Eur Arch Psychiatry Clin Neurosci (2004) 254:273–280 DOI 10.1007/s00406-004-0491-4

ORIGINAL PAPER

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

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

A magnetic resonance imaging study

Received: 5 May 2003 / Accepted: 11 December 2003

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

T. Takahashi (✉) · M. Suzuki · S-Y. Zhou · H. Hagino · Y. Kawasaki · I. Yamashita · S. Nohara · K. Nakamura · M. Kurachi
Dept. 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

H. Seto
Dept. of Radiology
Toyama Medical and Pharmaceutical University

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.

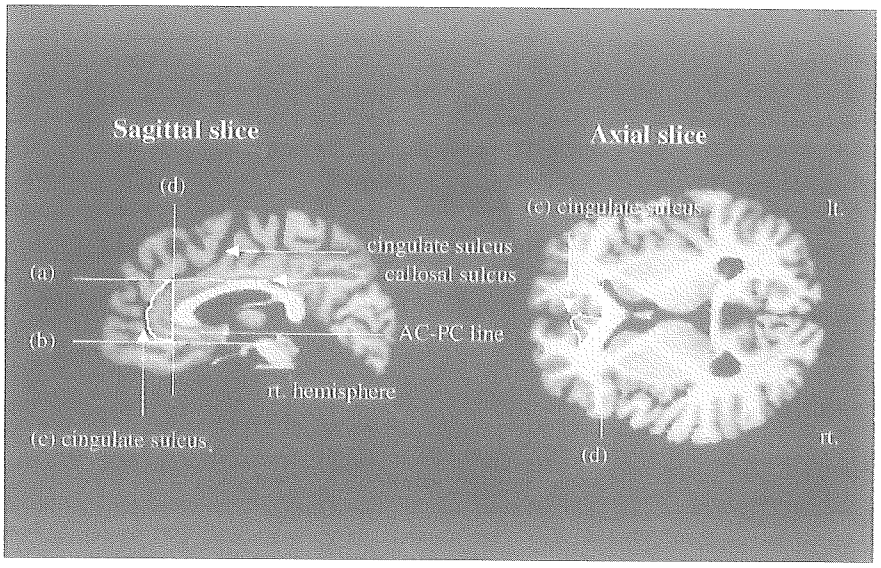

Fig. 1 Boundaries for the perigenual cingulate gyrus. The perigenual cingulate gyrus was traced bilaterally in consecutive axial 1-mm slices parallel to the anterior commissure-posterior commissure (AC-PC) line. The most dorsal axial plane showing the corpus callosum (**a**) and the most ventral axial 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

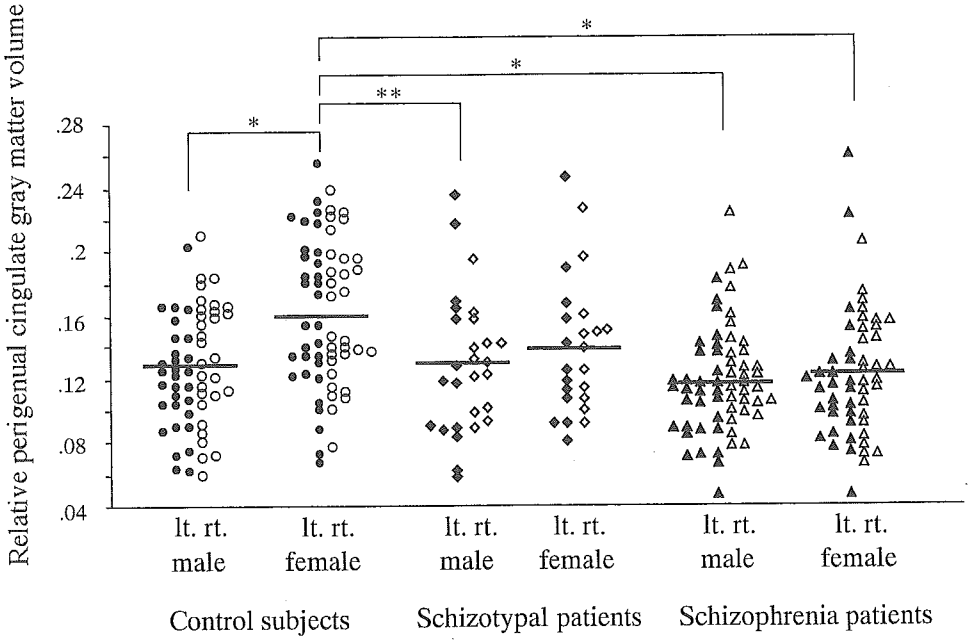

Fig. 2 Relative volume of the perigenual cingulate gray matter in the normal control subjects, patients with schizotypal disorder, and patients with schizophrenia. Horizontal lines indicate mean values. Post hoc Scheffé's test: * $p < 0.01$, ** $p < 0.05$

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.

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. Alpert NM, Berdichevsky D, Levin Z, Morris ED, Fischman AJ (1996) Improved methods for image registration. Neuroimage 3:10–18
2. American Psychiatric Association (1994) Diagnostic and Statistical Manual of Mental Disorders, 4th edn. American Psychiatric Association Press, Washington, DC
3. Andreasen NC (1984a) The Scale for the Assessment of Negative Symptoms (SANS). University of Iowa, Iowa City, Iowa
4. Andreasen NC (1984b) The Scale for the Assessment of Positive Symptoms (SAPS). University of Iowa, Iowa City, Iowa
5. 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
6. Baleydier C, Mauguiere F (1980) The duality of the cingulate gyrus in monkey. Brain 103:525–554
7. Braus DF, Ende G, Weber-Fahr W, Demirakca T, Tost H, Henn FA (2002) Functional and neuronal viability of the anterior cingulate neurons following antipsychotic treatment: MR-spectroscopic imaging in chronic schizophrenia. Eur Neuropsychopharmacol 12:145–152
8. Buchsbaum MS, Yang S, Hazlett E, Siegel Jr BV, Germans M, Haznedar M, O'Flaithbheartaigh S, Wei T, Silverman J, Siever LJ (1997) Ventricular volume and asymmetry in schizotypal personality disorder and schizophrenia assessed with magnetic resonance imaging. Schizophr Res 27:45–53
9. 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
10. 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
11. De Lacoste MC, Holloway RL, Woodward DJ (1986) Sex differences in the fetal human corpus callosum. Hum Neurobiol 5: 93–96
12. De Lacoste MC, Horvath DS, Woodward DJ (1991) Possible sex differences in the developing human fetal brain. J Clin Exp Neuropsychol 13:831–846
13. Devinsky O, Morrell MJ, Vogt BA (1995) Contributions of anterior cingulate cortex to behavior. Brain 118:279–306
14. 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
15. 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
16. Dickey CC, McCarley RW, Shenton ME (2002a) The brain in schizotypal personality disorder: a review of structural MRI and CT findings. Harvard Rev Psychiatry 10:1–15
17. Dickey CC, McCarley RW, Voglmaier MM, Frumin M, Niznikiewicz MA, Hirayasu Y, Fraone S, Seidman LJ, Shenton ME (2002b) Smaller left Heschl's gyrus volume in patients with schizotypal personality disorder. Am J Psychiatry 159:1521–1527
18. Dickey CC, McCarley RW, Voglmaier MM, Niznikiewicz MA, Seidman LJ, Frumin M, Toner S, Demeo S, Shenton ME (2003) A MRI study of fusiform gyrus in schizotypal personality disorder. Schizophr Res 64:35–39
19. Downhill JE Jr, Buchsbaum MS, Wei T, Spiegel-Cohen J, Hazlett EA, Haznedar MM, Silverman J, Siever LJ (2000) Shape and size of the corpus callosum in schizophrenia and schizotypal personality disorder. Schizophr Res 42:193–20
20. 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 48:187–219
21. 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
22. George MS, Ketter TA, Gill DS, Haxby JV, Ungerleider LG, Herscovitch P, Post RM (1993) Brain regions involved in recognizing facial emotion or identity: an oxygen-15 PET study. J Neuropsychol Clin Neurosci 5:384–394

