjects. Previous MRI (Paus et al. 1996; Pujol et al. 2002) and postmortem (Albanese et al. 1995) studies have reported that structural asymmetry of the ACG is very common among healthy subjects and that a right-greater-than-left asymmetry is more frequent in females than males. The present finding of female-specific normal structural asymmetry of the ACG is consistent with these previous studies. The reason why the ACG asymmetry is limited to female subjects is not clear, but it may be related to the differences in the basic dimensions of personality traits between males and females. Interestingly, Pujol et al. (2002) investigated the relationship between

the cingulate gyrus morphology and behavioral styles in healthy subjects using MRI and showed that a large right ACG is related to a temperamental disposition to fear and anticipatory worry. Their results also suggested a higher prevalence of these traits in healthy female subjects.

One major finding of the present study was the lack of normal asymmetry of the ACG in the female patients with schizotypal disorder. This female-specific reduction in normal structural asymmetry of the ACG is similar to that seen in schizophrenia (Albanese et al. 1995; Takahashi et al. 2002). Recent MRI (Bilder et al. 1994; Turetsky et al. 1995; DeLisi et al. 1997a; Bryant et al. 1999; reviewed by Pearlson and Marsh, 1999; Sharma et al. 1999) and postmortem (Highley et al. 1998, 1999; McDonald et al. 2000) studies of schizophrenia have revealed a reversal or reduction in normal cerebral asymmetry to be one of the most characteristic features of the brain in schizophrenia. Interestingly, Sharma et al. (1999) used MRI to investigate cerebral asymmetries in familial schizophrenic patients and their non-psychotic relatives and concluded that lack of the normal pattern of frontal and occipital asymmetry is a marker for genetic liability to schizophrenia in families multiply affected with schizophrenia. These previous MRI findings support the hypothesis by Crow et al. (Crow et al. 1989; Crow, 1990) that abnormal asymmetry of the brain represents a genetic/developmental abnormality in schizophrenia. Our findings suggest that both schizotypal and schizophrenic subjects share, at least in part, the same cerebral asymmetry abnormalities, possibly reflecting a pathophysiologic process common to both disorders.

In a comprehensive review of recent neuroimaging and neuropsychological studies, Siever et al. (2002) suggested that SPD shares a partially overlapping etiology with schizophrenia, with common temporal cortical abnormalities, but that schizotypal subjects do not appear to show the volumetric decrease in the prefrontal cortex that schizophrenic patients evidence. They also noted that there might be abnormalities in frontal activation in both disorders, but that schizotypal individuals can recruit alternative regions to accomplish tasks requiring frontal lobe activation that may help compensate (Buchsbaum et al. 1997a). The present results showing that ACG gray matter volume is relatively preserved in schizotypal disorder compared to schizophrenia may be partly consistent with those considerations, because the anterior cingulate cortex has rich connections with the prefrontal cortex via the thalamic mediodorsal nucleus (Baleydier and Mauguiere, 1980; Devinsky et al. 1995). Interestingly, in a recent positron emission tomography (PET) study, Buchsbaum et al. (2002) reported a significantly lower metabolic rate of the ACG (Brodmann area 24) in patients with schizophrenia but not in the SPD during a serial verbal learning task. Based on the results of functional imaging studies in patients with schizophrenia and animal studies with phencyclidine (PCP), Tamminga et al. (2000) hypothesized that the mechanism of psychosis in schizophrenia is a glutamatergic failure, occurring primarily within the hippocampus, the effects of which extend to other regions of limbic cortex, particularly the ACG. The present morphological and the previous functional (Buchsbaum et al. 2002) findings of the ACG may explain the possible reason for the absence of overt and sustained psychosis in schizotypal subjects. However, the characteristics of the brain structures and functions in schizotypal disorder or SPD have been less extensively studied than those in schizophrenia, and the findings have not always been consistent. Indeed, Raine et al. (1992) reported that high scores on schizotypy in a group of unmedicated normal subjects were correlated with a reduced prefrontal area on MRI scans. Several confounding factors, such as small sample size, differences in the severity of schizotypal patients (i. e., whether a clinical population or not), and differences in the gender ratios of subjects, may explain the inconsistencies between the studies.

