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Prefrontal abnormalities in patients with simple schizophrenia: Structural and functional brain-imaging studies in five cases

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Abstract

Simple schizophrenia is an uncommon disorder with unknown pathophysiology, and its position in the current diagnostic system is ambiguous. Brain-imaging studies may help to elucidate its pathophysiology. Five patients fulfilling both ICD-10 criteria for simple schizophrenia and DSM-IV criteria for simple deteriorative disorder underwent computed tomography, magnetic resonance imaging, and single photon emission computed tomography. These scans were assessed individually by visual inspection as well as automatically by comparison with scans in normal controls or other schizophrenia subtype patients using voxel-based image analyses. Three of the five simple schizophrenia patients had findings of atrophy and reduced cerebral perfusion in the frontal areas. Voxel-based analyses also showed prefrontal grey matter deficits and hypoperfusion in simple schizophrenia patients compared with the controls. Although this study is limited by the small number of patients with simple schizophrenia, the results suggest that simple schizophrenia, or at least this subpopulation, may have rather homogeneous morphological and functional deficits in the prefrontal cortex. It is also suggested that simple schizophrenia may occupy an extreme position of the schizophrenic continuum where the prefrontal deficits and negative symptoms are most purely manifested.

Keywords: Simple schizophrenia; Prefrontal cortex; Magnetic resonance imaging; Single photon emission computed tomography

1. Introduction

Simple schizophrenia is an uncommon disorder identified by E. Bleuler (1911) as one of the traditional schizophrenic subtypes. In spite of its long history (for historical overview, see Black and Boffeli,

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1989), the position that simple schizophrenia occupies is ambiguous in current operational diagnostic systems. This category has been deleted from the Diagnostic and Statistical Manual of Mental Disorders, third edition (DSM-III; American Psychiatric Association, 1980) and subsequent revisions (American Psychiatric Association, 1987) because of its questionable validity, and it has been reclassified as schizoid and schizotypal personality disorders. However, since the concept of simple schizophrenia is not fully captured by any DSM-III or DSM-III-R category, operational criteria for simple schizophrenia have been proposed (Black and Boffeli, 1989). In addition, DSM-IV (American Psychiatric Association, 1994) includes proposed research criteria for "simple deteriorative disorder" in Appendix B provided for further study (Table 1). The essential feature of simple deteriorative disorder is the development of prominent negative symptoms, which represent a clear change from a preestablished baseline. Simple deteriorative disorder is distinguished from schizoid and schizotypal personality disorders by the requirement of a clear change in personality and marked deterioration in functioning from baseline.

On the other hand, the International Classification of Diseases, 10th edition (ICD-10; World Health Organization, 1992, 1993), retains simple schizophrenia as a subtype of schizophrenia. ICD-10 represents simple schizophrenia as a disorder in which there is an insidious but progressive development of negative features of schizophrenia in the absence of preceding overt psychotic symptoms. Diagnostic guidelines in ICD-10 (World Health Organization, 1992) suggest that the diagnosis is difficult to make with confidence because of its requirement that core features of the disorder develop over a long period. ICD-10 criteria for research on simple schizophrenia (Table 1) (World Health Organization, 1993) are essentially the same as those of simple deteriorative disorder in DSM-IV.

For the purposes of assessing the validity of the category, it is necessary to collect patients conforming to these operational diagnostic criteria and to conduct research on such strictly diagnosed patients. Brain-imaging studies may prove informative in elucidating the pathophysiology of simple schizophrenia. However, only a few brain-imaging studies have been performed on patients who meet operational criteria for simple schizophrenia (Galderisi et al., 1999; Serra-Mestres et al., 2000).

Table 1
Diagnostic criteria for simple schizophrenia in ICD-10 and for simple deteriorative disorder in DSM-IV

Simple deteriorative disorder (DSM-IV)

A. Progressive development over a period of at least a year of all of the following:
   (1) Marked decline in occupational or academic functioning
   (2) Gradual appearance and deepening of negative symptoms such as affective flattening, alogia, and avolition
   (3) Poor interpersonal rapport, social isolation, or social withdrawal
B. Criterion A for schizophrenia has never been met.
C. The symptoms are not better accounted for by Schizotypal or Schizoid Personality Disorder, a Psychotic Disorder, a Mood Disorder, an Anxiety Disorder, a dementia, or Mental Retardation and are not due to the direct physiological effects of a substance or a general medical condition.