23. George MS, Ketter TA, Parekh PI, Horwitz B, Herscovitch P, Post RM (1995) Brain activity during transient sadness and happiness in healthy women. Am J Psychiatry 152:341–351
24. Goldstein JM, Seidman LJ, O'brien LM, Holton NJ, Kennedy DN, Makris N, Caviness VS Jr, Faraone SV, Tsuang MT (2002) Impact of normal sexual dimorphisms on sex differences in structural brain abnormalities in schizophrenia assessed by magnetic resonance imaging. Arch Gen Psychiatry 59:154–164
25. 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
26. 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
27. 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
28. Haznedar MM, Buchsbaum MS, Luu C, Hazlett EA, Siegel BV Jr, Lohr J, Wu J, Haier RJ, Bunny WE Jr (1997a) Decreased anterior cingulate gyrus metabolic rate in schizophrenia. Am J Psychiatry 154:682–684
29. Haznedar MM, Buchsbaum MS, Metzger M, Solimando A, Spiegel-Cohen J, Hollander E (1997b) Anterior cingulate gyrus volume and glucose metabolism in autistic disorder. Am J Psychiatry 154:1047–1050
30. Job DE, Whalley HC, McConnell S, Glabus M, Johnstone EC, Lawrie SM (2002) Structural gray matter differences between first-episode schizophrenics and normal controls using voxel-based morphometry. Neuroimage 17:880–888
31. Keshavan MS, Bagwell WW, Haas GL, Sweeney JA, Schooler NR, Pettegrew JW (1994) Changes in caudate volume with neuroleptic treatment. Lancet 344:1434
32. 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
33. Kwon JS, Shenton ME, Hirayasu Y, Salisbury DF, Fischer IA, Dickey CC, Yurgelun-Todd D, Tohen M, Kikinis R, Jolesz FA, McCarley RW (1998) MRI study of cavum septi pellucidi in schizophrenia, affective disorder, and schizotypal personality disorder. Am J Psychiatry 155:509–515
34. Lahti AC, Holcomb HH, Weiler MA, Medoff DR, Tamminga CA (2003) Functional effects of antipsychotic drugs: comparing clozapine with haloperidol. Biol Psychiatry 53:601–608
35. Laurens KR, Ngan ETC, Bates AT, Kiehl KA, Liddle PF (2003) Rostral anterior cingulate cortex dysfunction during error processing in schizophrenia. Brain 126:610–622
36. Levitt JJ, McCarley RW, Dickey CC, Voglmaier MM, Niznikiewicz MA, Seidman LJ, Hirayasu Y, Ciszewski AA, Kikinis R, Jolesz FA, Shenton ME (2002) MRI study of caudate nucleus volume and its cognitive correlates in neuroleptic-naive patients with schizotypal personality disorder. Am J Psychiatry 159:1190–1197
37. Pantelis C, Velakoulis D, McGorry PD, Wood SJ, Suckling J, Phillips LJ, Yung AR, Bullmore ET, Brewer W, Soulsby B, Desmond P, McGuire PK (2003) Neuroanatomical abnormalities before and after onset of psychosis: a cross-sectional and longitudinal MRI comparison. Lancet 361:281–288
38. 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-rostral sulci: hemispheric asymmetries, gender differences and probability maps. J Comp Neurol 376:664–673
39. Pearlson GD, Marsh L (1999) Structural brain imaging in schizophrenia: a selective review. Biol Psychiatry 46:627–649
40. Ploghaus A, Narain C, Beckmann CF, Clare S, Bantick S, Wise R, Matthews PM, Rawlins JN, Tracey I (2001) Exacerbation of pain by anxiety is associated with activity in a hippocampal network. J Neurosci 21:9896–9903
41. 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
42. Shenton ME, Dickey CC, Frumin M, McCarley RW (2001) A review of MRI findings in schizophrenia. Schizophr. Res 49:1–52
43. Shihabuddin L, Buchsbaum MS, Hazlett EA, Silverman J, New A, Brickman AM, Mitropoulou V, Nunn M, Fleischman MB, Tang C, Siever LJ (2001) Striatal size and relative glucose metabolic rate in schizotypal personality disorder and schizophrenia. Arch Gen Psychiatry 58:877–884
44. Siever LJ, Kalus OF, Keefe RSE (1993) The boundaries of schizophrenia. Psychiatr Clin North Am 16:217–244
45. 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
46. 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
47. 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
48. 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. Schizophr Res 55:41–54
49. Takahashi T, Kawasaki Y, Kurokawa K, Hagino H, Nohara S, Yamashita I, Nakamura K, Murata M, Matsui M, Suzuki M, Seto H, Kurachi M (2002a) 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
50. Takahashi T, Suzuki M, Kawasaki Y, Kurokawa K, Hagino H, Yamashita I, Zhou SY, Nohara S, Nakamura K, Seto H, Kurachi M (2002b) Volumetric magnetic resonance imaging study of the anterior cingulate gyrus in schizotypal disorder. Eur Arch Psychiatry Clin Neurosci 252:268–277
51. Takahashi T, Suzuki M, Kawasaki Y, Hagino H, Yamashita I, Nohara S, Nakamura K, Seto H, Kurachi M (2003) Perigenual cingulate gyrus volume in patients with schizophrenia: a magnetic resonance imaging study. Biol Psychiatry 53:593–600
52. Tibbo P, Nopoulos P, Arndt S, Andreasen NC (1998) Corpus callosum shape and size in male patients with schizophrenia. Biol Psychiatry 44:405–412
53. Toru M (2001) Psychotropic Manual, Second Edition. IGAKU-SHOIN, Tokyo (in Japanese)
54. Whalen PJ, Bush G, McNally RJ, Wilheim S, McInerney SC, Jenike MA, Rauch SL (1998) The emotional counting Stroop paradigm: a functional magnetic resonance imaging probe of the anterior cingulate affective division. Biol Psychiatry 44:1219–1228
55. Woodruff PWR, Pearlson GD, Geer MJ, Barta PE, Chilcoat HD (1993) A computerized magnetic resonance imaging study of corpus callosum morphology in schizophrenia. Psychol Med 23: 45–56
56. Woodruff PWR, McManus IC, David AS (1995) Meta-analysis of corpus callosum size in schizophrenia. J Neurol Neurosurg Psychiatry 58:457–461
57. World Health Organization (1992) The ICD-10 Classification of Mental and Behavioural Disorders: clinical descriptions and diagnostic guidelines. World Health Organization, Geneva
58. World Health Organization (1993) The ICD-10 Classification of Mental and Behavioural Disorders: Diagnostic Criteria for Research. World Health Organization, Geneva
59. Yamasue H, Fukui T, Yamada H, Yamasaki S, Kuroki N, Abe O, Kasai K, Tsujii K, Iwanami A, Aoki S, Ohtomo K, Kato N, Kato T (2002) ^{1}H-MR spectroscopy and gray matter volume of the anterior cingulate cortex in schizophrenia. Neuroreport 13:2133–2137

Available online at www.sciencedirect.com

SCIENCE DIRECT®

ELSEVIER

Schizophrenia Research 74 (2005) 91–100

SCHIZOPHRENIA RESEARCH

www.elsevier.com/locate/schres

Disorganization of semantic memory underlies alogia in schizophrenia: An analysis of verbal fluency performance in Japanese subjects

Chika Sumiyoshi[a,*], Tomiki Sumiyoshi[b,c], Shigeru Nohara[b], Ikiko Yamashita[b], Mié Matsui[d], Masayoshi Kurachi[b], Shinichi Niwa[e]

[a]*Faculty of Education, Department of Developmental and Clinical Psychology, Fukushima University, 1 Kanayagawa, Fukushima 960-1296, Japan*

[b]*Department of Neuropsychiatry, Toyama Medical and Pharmaceutical University School of Medicine, Toyama, Japan*

[c]*Department of Psychiatry, Vanderbilt University School of Medicine, Nashville, TN, USA*