The schizotypal patients in this study included adolescents and the follow-up periods were relatively short; they might have been highly at risk for developing psychosis later. Since schizotypal disorder "occasionally evolves into overt schizophrenia" (ICD-10; World Health Organization, 1992), the present cross-sectional finding of less severe structural abnormalities in the ACG of patients with schizotypal disorder also suggests that there is a possible further change in neuroanatomy of the ACG that occurs during the prodromal phase and/or after the onset of schizophrenia in individuals predisposed to this illness. Indeed, progressive structural changes in the lateral ventricle, left and right hemispheres (DeLisi et al. 1997b), and frontal lobe (Gur et al. 1998) have been reported in first-episode schizophrenia. A longitudinal study to assess progressive changes over time will be required to determine whether the structural abnormalities of the ACG in schizophrenia-spectrum disorders are neurodevelopmental and/or degenerative in nature. It is of particular interest to clarify whether there are differences in progressive structural changes of the brain between two groups of patients who later develop schizophrenia or not.

In the present study, asymmetry abnormalities of the ACG in schizophrenia-spectrum disorders were found only in females. In schizophrenia, structural brain abnormalities such as ventricular enlargement or volume reductions of the temporal lobe structures have been suggested to be greater in male patients than in female patients (Lawrie and Abukmeil 1998; Pearlson and Marsh 1999). In contrast, gray matter reductions in the frontal areas (Nasrallah et al. 1990; Suzuki et al. 2002) have been observed predominantly in female patients. Although little is known about the gender differences of the brain morphology in schizotypal patients, male and female patients with schizophrenia-spectrum disorders may have, at least in part, different patterns of structural brain abnormalities.

Several limitations of this study need to be taken into account before any conclusion can be drawn. First, most patients with schizotypal disorder in the present study

were on neuroleptic medication. Medication may have influenced our findings, because a 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). Although the dosage of neuroleptic medication taken at the time of the scan was not related to the ACG volume in the present study, the effects of cumulative years of medication treatment cannot be ruled out. A second limitation is that the patients with schizotypal disorder in this study were younger than the patients with schizophrenia (mean age = 22.7 years, range = 16–32). We therefore controlled for the age difference by covarying age in all of the MANCOVA analyses. Moreover, the results were unchanged even after matching age in the three groups by excluding four of the patients with schizophrenia (two males, two females). Another confounding factor in this study concerning age is that we included teenagers as subjects (7 male controls, 6 female controls, 6 male schizotypal patients, 2 female schizotypal patients, 1 male schizophrenic patient, and 3 female schizophrenic patients), since the brain, particularly the white matter is not fully developed at this age (Paus et al. 1999). This might have interfered with the results. A third limitation is that the control subjects in the present study were not selected to be educationally equivalent to the patients with both disorders. However, we optimally matched the parental education among the three groups according to the notion that matching on the basis of the educational level of the parents may reduce confounding factors in selection of control groups when brain measures are studied (Andreasen et al. 1990). In addition to these limitations, the relatively small sample of patients with schizotypal disorder also limits our 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 ACG volume in patients with schizotypal disorder.

In summary, the present results suggest that both schizotypal and schizophrenic subjects may share, at least in part, the same cerebral asymmetry abnormalities. It is also suggested that additional changes in ACG anatomy may occur during the prodromal period and/or after the onset of schizophrenia in individuals predisposed to this illness.

Acknowledgments This study was supported in part by a Research Grant (11–3) for Nervous and Mental Disorders from the Ministry of Health and Welfare (Japan).