Simple schizophrenia (ICD-10)

A. There is slow but progressive development, over a period of at least 1 year, of all three of the following:
   (1) A significant and consistent change in the overall quality of some aspects of personal behaviour, manifest as loss of drive and interests, aimlessness, idleness, a self-absorbed attitude, and social withdrawal;
   (2) Gradual appearance and deepening of "negative" symptoms such as marked apathy, paucity of speech, under-activity, blunting of affect, passivity and lack of initiative, and poor non-verbal communication (by facial expression, eye contact, voice modulation, and posture);
   (3) Marked decline in social, scholastic, or occupational performance.
B. At no time are there any of the symptoms referred to in criterion G1 for F20.0–F20.3, nor are there hallucinations or well formed delusions of any kind, i.e. the individual must never have met the criteria for any other type of schizophrenia or any other psychotic disorder.
C. There is no evidence of dementia or any other organic mental disorder listed in F00–F09.

In this study, we examined findings of brain structural and functional imaging in a series of patients who met ICD-10 criteria for simple schizophrenia as well as DSM-IV criteria for simple deteriorative disorder.

2. Methods

2.1. Subjects

Among all subjects consecutively admitted to the inpatient unit of the Department of Neuropsychiatry,

Toyama Medical and Pharmaceutical University Hospital, from June 1993 to March 2003, five patients (three males and two females) had received a diagnosis of simple schizophrenia according to the ICD-10 criteria for research (World Health Organization, 1993). All of the five patients also fulfilled the DSM-IV criteria for simple deteriorative disorder (American Psychiatric Association, 1994). All available clinical information and data were obtained from a detailed review of the clinical records and structured interviews performed by psychiatrists using the Comprehensive Assessment of Symptoms and History (CASH) (Andreasen et al., 1992). Families or relatives of the patients were also interviewed concerning the patients' histories in detail, especially focusing on their birth and development. Subjects were diagnosed by consensus of at least two experienced psychiatrists based on these data. When the diagnostic criteria for simple schizophrenia proposed by Black and Boffeli (1989), essentially similar to but more detailed than those of ICD-10 and DSM-IV, were adopted, all the patients also satisfied them. However, with regard to the symptoms referred to in criterion A, odd beliefs or magical thinking and unusual perceptual experiences were not remarkable in these patients. Clinical symptoms were assessed using the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984) and the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1983). All the patients were receiving psychotropic medication at the time of study. Their mean age on admission was 38.8 ± 5.0 (S.D.) years (range=32–44). They underwent computed tomography (CT), magnetic resonance imaging (MRI), and single photon emission computed tomography (SPECT) as a routine clinical procedure for the differential diagnosis of neuropsychiatric disorders. They were also given the Wechsler Adult Intelligence Scale-Revised (WAIS-R).

In the MRI study, the four patients with simple schizophrenia who underwent three-dimensional MRI (3D-MRI) scans were compared with 20 healthy comparison subjects and 22 medicated patients with schizophrenia who met the ICD-10 criteria for research on schizophrenia other than the simple subtype (World Health Organization, 1993). The healthy comparison subjects included 10 males and 10 females, and their mean age was 36.7 ± 6.1 years. The schizophrenia patients other than the simple subtype consisted of 11 males and 11 females, and their mean age was 36.9 ± 5.1 years. They were selected from the subjects with schizophrenia who underwent 3D-MRI to match the subjects with simple schizophrenia on demographic characteristics. They consequently included five paranoid, one hebephrenic, eight undifferentiated, and eight residual subtypes of schizophrenia.

In the SPECT study, the five patients with simple schizophrenia were compared with 21 healthy comparison subjects and 25 medicated patients with schizophrenia other than the simple subtype diagnosed according to the ICD-10 criteria for research (World Health Organization, 1993). The healthy comparison subjects consisted of 14 males and 7 females, and their mean age was 38.8 ± 9.1 years. The schizophrenia patients other than the simple subtype consisted of 14 males and 11 females, and their mean age was 34.0 ± 9.4 years. They included seven paranoid, one hebephrenic, nine undifferentiated, and eight residual subtypes of schizophrenia.

Table 2 presents the demographic characteristics of the subjects, as well as the patients' scores on the SAPS and the SANS. The healthy comparison subjects consisted of healthy volunteers recruited from among the community and hospital staff. They were interviewed by psychiatrists using the questionnaire concerning their family and past histories, and present illness. None of the patients or control subjects had histories of head trauma, serious medical or surgical illness, or substance abuse disorder. The simple schizophrenia patient group matched the comparison groups for age, sex, and handedness. Educational levels in the patient groups with other subtypes of schizophrenia were lower than those in the simple schizophrenia patient group and the healthy comparison groups, but these differences did not reach statistical significance. The purpose and procedures of the study were explained to all subjects, and written informed consent was obtained. From case 1, whose history was individually described, written informed consent was obtained again after he read a part of the manuscript. This study was approved by the Committee on Medical Ethics of Toyama Medical and Pharmaceutical University.