[d]*Department of Psychology, Toyama Medical and Pharmaceutical University School of Medicine, Toyama, Japan*

[e]*Department of Neuropsychiatry, Fukushima Medical University, School of Medicine, Fukushima, Japan*

Received 15 March 2004; received in revised form 26 May 2004; accepted 26 May 2004
Available online 28 July 2004

Abstract

Patients with schizophrenia exhibit impaired semantic memory as well as deficits in a wide range of language-related functions, such as verbal fluency, comprehension and production of complex sentences. Since language and memory disturbances may underlie some of the psychotic symptoms of schizophrenia, the present study investigated the specific association between alogia (i.e. poverty of speech, poverty of content of speech, blocking, and increased latency of response) and semantic memory organization using the category fluency task (CFT) as a measure of verbal fluency. Thirty-eight patients with schizophrenia and an equal number of normal controls entered the study. Semantic structure was derived from multidimensional scaling analysis using sequential word outputs from the CFT. Patients with schizophrenia revealed disorganized semantic structure (e.g. irregular association of category members) compared with controls, consistent with previous reports. The patients were then divided into two groups, i.e. alogia- and non-alogia subjects, based on the Alogia scores from the Scale for the Assessment of Negative Symptoms (SANS). The symptom-based analysis showed that the semantic structure for the alogia group (Alogia score ≥ 2) was more disorganized than that for the non-alogia group (Alogia score ≤ 1) although the number of words produced did not differ between the two groups. The results of cluster analysis revealed the presence of bizarre coherence specifically in the alogia group. These results indicate that semantic memory disorganization may contribute to the symptom of alogia in schizophrenia. In addition, this is one of the few studies that examined verbal

* Corresponding author. Current address: Faculty of Education, Department of Developmental and Clinical Psychology, Fukushima University, 1 Kanayagawa, Fukushima, Fukushima 960-1296, Japan. Tel.: +81 24 548 8161; fax: +81 24 548 8161.

E-mail address: sumiyoshi@educ.fukushima-u.ac.jp (C. Sumiyoshi).

0920-9964/$ - see front matter
doi:10.1016/j.schres.2004.05.011

fluency in Japanese patients with schizophrenia and suggest that the language abnormalities in schizophrenia are universal.

Keywords: Category fluency; Semantic structure; Alogia; Schizophrenia; Multidimensional scaling analysis; Cluster analysis

1. Introduction

Patients with schizophrenia exhibit a wide range of the language-related disorders, including speech comprehension, semantic or grammar consistency, verbal fluency, and sentence complexity (for a review, see DeLisi, 2001). However, the mechanisms underlying these deficits, a core feature of schizophrenia, have not yet been fully clarified. DeLisi (2001) suggested that the language-related disturbances originate either from dysfunctions of the language ability specific to humans, or from more general cognitive deficits such as executive and/or memory dysfunction. The verbal fluency tasks (VFTs) are useful to assess such manifold disorders, as they evaluate both executive and semantic memory functions requiring language skills such as quick and spontaneous word production. Because of their versatility, the VFTs have been used to predict the functional outcomes and quality of life in patients with schizophrenia (Buchanan et al., 1994; Green, 1996; McGurk and Meltzer, 2000).

Typically, two types of the VFTs are used in the clinical assessment. One is the category fluency task (CFT), in which subjects are instructed to produce as many words of a certain category (e.g. dog, cat... etc. for the ANIMAL category) as possible within a designated time (e.g. 1 min). The other is the letter fluency task (LFT), in which an initial letter is given as a cue (e.g. F, A, S); subjects are requested to produce the words beginning with one of the letters (e.g. *f*lower, *f*urniture,... etc. for the "F" cue). The time limitation requires subjects to concentrate on the quick search, retrieval, and monitoring of verbal outputs with a minimal amount of intrusion and repetition. Thus, the CFT and LFT have been considered to be useful to assess an aspect of executive function. The CFT has also been used to evaluate semantic memory organization in patients with schizophrenia, as well-formed semantic associations based on certain criteria (e.g. size, domesticity, predation) are necessary to maximize production of words belonging to a certain category. Previous studies (Aloia et al., 1996; Moelter et al., 2001; Paulsen et al., 1996; Rossell et al., 1999; Sumiyoshi et al., 2001) visualized semantic organization in the form of a "map" that is derived from the multidimensional scaling (MDS) analysis (Kruskal and Wish, 1978) by using sequential verbal outputs from the CFT.

Several investigations have indicated that verbal fluency performance is affected by cognitive or demographic status in patients with schizophrenia. For example, the severity of impairment in organization of semantic memory has been shown to be dependent, in part, on age at onset of the illness (Paulsen et al., 1996; Sumiyoshi et al., 2001). Others report that the number of words produced in the LFT (Bolla et al., 1990; Cauthen, 1978; Crawford et al., 1993) or CFT (Sumiyoshi et al., 2001) depends on verbal intelligence in patients with schizophrenia. Furthermore, we have recently found the degree of impairment in the performance on the LFT depends on the orthography systems (e.g. alphabetical versus non-alphabetical) used by patients (Sumiyoshi et al., 2004).

Attempts have been made to find the relationship between positive or negative psychotic symptoms of schizophrenia and verbal fluency performance. Thus, patients with severe thought disorders have been reported to show overall deficits in verbal fluency performance (Kuperberg et al., 1998) or selective impairment in the performance on the CFT (Aloia et al., 1996; Feinstein et al., 1998; Goldberg et al., 1998; Gourovitch et al., 1996). Several studies (Allen et al., 1993; Howanitz et al., 2000) have indicated that negative symptoms as a whole also inhibit rigorous word productions in patients with schizophrenia. On the other hand, specific domains of negative symptoms, such as withdrawal-retardation (Mahurin et al.,

1998) and alogia representing "difficulties in fluent and logical thinking", (i.e. poverty of speech, poverty of content of speech, blocking, and increased latency of response) have been reported to be associated with verbal fluency performance (Joyce et al., 1996; Stolar et al., 1994; Sumiyoshi et al., 2004). Specifically, Joyce et al. (1996) found a significant negative correlation between the Alogia score from the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1984a) and the enhancement of verbal outputs by cueing. Stolar et al. (1994) also reported that the severity of alogia, but not affective flattening, was negatively correlated with the number of words produced. Overall, these findings suggest that the reduction of verbal outputs in the CFT is related with the alogia symptoms in patients with schizophrenia. However, the specific association between organization of semantic memory, as measured by the CFT, and alogia symptoms has never been examined.

The purpose of the present study was to investigate the relation between psychotic symptoms, specifically alogia, and the degradation of semantic memory organization in patients with schizophrenia. Based on the previous findings, as discussed above, we hypothesized that schizophrenia subjects with severe alogia symptoms would exhibit more disturbed semantic memory organization compared to those with less alogia. Firstly, multiple regression analysis was conducted to examine the correlation between psychotic symptoms, as assessed by the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984b) and SANS, and word production as measured by the VFTs. Next, multidimensional scaling (MDS) analysis, using data from the CFT, was performed evaluate the semantic structure in patients with schizophrenia as a whole. Finally, we compared semantic structures between patients with severe alogia and those with less alogia by applying MDS and cluster analyses.

2. Method

2.1. Subjects

Thirty-eight subjects (male/female=20/18) who met DSM-IV criteria (American Psychiatric Association, 1994) for schizophrenia, and an equal number of normal control volunteers entered the study. They were recruited from Toyama Medical and Pharmaceutical University Hospital and Fukushima Medical University Hospital. Diagnosis was made by experienced psychiatrists using medical history and all available information. Patients known to be abusing alcohol or other illicit drugs, or those with epilepsy, brain damage, or neurologic disorders, were excluded from the study. The dose of concurrently administered neuroleptics was converted into the equivalent amount of haloperidol in milligrams per day. The volunteers, who did not meet any criteria for DSM-IV disorders, were recruited as normal controls. Both patients and normal controls were provided with a detailed description of the study, and gave written informed consent. This study was approved by the Institutional Review Board at each site. The Vocabulary and Block Design subtests from the WAIS-R (Wechsler, 1981) were administered to most patients (N=36) and all normal controls to assess the level of intelligence. The two subtests were chosen because they are considered to be representative of verbal- and performance intelligence, respectively (Silverstein, 1982).