References

1. Albanese AM, Merlo AB, Mascitti TA, Tornese EB, Gómez EE, Konopka V, Albanese EF (1995) Inversion of the hemispheric laterality of the anterior cingulate gyrus in schizophrenics. Biol Psychiatry 38:13–21
2. Alpert NM, Berdichevsky D, Levin Z, Morris ED, Fischman AJ (1996) Improved methods for image registration. Neuroimage 3:10–18
3. American Psychiatric Association (1994) Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. American Psychiatric Association Press, Washington, DC
4. Andreasen NC (1984a) The Scale for the Assessment of Negative Symptoms (SANS). University of Iowa, Iowa City, Iowa
5. Andreasen NC (1984b) The Scale for the Assessment of Positive Symptoms (SAPS). University of Iowa, Iowa City, Iowa
6. Andreasen NC, Ehrhardt JC, Swayze II VW, Alliger RJ, Yuh WT, Cohen G, et al. (1990) Magnetic resonance imaging of the brain in schizophrenia: the pathophysiologic significance of structural abnormalities. Arch Gen Psychiatry 47:35–45
7. Andreasen NC, Flaum M, Arndt S (1992) The Comprehensive Assessment of Symptoms and History (CASH): an instrument for assessing diagnosis and psychopathology. Arch Gen Psychiatry 49:615–623
8. Baleydier C, Mauguiere F (1980) The duality of the cingulate gyrus in monkey. Brain 103:525–554
9. Bilder RM, Wu H, Bogerts B, Degreef G, Ashtari M, Alvir JMJ, Snyder PJ, Lieberman JA (1994) Absence of regional hemispheric volume asymmetries in first-episode schizophrenia. Am J Psychiatry 151:1437–1447
10. Bryant NL, Buchanan RW, Vladar K, Breier A, Rothman M (1999) Gender differences in temporal lobe structures of patients with schizophrenia: a volumetric MRI study. Am J Psychiatry 156: 603–609
11. Buchsbaum MS, Trestman RL, Hazlett E, Siegel BV Jr, Schaefer CH, Luu-Hsia C, Tang C, Herrera S, Solimando AC, Losonczy M, Serby M, Silverman J, Siever LJ (1997a) Regional cerebral blood flow during the Wisconsin Card Sort Test in schizotypal personality disorder. Schizophr Res 27:21–28
12. Buchsbaum MS, Yang S, Hazlett E, Siegel BV Jr, Germans M, Haznedar M, O'Flaithbheartaigh S, Wei T, Silverman J, Siever LJ (1997b) Ventricular volume and asymmetry in schizotypal personality disorder and schizophrenia assessed with magnetic resonance imaging. Schizophr Res 27:45–53
13. Buchsbaum MS, Nenadic I, Hazlett E, Spiegel-Cohen J, Fleischman MB, Akhavan A, Silverman J, Siever LJ (2002) Differential metabolic rates in prefrontal and temporal Brodmann areas in schizophrenia and schizotypal personality disorder. Schizophr Res 54:141–150
14. Byne W, Buchsbaum MS, Kemether E, Hazlett EA, Shinwari A, Mitropoulou V, Siever LJ (2001) Magnetic resonance imaging of the thalamic mediodorsal nucleus and pulvinar in schizophrenia and schizotypal personality disorder. Arch Gen Psychiatry 58: 133–140
15. Cadenhead KS, Perry W, Shafer K, Braff DL (1999) Cognitive functions in schizotypal personality disorder. Schizophr Res 37:123–132
16. Chakos MH, Lieberman JA, Alvir J, Bilder R, Ashtari M (1995) Caudate nuclei volumes in schizophrenic patients treated with typical antipsychotics and clozapine. Lancet 345:456–457
17. Condray R, Steinhauer SR (1992) Schizotypal personality disorder in individuals with and without schizophrenic relatives: similarities and contrasts in neurocognitive and clinical functioning. Schizophr Res 7:33–41
18. Crow TJ, Ball J, Bloom SR, Brown R, Bruton CJ, Colter N, Frith CD, Johnstone EC, Owens DGC, Roberts GW (1989) Schizophrenia as an anomaly of development of cerebral asymmetry: a postmortem study and a proposal concerning the genetic basis of the disease. Arch Gen Psychiatry 46:1145–1150
19. Crow TJ (1990) Temporal lobe asymmetries as the key to the etiology of schizophrenia. Schizophr Bull 16:433–443
20. DeLisi LE, Sakuma M, Kushner M, Finer DL, Hoff AL, Crow TJ (1997a) Anomalous cerebral asymmetry and language processing in schizophrenia. Schizophr Bull 23:255–271
21. DeLisi LE, Sakuma M, Tew W, Kushner M, Hoff AL, Grimson R (1997b) Schizophrenia as a chronic active brain process: a study of progressive brain structural change subsequent to the onset of schizophrenia. Psychiatry Res Neuroimaging 74:129–140