Table 2
Demographic characteristics of patients and comparison subjects, and symptom rating scores in three groups of patients with schizophrenia

	Simple schizophrenia patients	Comparison subjects for MRI		Comparison subjects for SPECT	
		Healthy subjects	Schizophrenia patients with other subtypes	Healthy subjects	Schizophrenia patients with other subtypes
	(*N*=5)	(*N*=20)	(*N*=22)	(*N*=21)	(*N*=25)
Male/female	3/2	10/10	11/11	14/7	14/11
Handedness	5 right	20 right	22 right	21 right	25 right
Age (years)	38.8 ± 5.0	36.7 ± 6.1	36.9 ± 5.1	38.8 ± 9.1	34.0 ± 9.4
Education (years)	15.6 ± 0.9	15.5 ± 2.8	14.0 ± 2.1	16.0 ± 2.5	14.0 ± 2.2
Age at onset (years)[a]	–	–	25.5 ± 6.1	–	26.6 ± 5.7
Duration of illness (years)[b]	–	–	9.7 ± 7.8	–	7.6 ± 8.0
Drug dose (mg/day, haloperidol equivalent)	7.1 ± 4.1	–	13.8 ± 16.0	–	9.8 ± 8.8
SAPS					
Hallucinations	0.1 ± 0.2	–	7.9 ± 9.2	–	5.3 ± 5.4
Delusions	1.1 ± 2.2	–	12.3 ± 11.5	–	7.0 ± 7.4
Bizarre behaviour	1.4 ± 1.4	–	3.6 ± 4.4	–	1.9 ± 2.0
Positive formal thought disorder	0.0 ± 0.0	–	5.3 ± 7.0	–	3.5 ± 4.4
Total	2.7 ± 2.1	–	32.5 ± 24.2**	–	17.9 ± 14.0*
SANS					
Affective flattening or blunting	17.6 ± 10.4	–	10.3 ± 7.8	–	7.9 ± 6.2*
Alogia	6.5 ± 6.5	–	4.8 ± 4.2	–	2.7 ± 2.6
Avolition-apathy	9.8 ± 5.0	–	7.2 ± 4.6	–	5.0 ± 2.5*
Anhedonia-asociality	10.5 ± 4.2	–	8.9 ± 6.7	–	6.1 ± 3.9
Attention	7.1 ± 3.5	–	5.7 ± 4.6	–	3.2 ± 2.3
Total	51.5 ± 26.6	–	36.8 ± 21.6	–	24.9 ± 14.2*

Values represent mean ± S.D.
[a,b] Onset of illness was insidious and difficult to determine in patients with simple schizophrenia. Approximate age at onset in each patient is shown in Table 3.
*$P<0.05$, **$P<0.01$, compared with simple schizophrenia (analysis of variance followed by post hoc Scheffé tests).
SAPS, the Scale for the Assessment of Positive Symptoms; SANS, the Scale for the Assessment of Negative Symptoms.

2.2. Data acquisition

2.2.1. CT and MRI

CT scans were performed using a TCT-900S scanner (Toshiba, Tokyo, Japan). Ten to eleven contiguous transaxial slices of 10 mm thickness were obtained parallel to the superior orbitomeatal line.

In case 1, two-dimensional MRI scans were performed using a Siemens Magnetom 0.5-Tesla scanner (Siemens, Inc., Erlangen, Germany). T1-weighted coronal and T2-weighted transaxial slices were obtained. In cases 2–5, three-dimensional MR images were acquired on a 1.5-Tesla Siemens Magnetom Vision (Siemens, 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 as follows: repetition time (TR)=24 ms, echo time (TE)=5 ms, flip angle=40°, field of view=256 mm, and matrix size=256 × 256. The voxel size was 1.0 × 1.0 × 1.0 mm. Two-dimensional transaxial T2-weighted images (TR=2500 ms, TE=90 ms) were also obtained in cases 2–5.