2.2. Procedure

The CFT and LFT, as well as the subtests from the WAIS-R, were administered by well-trained psychologists. SAPS and SANS were administered by experienced psychologists or stuff doctors. The intra-class correlations for these psychopathology measures were higher than 0.80 (Sumiyoshi et al., 2001a,b). The instruction of the VFTs followed the usual norm (Spreen and Strauss, 1998); subjects were asked to produce as many words as possible within 1 min. The verbatim responses were recorded by the examiners in the generated order. ANIMAL and FRUIT were used for the cues in the CFT, while "KA" and "TA" were used for the LFT according to our previous study (Sumiyoshi et al., 2004). These letters were chosen because the frequency of words beginning with "KA" was higher than that of "TA" in the Japanese lexicon (Amano and Kondo, 2000). This frequency contrast was analogous to that between "S" and "F" in the FAS form of the LFT in English.

2.3. Data analysis

Multivariate analysis of variance (MANOVA) was conducted to compare the demographic and cognitive variables between normal controls and patients with schizophrenia. The number of words generated in the VFTs was analyzed by two-way analysis of variance (ANOVA) with the group (patients versus normal controls) as between-subject factor and task type (ANIMAL versus FRUIT versus KA versus TA) as within-subject factor. Multiple comparisons by Bonferroni/Dunn method were conducted when the main effect was significant.

For multiple regression analysis, the subscales of SAPS and SANS were classified into the following four domains; (1) Positive Symptom factor (delusions and hallucinations), (2) Disorganization factor (bizarre behavior and positive formal thought disorder), (3) Negative Symptom factor (affective flattening or blunting, avolition-apathy, anhedonia-associality, and attention), and (4) Alogia factor (alogia). The classification was based on previous studies of the relationship between verbal fluency performance and psychotic symptoms (Allen et al., 1993; Aloia et al., 1996; Feinstein et al., 1998; Goldberg et al., 1998; Howanitz et al., 2000; Joyce et al., 1996; Kuperberg et al., 1998; Mahurin et al., 1998; Rossell et al., 1999; Stolar et al., 1994). Because the max values differed between factors, raw scores were converted into the percentage score. Then, angular transformation was applied to the percentage scores for further analyses. Four independent multiple regression analyses for each task score (i.e. ANIMAL, FRUIT, "KA", and "TA") were conduced using the four psychosis domains (i.e. positive symptoms, disorganization, negative symptoms, alogia) as independent variables.

In the subgroup analysis, the patients were divided into two groups according to the Alogia score from the SANS (the sum of Poverty of Speech, Poverty of Content of Speech, Blocking, and Increased latency of Speech; MAX=20). The "alogia group" consisted of patients who showed an Alogia score of more than 1. The "non-alogia group" included patients with the Alogia score of 0 or 1. The mean Alogia score, as well as the demographic and cognitive variables, for these two subgroups are summarized in Table 1. The Alogia scores of the two groups were compared by *t*-test. In order to determine the difference in severity of language-related positive symptoms, scores of the Positive Formal Thought Disorder subscale from the SAPS (i.e. Tangentiality, Incoherence, Illogicality, Circumstantiality, Pressure of Speech, Distractible Speech, and Clanging; MAX=40) were also compared between alogia group and non-alogia group by *t*-test. MANOVA and two-way ANOVA were conducted for other variables.

Table 1
Demographic and cognitive variables for alogia- and non-alogia patients

	Alogia patients (N=21)	Non-alogia patients (N=17)
Male/female	8/13	9/8
Age (years)	27.17 (9.10)	34.18 (10.02)*,[a]
Education (years)	13.40 (2.60)	13.50 (2.16)
Neuroleptic dose (mg/day)[b]	9.71 (8.12)	8.58 (8.52)
Onset of illness (years)	20.48 (7.01)	22.33 (10.35)
Duration of illness (years)	6.09 (7.03)	12.00 (9.42)
SANS Alogia score	4.90 (3.01)**,[c]	0.18 (0.38)
Block Design (WAIS-R)	8.95 (2.97)	9.87 (3.58)
Vocabulary (WAIS-R)	8.33 (2.87)	9.27 (2.82)
CFT		
ANIMAL	14.57 (5.16)	16.59 (3.65)
FRUIT	10.11(3.03)	11.06 (3.68)
LFT		
"KA"	9.15 (4.22)	9.63 (3.62)
"TA"	8.05 (3.92)	9.38 (3.35)

WAIS-R, Wechsler Adult Intelligence Scale-Revised. CFT, Category Fluency Task; LFT, Letter Fluency Task; SANS, Scale for Assessment of Negative Symptoms. Values represent mean (standard deviation).

[a] Results from MANOVA.
[b] Haloperidol equivalent.
[c] Results from *t*-test.
* $p<0.05$.
** $p<0.01$.

MDS analysis was conducted to visualize semantic structures using data from the CFT. Hierarchical cluster analysis was performed to examine the coherence of the category items in the semantic structures for the alogia group and non-alogia group, respectively. In MDS and cluster analyses, specific algorithm was used to obtain the dissimilarity matrices from the sequential verbal outputs from the CFT. The details of the algorithm have been described in previous studies (Chan et al., 1993; Paulsen et al., 1996; Sumiyoshi et al., 2001). MDS and cluster analyses were carried out using SPSS version 10.0. Interval scales were applied for MDS analysis while the average linkage method was used for cluster analysis.

3. Results

3.1. Comparison between normal controls and schizophrenia patients

The results of MANOVA revealed a significant group difference between normal controls and patients with schizophrenia (Wilks' lambda=0.85, F=3.14, df=4,69, p<0.05). Normal controls outperformed the patients in the Block Design (normal controls=11.90 (S.D.=2.81), patients=9.32 (3.19); F=10.73, df=1,72, p<0.01) and Vocabulary (normal controls=11.50 (2.64), patients=9.33 (2.23); F=3.84, df=1,72=3.84, p<0.05). On the other hand, age (normal controls=29.50 (11.40), patients=30.30 (10.03); F=0.01, df=1,72, *n.s.*) and education (normal controls=14.18 (1.55), patients=13.45 (2.37); F=1.92, df=1,72, *n.s.*) did not differ between the two groups. As for the performance on the VFTs, normal controls (ANIMAL=18.95 (3.86), FRUIT=13.71 (3.26), KA=12.07 (3.54), TA=10.10 (2.01)) produced more words than the patients (ANIMAL=15.47 (4.66), FRUIT=10.56 (3.39), KA=9.36 (3.97), TA=8.62 (3.74)). ANOVA revealed significant main effects of group (F=10.44, df=1,61 p<0.01) and task type (F=98.74, df=3, 183, p<0.01) factors. Multiple comparisons of task type factor revealed significant differences between ANIMAL versus other tasks (p<0.01), FRUIT versus TA task (p<0.01), and KA versus TA (p<0.01) task.

The correlation coefficients between the VFT scores and the four symptom domains are presented in Table 2. Significant multiple regression models were derived only from the ANIMAL and TA scores. The Alogia factor remained as a significant independent variable in the model of the ANIMAL score (B=−3.67, t=−2.37, p<0.05), while the Negative factor was significant (B=−3.67, t=−2.35, p<0.05) in the model of the TA score.

Table 2
Correlation coefficients between verbal fluency scores and psychotic symptoms

	Animal	Fruit	KA	TA
POSITIVE	−0.11	−0.46	−2.44	−0.21
DISORG.	−0.09	0.09	0.1	0.02
NEGATIVE	−0.29*	−0.01	−0.28*	−0.37**,[a]
ALOGIA	−0.37**,[a]	−0.21	−0.05	−0.17

POSITIVE, positive symptom domains; DISORG., disorganization. NEGATIVE, negative symptom domains.
[a] Significant predictive variables in multiple regression models.
* p<0.05.
** p<0.01.