22. Devinsky O, Morrell MJ, Vogt BA (1995) Contributions of anterior cingulate cortex to behavior. Brain 118:279–306
23. Dickey CC, McCarley RW, Voglmaier MM, Niznikiewicz MA, Seidman LJ, Hirayasu Y, Fischer I, Teh EK, Van Rhoads R, Jakab M, Kikinis R, Jolesz FA, Shenton ME (1999) Schizotypal personality disorder and MRI abnormalities of temporal lobe gray matter. Biol Psychiatry 45:1393–1402
24. Dickey CC, Shenton ME, Hirayasu Y, Fischer I, Voglmaier MM, Niznikiewicz MA, Seidman LJ, Fraone S, McCarley RW (2000) Large CSF volume not attributable to ventricular volume in schizotypal personality disorder. Am J Psychiatry 157:48–54
25. Diforio D, Walker EF, Kestler LP (2000) Executive functions in adolescents with schizotypal personality disorder. Schizophr Res 42:125–134
26. Downhill JE Jr, Buchsbaum MS, Hazlett EA, Barth S, Lees Roitman S, Nunn M, Lekarev O, Wei T, Shihabuddin L, Mitropoulou V, Silverman J, Siever LJ (2001) Temporal lobe volume determined by magnetic resonance imaging in schizotypal personality disorder and schizophrenia. Schizophr Res 48:187–199
27. Eritaia J, Wood SJ, Stuart GW, Bridle N, Dudgeon P, Maruff P, Velakoulis D, Pantelis C (2000) An optimal method for estimating intracranial volume from magnetic resonance images. Magn Reson Med 44:973–977
28. Gur RC, Mozley LH, Mozley PD, Resnick SM, Karp JS, Alavi A, Arnold SE, Gur RE (1995) Sex differences in regional cerebral glucose metabolism during a resting state. Science 267:528–531
29. Gur RE, Cowell P, Turetsky BI, Gallacher F, Cannon T, Bilker W, Gur RC (1998) A follow-up magnetic resonance imaging study of schizophrenia. Arch Gen Psychiatry 55:145–152
30. Hazlett EA, Buchsbaum MS, Byne W, Wei T, Spiegel-Cohen J, Geneve C, Kinderlehrer R, Haznedar MM, Shihabuddin L, Siever LJ (1999) Three-dimensional analysis with MRI and PET of the size, shape, and function of the thalamus in the schizophrenia spectrum. Am J Psychiatry 156:1190–1199
31. Highley JR, Esiri MM, McDonald B, Cortina-Borja M, Cooper SJ, Herron BM, Crow TJ (1998) Anomalies of cerebral asymmetry in schizophrenia interact with gender and age of onset: a post-mortem study. Schizophr Res 34:13–25
32. Highley JR, McDonald B, Walker MA, Esiri MM, Crow TJ (1999) Schizophrenia and temporal lobe asymmetry: a post-mortem stereological study of tissue volume. Br J Psychiatry 175:127–134
33. Keshavan MS, Bagwell WW, Haas GL, Sweeney JA, Schooler NR, Pettegrew JW (1994) Changes in caudate volume with neuroleptic treatment. Lancet 344:1434
34. Keshavan MS, Haas GL, Kahn CE, Aguilar E, Dick EL, Schooler NR, Sweeney JA, Pettegrew JW (1998) Superior temporal gyrus and the course of early schizophrenia: progressive, static, or reversible?. J Psychiatr Res 32:161–167
35. Lawrie SM, Abukmeil SS (1998) Brain abnormality in schizophrenia: a systematic and quantitative review of volumetric magnetic resonance imaging studies. Br J Psychiatry 172: 110–120
36. McDonald B, Highley JR, Walker MA, Herron BM, Cooper SJ, Esiri MM, Crow TJ (2000) Anomalous asymmetry of fusiform and parahippocampal gyrus gray matter in schizophrenia: a postmortem study. Am J Psychiatry 157:40–47
37. Nasrallah HA, Schwarzkopf SB, Olson SC, Coffman JA (1990) Gender differences in schizophrenia on MRI brain scans. Schizophr Bull 16:205–210
38. Overall JE, Gorham DR (1962) The brief psychiatric rating scale. Psychol Rep 10:799–812
39. Paus T, Otaky N, Caramanos Z, MacDonald D, Zijdenbos A, D'avirro D, Gutmans D, Holmes C, Tomaiuolo F, Evens AC (1996) In vivo morphometry of the intrasulcal gray matter in the human cingulate, paracingulate, and superior-rostal sulci: hemispheric asymmetries, gender differences and probability maps. J Comp Neurol 376:664–673
40. Paus T, Zijdenbos A, Worsley K, Collins DL, Blumenthal J, Giedd JN, Rapoport JL, Evans AC (1999) Structural maturation of neural pathways in children and adolescents: in vivo study. Science 283:1908–1911
41. Pearlson GD, Marsh L (1999) Structural brain imaging in schizophrenia: a selective review. Bilo Psychiatry 46:627–649
42. Perlmutter JS, Powers WJ, Herscovitch P, Fox PT, Raichle ME (1987) Regional asymmetries of cerebral blood flow, blood volume, and oxygen utilization and extraction in normal subjects. J Cereb Blood Flow Metab 7:64–67
43. Pujol J, López A, Deus J, Cardoner N, Vallejo J, Capdevila A, Paus T (2002) Anatomical variability of the anterior cingulate gyrus and basic dimensions of human personality. Neuroimage 15: 847–855
44. Raine A, Sheard C, Reynolds GP, Lencz T (1992) Pre-frontal structural and functional deficits associated with individual differences in schizotypal personality. Schizophr Res 7:237–247
45. Seidman LJ, Faraone SV, Goldstein JM, Goodman JM, Kremen WS, Toomey R, Tourville J, Kennedy D, Makris N, Caviness VS, Tsuang MT (1999) Thalamic and amygdala-hippocampal volume reductions in first-degree relatives of patients with schizophrenia: an MRI-based morphometric analysis. Biol Psychiatry 46:941–954
46. Sharma T, Lancaster E, Sigmundsson T, Lewis S, Takei N, Gurling H, Barta P, Pearlson G, Murray R (1999) Lack of normal pattern of cerebral asymmetry in familial schizophrenic patients and their relatives – The Maudsley family study. Schizophr Res 40: 111–120
47. Siever LJ, Kalus OF, Keefe RSE (1993) The boundaries of schizophrenia. Psychiatr Clin North Am 16:217–244
48. Siever LJ, Rotter M, Losonczy M, Guo SL, Mitropoulou V, Trestman R, Apter S, Zemishlany Z, Silverman J, Horvath TB, Davidson M, Mohs R, Davis KL (1995) Lateral ventricular enlargement in schizotypal personality disorder. Psychiatry Res 57:109–118
49. Siever LJ, Koenigsberg HW, Harvey P, Mitropoulou V, Laruelle M, Abi-Dargham A, Goodman M, Buchsbaum M (2002) Cognitive and brain function in schizotypal personality disorder. Schizophr. Res 54:157–167
50. Silverman JM, Smith CJ, Guo SL, Mohs RC, Siever LJ, Davis KL (1998) Lateral ventricular enlargement in schizophrenic probands and their siblings with schizophrenia-related disorders. Biol Psychiatry 43:97–106
51. Sumiyoshi T, Kurachi M, Kurokawa K, Yotsutsuji T, Uehara T, Itoh H, Saitoh O (2000) Plasma homovanillic acid in the prodromal phase of schizophrenia. Biol Psychiatry 47:428–433
52. Suzuki M, Nohara S, Hagino H, Kurokawa K, Yotsutsuji T, Kawasaki Y, Takahashi T, Matsui M, Watanabe N, Seto H, Kurachi M (2002) Regional changes in brain gray and white matter in patients with schizophrenia demonstrated with voxel-based analysis of MRI. Schzophr Res 55:41–54
53. Takahashi T, Kawasaki Y, Kurokawa K, Hagino H, Nohar S, Yamashita I, Nakamura K, Murata M, Matsui M, Suzuki M, Seto H, Kurachi M (2002) Lack of normal structural asymmetry of the anterior cingulate gyrus in female patients with schizophrenia: a volumetric magnetic resonance imaging study. Schizophr Res 55:69–81
54. Tamminga CA, Vogel M, Gao X-M, Lahti AC, Holcomb HH (2000) The limbic cortex in schizophrenia: focus on the anterior cingulate. Brain Res Rev 31:364–370
55. Toru M (2001) Psychotropic Manual, Second Edition. IGAKU-SHOIN, Tokyo (in Japanese)
56. Trestman RL, Keefe RSE, Mitropoulou V, Harvey PD, deVegvar ML, Lees-Roitman S, Davidson M, Aronson A, Silverman J, Siever LJ (1995) Cognitive function and biological correlates of cognitive performance in schizotypal personality disorder. Psychiatry Res 59:127–136
57. Turetsky B, Cowell PE, Gur RC, Grossman RI, Shtasel DL, Gur RE (1995) Frontal and temporal lobe brain volumes in schizophrenia: relationship to symptoms and clinical subtype. Arch Gen Psychiatry 52:1061–1070
58. Voglmaier MM, Seidman LJ, Salisbury D, McCarley RW (1997) Neuropsychological dysfunction in schizotypal personality disorder: a profile analysis. Biol Psychiatry 41:530–540

59. Voglmaier MM, Seidman LJ,Niznikiewicz MA, Dickey CC, Shenton ME, McCarley RW (2000) Verbal and nonverbal neuropsychological test performance in subjects with schizotypal personality disorder. Am J Psychiatry 157:787–793
60. Walters GD (1983) The MMPI and schizophrenia: a review. Schizophr Bull 9:226–246
61. World Health Organization (1992) The ICD-10 Classification of Mental and Behavioural Disorders: clinical descriptions and diagnostic guidelines. World Health Organization, Geneva
62. World Health Organization (1993) The ICD-10 Classification of Mental and Behavioural Disorders: Diagnostic Criteria for Research. World Health Organization, Geneva