For the MDS analysis, 11 animals (CAT, DOG, COW, BEAR, ELEPHANT, GIRAFFE, LION, HORSE, MONKEY, TIGER, RABBIT) were selected based on the verbal outputs in the CFT; they were most frequently produced across the two groups. The semantic structures based on those items are presented in Fig. 1. Normal control subjects yielded a wild-domestic dimension (as the vertical axis: Fig. 1, left) while no clear dimension was detected in the patients (Fig. 1, right). Although the stress values were not so much different between the two groups, the RSQ value for the normal controls was greater than that for the patients (Fig. 1), suggesting a better-fit configuration for the normal control group.

3.2. Comparison between alogia- and non-alogia patients

The results of comparisons of demographic and cognitive variables between the alogia- and non-alogia patients are presented in Table 1. The Alogia score for the alogia group was significantly higher than that for the non-alogia group (t=6.27, df=36, p<0.01). On the other hand, scores of the Positive Formal Thought Disorder subscale from the SAPS did not significantly differ between the two groups (alogia group=2.05 (5.51), non-alogia group=2.18 (3.11); t=0.09, df=36, *n.s.*). MANOVA showed no overall group difference (Wilks' lambda=0.79, F=2.11, df=4,31, *n.s.*) although age was significantly higher for the non-alogia group (F=4.72, df=1,34, p<0.05). The numbers of words produced in the CFT and LFT are also shown in Table 1. ANOVA revealed that task (F=53.03, df=3,93, p<0.01) but not group (F=0.35, df=1,31, *n.s.*) effect was significant, indicating verbal outputs did not differ significantly between the two groups for any measure of the VFTs.

The organization of semantic structure, as revealed by MDS analysis, is shown in Fig. 2. The most frequently produced 11 animals (CAT, DOG, BEAR, ELEPHANT, GIRAFFE, LION, HORSE, MONKEY, TIGER, RABBIT, SHEEP) across the two groups were chosen for the analysis. In the semantic configuration of the non-alogia group, carnivorous animals were located in the left and herbivorous ones

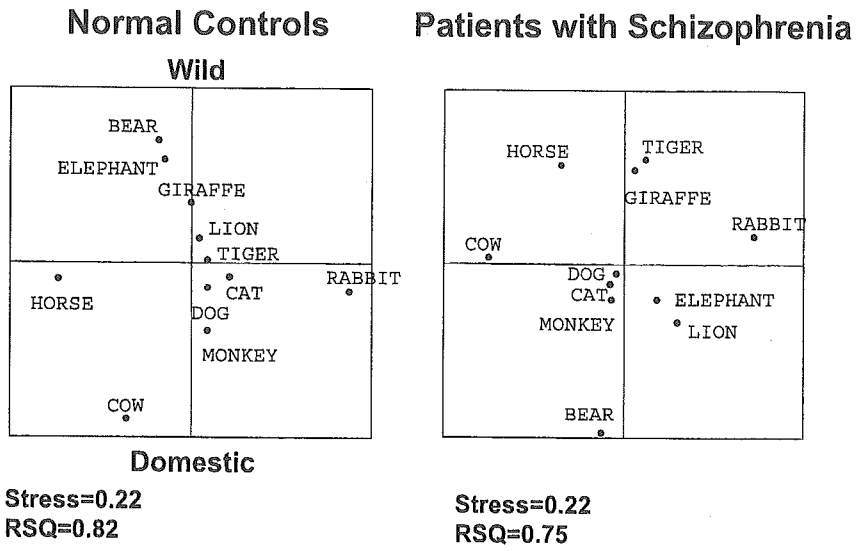

Fig. 1. Two-dimensional semantic structure as revealed by multidimensional scaling analysis in normal controls (N=38; left) and patients with schizophrenia (N=38; right).

in the right, thus creating a predation dimension (Fig. 2, left). On the other hand, no meaningful dimension was observed in the alogia group (Fig. 2, right).

The qualitative difference in the organization of semantic structure between the two groups of patients with schizophrenia became more apparent by cluster analysis. The circles in Fig. 2 represent highly cohesive clusters. In the non-alogia group, the clusters did not seem to represent specific meanings. On the other hand, the alogia group demonstrated oddly coherent clusters. For example, DOG and ELEPHANT made one cluster while CAT and MONKEY formed another one, and so on.

4. Discussion

The results of the present study confirmed the relationship between alogia symptoms and the performance on the VFTs in patients with schizophrenia. The Alogia factor remained as a significant independent variable in multiple regression analysis of the

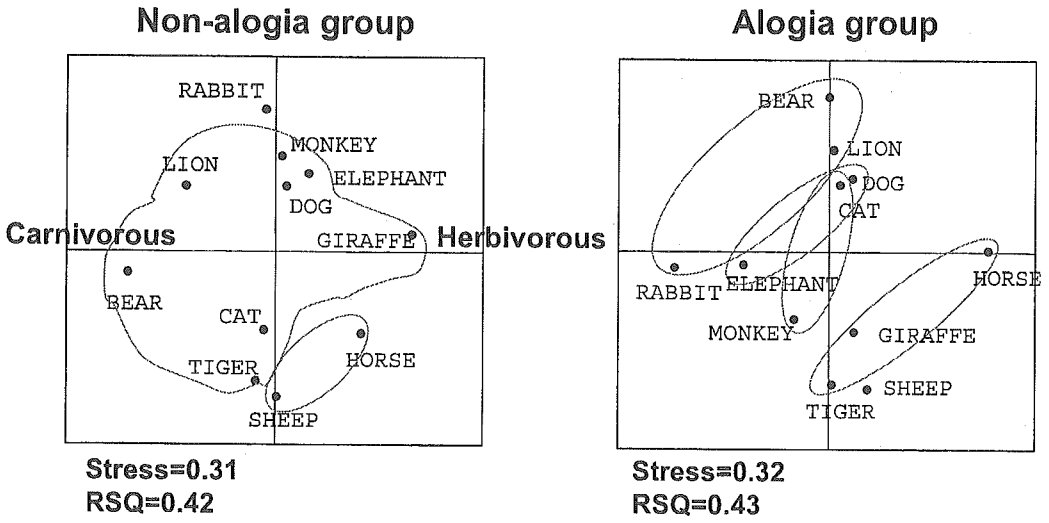

Fig. 2. Two-dimensional semantic structure for non-alogia (N=21; left) and alogia (N=17; right) patients with schizophrenia. The circles represent highly cohesive assemblies as revealed by cluster analysis.

ANIMAL score, indicating rigorous search of words in the CFT is negatively correlated with severity of alogia symptoms. The selective association of negative, but not positive, symptoms of schizophrenia with the degradation of semantic memory was further supported by the lack of difference in scores of the positive Formal Thought Disorder Subscale from SAPS between subjects with alogia symptoms and those without alogia. MDS analysis demonstrated that the semantic structure in patients with alogia symptoms had no meaningful dimension (i.e. semantically plausible criteria for the association of category members), in contrast to the non-alogia patients who exhibited a predation dimension. Furthermore, cluster analysis revealed the presence of oddly coherent clusters in the alogia group, in contrast to neutral clusters in the non-alogia patients. Overall, these results suggest that the disorganized semantic structure may underline alogia symptoms in patients with schizophrenia.

Stolar et al. (1994) reported a negative correlation between the number of words produced in the LFT and severity of alogia symptoms in subjects with schizophrenia, while the present study did not find a significant difference in the LFT score between alogia- and non-alogia patients. This discrepancy may be explained by the use of the different Alogia scores. Stolar et al. (1994) did not include "poverty of content of speech" in the Alogia score while we included this item, since it was assumed to be affected by the organization of semantic memory as measured by the CFT.

The comparison of data between schizophrenia patients as a whole and normal controls indicated impaired semantic structure in the patient group, in addition to decreased word production. Control subjects demonstrated a domestic–wild dimension in the semantic configuration, while it was dimensionless in patients with schizophrenia (Fig. 1). The deteriorated semantic structure in schizophrenia is consistent with the results of previous reports (Aloia et al., 1996; Paulsen et al., 1996; Rossell et al., 1999; Sumiyoshi et al., 2001a).

Several studies found that the disturbances in verbal fluency performance are associated with impairment in executive function (i.e. improper searching or retrieval) in subjects with schizophrenia (Allen et al., 1993; Joyce et al., 1996; Maron et al., 2004). Joyce et al. (1996) observed increased word production by providing a cue (e.g. farm animal) in schizophrenia patients, suggesting that the impaired performance on the VFTs is the result of a disturbed retrieval process. On the other hand, other researchers argued that disorganization of semantic memory causes the deficits in the verbal fluency performance (Goldberg et al., 1998; Paulsen et al., 1996; Sumiyoshi et al., 2001a). This assumption is supported by several other studies (Aloia et al., 1996; Gourovitch et al., 1996; Phillips et al., in press) reporting that execution of the LFT was relatively intact compared with that of the CFT in patients with schizophrenia. Disproportionate degradation between the LFT and CFT in schizophrenia has been confirmed by a recent meta-analysis study (Bokat and Goldberg, 2003). Since well-formed semantic networks are required for efficient search and retrieval of words (Gruenewald and Gregory, 1980), the latter hypothesis that performance on the VFTs would depend largely on semantic organization appears more convincing. Phillips et al. (in press) also lend support to this concept, arguing that lexicon size is not remarkably reduced in patients with schizophrenia, as has been reported by Joyce et al. (1996) and Elvevag et al. (2001).

The present study showed the word production in the CFT (ANIMAL) was exclusively correlated with alogia symptoms. This finding is in agreement with Joyce et al. (1996) who suggested that the same domain of cognitive abnormality mediates both alogia and poor verbal fluency. We further speculate that the degradation of semantic memory precedes the emergence of psychotic symptoms in schizophrenia. Consistent with this hypothesis, cohort studies (Chen et al., 2000; Keefe et al., 1994) report the impaired performance on the CFT in family members of patients with schizophrenia. Furthermore, Chen et al. (2000) found selective deficits in the execution of the CFT, but not other cognitive tasks, in non-psychotic siblings of schizophrenia subjects. Based on these findings, Phillips et al. (in press) suggested that impaired performance on the CFT may predict the emergence of psychotic symptoms at a later stage in subjects who are vulnerable to developing schizophrenia.

Recent investigations have indicated that other language-related disturbances also represent trait markers of schizophrenia (for a review, see DeLisi,

2001). Several studies (e.g. DeLisi, 2001; Shedlack et al., 1997) found that sentence complexity is slightly reduced in family members of patients with schizophrenia. So far, some investigators from Japan have reported disturbances in information-processing (Sumiyoshi et al., 2000) and verbal memory (Matsui et al., 2004) in subjects who are susceptible to developing schizophrenia.

Neuroimaging studies have attempted to clarify the neural basis for degraded performance on the VFTs in patients with schizophrenia. An fMRI study (Curtis et al., 1998) reported that patients with schizophrenia showed poor activation of prefrontal cortex during the performance on the VFTs. In addition, other investigators have reported that poor prefrontal activations are associated with negative symptoms in subjects with schizophrenia (Liddle, 1996; Liddle et al., 1992). These findings indicate that attenuated neural activity in the prefrontal cortex is responsible for poor verbal fluency performance and negative symptoms in patients with schizophrenia. Moreover, the anterior part of the left prefrontal region is likely to be involved in semantic processing (Fiez, 1997). Functional disturbances of this part of the brain may possibly be associated with disorganized semantic memory in subjects with schizophrenia.

The effect of the language system or nationality should also be considered when assessing verbal fluency in patients with schizophrenia. Harvey et al. (2003) have reported the cross-national (e.g. U.S., U.K., and Canada) uniformity regarding the pattern of inefficient execution of the VFTs in patients with schizophrenia, i.e. less impaired performance on the LFT compared with the CFT. On the other hand, we have recently found a language-specific disturbance in the execution of the VFTs; the performance on the CFT and LFT are equally impaired in Japanese patients, unlike the cases with alphabetical-language speakers with schizophrenia (Sumiyoshi et al., 2004). Interestingly, recent neuroimaging studies (Callan et al., 2003; Paulesu et al., 2000; Sumiyoshi et al., 2003) have demonstrated the language-dependent differences in the patterns of the brain activities in normal control subjects undertaking cognitive tasks. It is speculated that similar effects of the language system, or orthography, on cognitive performance may be present in the brain activities of patients with schizophrenia.

The usefulness of analyzing semantic structures using the VFTs should be mentioned here. Since these tasks only require free recall of words, they are applicable to in patients with a wide range of clinical symptoms (van Beilen et al., in press). Elvevag et al. (2001) reported the limitation of MDS analysis of sequential verbal outputs from the CFT. They claimed that the verbal outputs are not uniform across patients with schizophrenia as a whole, resulting in a poor fit between the dissimilarity matrix and the spatial configuration. However, this type of variability could be reduced by classifying the patients into subgroups based on the source of idiosyncrasy, such as presence or absence of psychotic symptoms. In fact, the symptom-based subgroup analysis in our study revealed a group-specific degradation in the semantic structure (Fig. 2), suggesting the intra-group uniformity regarding verbal outputs.

In summary, using data from the CFT, we have demonstrated that alogia symptoms are highly correlated with disorganization of semantic memory in patients with schizophrenia. The results of the symptom-based subgroup analysis further indicate that the semantic memory deficits underlie the manifestation of negative symptoms such as alogia.

Acknowledgement

This work was supported by a Grant-in-Aid from the Ministry of Education and Science of Japan (No. 14710065) to Dr. Chika Sumiyoshi, as well as a Young Investigator Award from NARSAD, a Pharmacopsychiatry Research Grant from the Mitsubishi Pharma Research Foundation, and a fellowship and a Grant-in-Aid for Scientific Research (No. 16591126) from the Ministry of Education and Science of Japan to Dr. Tomiki Sumiyoshi.

The authors are grateful to Dr. Lynn E. DeLisi, M.D. for helpful comments.

References

Allen, H.A., Liddle, P.F., Frith, C.D., 1993. Negative features, retrieval processes and verbal fluency in schizophrenia. Br. J. Psychiatry 163, 769–775.

Aloia, M.S., Gourovitch, M.L., Weinberger, D.R., Goldberg, T.E., 1996. An investigation of semantic space in patients with schizophrenia. J. Int. Neuropsychol. Soc. 2, 267–273.

Amano, S., Kondo, K., 2000. Nihongo-no Goitokusei (Lexical Properties of Japanese), NTT Database Series. Sanseido, Tokyo, Japan. 2nd release vol. 7 frequency.

American Psychiatric Association, 1994. DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th Rev. ed. American Psychiatric Press, Washington, DC.

Andreasen, N.C., 1984a. Scale for the Assessment of Negative Symptoms (SANS). University of Iowa, Iowa City, IA.

Andreasen, N.C., 1984b. Scale for the Assessment of Positive Symptoms (SAPS). University of Iowa, Iowa City, IA.

Bokat, C.E., Goldberg, T.E., 2003. Letter and category fluency in schizophrenic patients: a meta-analysis. Schizophr. Res. 64, 73–78.

Bolla, K.I., Lindgren, K.N., Bonaccorsy, C., Bleecker, M.L., 1990. Predictors of verbal fluency (FAS) in the healthy elderly. J. Clin. Psychol. 46, 623–628.

Buchanan, R.W., Holstein, C., Breier, A., 1994. The comparative efficacy and long-term effect of clozapine treatment on neuropsychological test performance. Biol. Psychiatry 36, 717–725.

Callan, D.E., Tajima, K., Callan, A.M., Kubo, R., Masaki, S., Akahane-Yamada, R., 2003. Learning-induced neural plasticity associated with improved identification performance after training of a difficult second-language phonetic contrast. NeuroImage 19, 113–124.

Cauthen, N.R., 1978. Verbal fluency: normative data. J. Clin. Psychol. 34, 126–129.

Chan, A.S., Butters, N., Salmon, D.P., McGuire, K.A., 1993. Dimensionality and clustering in the semantic network of patients with Alzheimer's disease. Psychol. Aging 8, 411–419.

Chen, Y.L., Chen, Y.H., Lieh-Mak, F., 2000. Semantic verbal fluency deficit as a familial trait marker in schizophrenia. Psychiatry Res. 95, 133–148.

Crawford, J.R., Obonsawin, M.C., Bremner, M., 1993. Frontal lobe impairment in schizophrenia: relationship to intellectual functioning. Psychol. Med. 23, 787–790.

Curtis, V.A., Bullmore, E.T., Brammer, M.J., Wright, I.C., Williams, S.C., Morris, R.G., Sharma, T.S., Murray, R.M., McGuire, P.K., 1998. Attenuated frontal activation during a verbal fluency task in patients with schizophrenia. Am. J. Psychiatry 155, 1056–1063.

DeLisi, L.E., 2001. Speech disorder in schizophrenia: review of the literature and exploration of its relation to the uniquely human capacity for language. Schizophr. Bull. 27, 481–496.

Elvevag, B., Weinstock, D.M., Akil, M., Kleinman, J.E., Goldberg, T.E., 2001. A comparison of verbal fluency tasks in schizophrenic patients and normal controls. Schizophr. Res. 51, 119–126.

Feinstein, A., Goldberg, T.E., Nowlin, B., Weinberger, D.R., 1998. Types and characteristics of remote memory impairment in schizophrenia. Schizophr. Res. 30, 155–163.

Fiez, J.A., 1997. Phonology, semantics, and the role of the left inferior prefrontal cortex. Hum. Brain Mapp. 5, 79–83.

Goldberg, T.E., Aloia, M.S., Gourovitch, M.L., Missar, D., Pickar, D., Weinberger, D.R., 1998. Cognitive substrates of thought disorder: I. The semantic system. Am. J. Psychiatry 155, 1671–1676.

Gourovitch, M.L., Goldberg, T.E., Weinberger, D.R., 1996. Verbal fluency deficits in patients with schizophrenia: semantic fluency is differently impaired as compared with phonological fluency. Neuropsychology 10, 573–577.

Green, M.F., 1996. What are the functional consequences of neurocognitive deficits in schizophrenia? Am. J. Psychiatry 153, 321–330.

Gruenewald, P.J., Gregory, G.R., 1980. The free recall of category examples. J. Exp. Psychol. Hum. Learn. 6, 225–240.

Harvey, P.D., Artiola, I., Fortuny, L., Vester-Blockland, E., De Smedt, G., 2003. Cross-national cognitive assessment in schizophrenia clinical trials: a feasibility study. Schizophr. Res. 59, 243–251.

Howanitz, E., Cicalese, C., Harvey, P.D., 2000. Verbal fluency and psychiatric symptoms in geriatric schizophrenia. Schizophr. Res. 42, 167–169.

Joyce, E.M., Collinson, S.L., Crichton, P., 1996. Verbal fluency in schizophrenia: relationship with executive function, semantic memory and clinical alogia. Psychol. Med. 26, 39–49.

Keefe, R.S., Silverman, J.M., Roitman, S.E., Harvey, P.D., Duncan, M.A., Alroy, D., Siever, L.J., Davis, K.L., Mohs, R.C., 1994. Performance of nonpsychotic relatives of schizophrenic patients on cognitive tests. Psychiatry Res. 53, 1–12.

Kruskal, J.B., Wish, M., 1978. Multidimensional Scaling. Sage Publications, Beverly Hills, CA.

Kuperberg, G.R., McGuire, P.K., David, A.S., 1998. Reduced sensitivity to linguistic context in schizophrenic thought disorder: evidence from on-line monitoring for words in linguistically anomalous sentences. J. Abnorm. Psychology 107, 423–434.

Liddle, P.F., 1996. Functional imaging-schizophrenia. Br. Med. Bull. 52, 486–494.

Liddle, P.F., Friston, K.J., Frith, C.D., Hirsch, S.R., Jones, T., Frackowiak, R.S., 1992. Patterns of cerebral blood flow in schizophrenia. Br. J. Psychiatry 160, 179–186.

Mahurin, R.K., Velligan, D.I., Miller, A.L., 1998. Executive-frontal lobe cognitive dysfunction in schizophrenia: a symptom subtype analysis. Psychiatry Res. 79, 139–149.

Maron, M.L., Carlson, M.D., Minassian, A., Perry, W., 2004. A process approach to verbal fluency in patients with schizophrenia. Schizophr. Res. 68, 105–106.

Matsui, M., Sumiyoshi, T., Kato, K., Yoneyama, E., Kurachi, M., 2004. Neuropsychological profile in patients with schizotypal personality disorder or schizophrenia. Psychol. Rep. 94, 387–397.

McGurk, S.R., Meltzer, H.Y., 2000. The role of cognition in vocational functioning in schizophrenia. Schizophr. Res. 45, 175–184.

Moelter, S.T., Hill, S.K., Ragland, J.D., Lunardelli, A., Gur, R.C., Gur, R.E., Moberg, P.J., 2001. Controlled and automatic processing during animal word list generation in schizophrenia. Neuropsychology 15, 502–509.

Paulesu, E., McCrory, E., Fazio, F., Menoncello, L., Brunswick, N., Cappa, S.F., Cotelli, M., Cossu, G., Corte, F., Lorusso, M., Pesenti, S., Gallagher, A., Perani, D., Price, C., Frith, C.D., Frith, U., 2000. A cultural effect on brain function. Nat. Neurosci. 3, 91–96.

Paulsen, J.S., Romero, R., Chan, A., Davis, A.V., Heaton, R.K., Jeste, D.V., 1996. Impairment of the semantic network in schizophrenia. Psychiatry Res. 63, 109–121.

Phillips, T.J., James, A.C.D., Crow, T.J., Collinson, S.L., in press. Semantic fluency is impaired but phonemic and design fluency are preserved in early-onset schizophrenia. Schizophr. Res.

Rossell, S.L., Rabe-Hesketh, S., Shapleske, J., David, A.S., 1999. Is semantic fluency differentially impaired in schizophrenic patients with delusions? J. Clin. Exp. Neuropsychol. 21, 629–642.

Shedlack, K., Lee, G., Sakuma, M., Xie, S.H., Kushner, M., Pepple, J., Finer, D.L., Hoff, A.L., DeLisi, L.E., 1997. Language processing and memory in ill and well siblings from multiplex families affected with schizophrenia. Schizophr. Res. 25, 43–52.

Silverstein, A.B., 1982. Two- and four-subtest short forms of the Wechsler Adult Intelligence Scale-Revised. J. Consult. Clin. Psychol. 50, 415–418.

Spreen, O.S., Strauss, E. (Eds.), 1998. A Compendium of Neuropsychhological Tests. New York: Oxford Univ. Press, pp. 447–464.

Stolar, N., Berenbaum, H., Banich, M.T., Barch, D., 1994. Neuropsychological correlates of alogia and affective flattening in schizophrenia. Biol. Psychiatry 35, 164–172.

Sumiyoshi, C., Matsui, M., Sumiyoshi, T., Yamashita, I., Sumiyoshi, S., Kurachi, M., 2001. Semantic structure in schizophrenia as assessed by the category fluency test: effect of verbal intelligence and age of onset. Psychiatry Res. 105, 187–199.

Sumiyoshi, C., Matsuo, K., Kato, C., Ozawa, F., Takehara, Y., Isoda, H., Isogai, S., Sakahara, H., Nakai, T., 2003. Orthography effect on brain activities in the working memory process for phonologically ambiguous syllables: a functional magnetic resonance imaging study using Japanese speakers. Neurosci. Lett. 336, 50–54.

Sumiyoshi, C., Sumiyoshi, T., Matsui, M., Nohara, S., Yamashita, I., Kurachi, M., Niwa, S., 2004. Effect of orthography on the verbal fluency performance in schizophrenia: examination using Japanese patients. Schizophr. Res. 69, 15–22.

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.

Sumiyoshi, T., Matsui, M., Nohara, S., Yamashita, I., Kurachi, M., Sumiyoshi, C., Jayathilake, K., Meltzer, H.Y., 2001a. Enhancement of cognitive performance in schizophrenia by addition of tandospirone to neuroleptic treatment. Am. J. Psychiatry 158, 1722–1725.

Sumiyoshi, T., Matsui, M., Yamashita, I., Nohara, S., Kurachi, M., Uehara, T., Sumiyoshi, S., Sumiyoshi, C., Meltzer, H.Y., 2001b. The effect of tandospirone, a serotonin$_{1A}$ agonist, on memory function in schizophrenia. Biol. Psychiatry 49, 861–868.

van Beilen, M., Pijnenborg, M., van Zomeren, E.H., van den Bosch, R.J., Withaar, F.K., Bouma, A., 2004. What is measured by verbal fluency tests in schizophrenia? Schizophr. Res. 69, 267–276.

Wechsler, D., 1981. WAIS-R Manual. The Psychological Corporation, New York.

Available online at www.sciencedirect.com

SCIENCE DIRECT®

Psychiatry Research: Neuroimaging 138 (2005) 209–220

PSYCHIATRY RESEARCH NEUROIMAGING

www.elsevier.com/locate/psychresns

Volumetric MRI study of the short and long insular cortices in schizophrenia spectrum disorders

Tsutomu Takahashi[a,*], Michio Suzuki[a,c], Shi-Yu Zhou[a,c], Hirofumi Hagino[a], Ryoichiro Tanino[a], Yasuhiro Kawasaki[a,c], Shigeru Nohara[a], Ikiko Yamashita[a], Hikaru Seto[b], Masayoshi Kurachi[a,c]

[a]*Department of Neuropsychiatry, Toyama Medical and Pharmaceutical University, 2630 Sugitani, Toyama 930-0194, Japan*
[b]*Department of Radiology, Toyama Medical and Pharmaceutical University, 2630 Sugitani, Toyama 930-0194, Japan*
[c]*Core Research for Evolutional Science and Technology, Japan Science and Technology Corporation, Tokyo, Japan*

Received 1 November 2004; received in revised form 5 February 2005; accepted 11 February 2005

Abstract

We have previously reported volume reductions of the insular cortex in schizophrenia, but it is still not clear whether insular cortex volume loss preferentially involves the anterior (short insular cortex) or posterior (long insular cortex) portion. On the other hand, no volumetric studies of the brain have examined changes in insular cortex volume in subjects with schizotypal features. In this study, we separately investigated the volumes of the short and long insular cortex portions using magnetic resonance imaging in 37 schizotypal disorder patients (24 males, 13 females), 62 schizophrenia patients (32 males, 30 females), and 69 healthy controls (35 males, 34 females). While the volumes of the short and long insular cortex were significantly reduced in schizophrenia patients compared with schizotypal disorder patients and control subjects, there was no difference between schizotypal disorder patients and control subjects. These results suggest that the volume reduction of the insular cortex may be specific to overt schizophrenia without topographically specific localization.

Keywords: Magnetic resonance imaging; Insula; Schizophrenia; Schizotypal disorder

1. Introduction

Post-mortem (Jakob and Beckmann, 1986, 1989) and functional neuroimaging (Curtis et al., 1998; Shergill et al., 2000; Crespo-Facorro et al., 2001a,b; Surguladze et al., 2001; Desco et al., 2003) studies have suggested that insular cortex abnormalities are involved in the pathophysiology of schizophrenia. With regard to the morphology of the insular cortex in schizophrenia, recent volumetric magnetic resonance imaging (MRI) studies have reported that schizophrenia patients have a significantly smaller insular cortex volume than do control subjects

* Corresponding author. Tel.: +81 76 434 2281; fax: +81 76 434 5030.
E-mail address: tsutomu@ms.toyama-mpu.ac.jp (T. Takahashi).

0925-4927/$ - see front matter © 2005 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.pscychresns.2005.02.004

(Crespo-Facorro et al., 2000; Kasai et al., 2003; Kim et al., 2003; Takahashi et al., 2004a). Several voxel-based analyses of MRI have also revealed a gray matter reduction of the insular cortex in patients with schizophrenia (Wright et al., 1999; Hulshoff Pol et al., 2001; Paillère-Martinot et al., 2001; Kubicki et al., 2002; Shapleske et al., 2002; Kawasaki et al., 2004).

There are distinct differences in the connectivities and functions of the anterior (short insular cortex) versus posterior (long insular cortex) portions of the insular cortex; these two subregions are diagonally divided by the central insular sulcus (Augustine, 1996; Duvernoy, 1999; Türe et al., 1999). However, most previous volumetric MRI studies (Crespo-Facorro et al., 2000; Kim et al., 2003; Takahashi et al., 2004a) have not taken into account these differences. Kasai et al. (2003) separately examined the short and long insular cortex and reported that insular volume loss associated with schizophrenia is not localized to a particular subregion, although their study might also have been limited in part by having bounded the two subregions not by their own anatomical boundaries but other anatomical landmarks, i.e. mamillary bodies. Thus, it remains unresolved whether the insular cortex volume reduction in schizophrenia preferentially involves the anterior (short insular cortex) or posterior (long insular cortex) portion.

Subjects with schizotypal features such as schizotypal disorder in ICD-10 (World Health Organization, 1992) or schizotypal personality disorder (SPD) in DSM-IV (American Psychiatric Association, 1994) share genetic, biological, and psychological features with schizophrenia and are thought to be part of the schizophrenia spectrum (Siever et al., 1993; Siever and Davis, 2004). Several recent brain structural imaging studies have identified specific structural abnormalities in schizotypal subjects similar to those seen in schizophrenia, although generally to a lesser degree and with the sparing of some brain regions (reviewed by Dickey et al., 2002a; Siever et al., 2002; Siever and Davis, 2004). The abnormalities include increased lateral ventricular size (Siever et al., 1995; Buchsbaum et al., 1997; Silverman et al., 1998), greater 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), and volume reduction in the thalamus (Hazlett et al., 1999; Seidman et al., 1999; Byne et al., 2001), basal ganglia (Shihabuddin et al., 2001; Levitt et al., 2002), and internal capsule (Suzuki et al., 2004), along with shape and size differences in the corpus callosum (Downhill et al., 2000) and asymmetry anomalies in the parahippocampal gyrus (Dickey et al., 1999) and the anterior cingulate gyrus (Takahashi et al., 2002b). 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 such as the insular cortex that have been identified previously as impaired in schizophrenia patients is one possible strategy for advancing our understanding of pathogenesis of schizophrenia spectrum disorders. In addition, it is of interest to know the morphologic characteristics of the insular cortex, a brain region interconnected with both temporal and frontal regions (Augustine, 1996; Türe et al., 1999), in schizotypal disorder patients since the differential involvement of the frontal regions has been suggested to underlie the differences in phenomenology between schizophrenia and schizotypal patients while the abnormalities in temporal regions have been considered to be common to both disorders (Kurachi, 2003a,b; Siever and Davis, 2004). To our knowledge, however, no volumetric MRI studies have examined the insular cortex volume in subjects with schizotypal features.

In the present study, we followed the course of the central insular sulcus and accurately distinguished between the short and long insular cortex using three-dimensional MRI. We separately measured the volumes of the short and long insular cortex in schizophrenia patients, schizotypal disorder patients, and normal control subjects. The aims of the present study were to determine if the short and long insular cortices exhibited different patterns in terms of structural abnormalities in schizophrenia and to test the hypothesis that schizotypal disorder patients would have structural abnormalities in the insular cortex that were partly similar to those seen in overt schizophrenia.