2.2.2. SPECT

Regional cerebral blood flow (rCBF) was measured using SPECT and ^{99m}Tc-hexamethyl propyleneamine oxime (^{99m}Tc-HMPAO). Measurements were carried out in a quiet, dimly lit room with the subjects at rest in the supine position and with their eyes open. SPECT imaging was performed with a three-headed rotating gamma camera system employing general purpose fanbeam collimators (GCA9300A; Toshiba, Tokyo, Japan). The resolution was 8 mm full width at half maximum (FWHM) in

the center of the reconstructed slice with the rotating radius at 13.2 cm. The SPECT data were obtained in a 128×128 format for 30 angles in a 120° arc for each camera with 30 s per angle. Acquisition of projection data was started from 5 min after intravenous injection of 1110 MBq of ^{99m}Tc-HMPAO and lasted for 15 min. The ramp back-projection method was used for SPECT image reconstruction after preprocessing the projection data with a Butterworth filter. The voxel size of the reconstructed images was $1.7 \times 1.7 \times 1.7$ mm.

2.3. Analysis of brain-imaging data

The brain morphology and rCBF distribution of the patients with simple schizophrenia were evaluated individually by visual inspection, as well as automatically by voxel-based analysis with statistical parametric mapping (SPM) in comparison with the normal controls or the patients with other subtypes of schizophrenia.

2.3.1. Voxel-based morphometry

Three-dimensional MR images were re-sliced in the axial plane and transformed to the ANALYZE format. Then they were processed with SPM99 software (Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK) running in MATLAB 5.3 (Mathworks Inc., Sherborn, MA, USA). Image processing and analyses using SPM 99 were performed according to the methodological description by Ashburner and Friston (2000). In SPM, the images were first reoriented to the anterior commissure–posterior commissure (AC-PC) plane. Then, they were spatially normalized into the standard space of Talairach and Tournoux (1988). The spatially normalized images were written out with $1.0 \times 1.0 \times 1.0$ mm voxels. Next, the normalized images were segmented into gray matter, white matter, cerebrospinal fluid, and other compartments using an automated and operator-independent process. The segmentation process used a modified mixture model cluster analysis technique with a correction for inhomogeneity of image intensity. The segmented images were then processed to automatically remove any remaining non-brain matter. The gray matter segment was smoothed with a 12-mm FWHM isotropic Gaussian kernel. Each voxel in the smoothed images contained the average concentration of gray matter from around the voxel (i.e., gray matter concentration).

Statistical comparison between groups was performed using an analysis of covariance (ANCOVA) model for global normalization (Friston et al., 1990). This procedure removes the global gray matter intensity for each subject and normalizes the segmented brain images to the same total amount of gray matter, while preserving regional differences in gray matter intensity. Age and gender were also treated as nuisance covariates. To test hypotheses about regionally specific group effects, the estimates were compared using each of two linear contrasts (more or less gray matter in simple schizophrenia patients than in controls or other subtype patients) (Friston et al., 1995). The resulting set of voxel values for each contrast constituted a statistical parametric map of the t statistic ($SPM_{\{t\}}$). Height threshold was set at $P<0.05$ corrected for all voxels.

2.3.2. SPM analysis of SPECT

SPECT data were re-sliced in the axial plane and transformed to ANALYZE format. Then they were processed with SPM99. After reorientation of the SPECT images roughly to the AC–PC plane, the images were spatially normalized into the standard stereotaxic space of Talairach and Tournoux (1988). The spatially normalized images were smoothed with a 12-mm FWHM isotropic Gaussian kernel. Global CBF for each subject was normalized to 50 ml/100 g/min by proportional scaling. Then adjusted rCBF images were used to compare the relative rCBF distributions between the two groups, treating age and gender as nuisance covariates. To test hypotheses about regionally specific group effects, the estimates were compared using each of two linear contrasts (more or less CBF in patients with simple schizophrenia than in controls or other subtype patients) (Friston et al., 1995). The resulting set of voxel values for each contrast constituted a statistical parametric map of the t statistic ($SPM_{\{t\}}$). Height and extent thresholds were set at $P<0.001$ (uncorrected) and $P<0.05$ (corrected), respectively.

2.3.3. Correlation analysis

Correlation analyses between regional gray matter or rCBF and clinical variables in the simple schizo-

phrenia patients were also performed using SPM. Each total or subscale score of the SANS or SAPS, or IQ or scaled scores of the Wechsler Adult Intelligence Scale—Revised (WAIS-R) subtests, was treated as a covariate. To test the hypotheses about regionally specific covariate effects, the estimates were compared using two linear contrasts (positive or negative correlation). Global normalization and statistical significance were the same as described above in the group comparison studies for MRI and SPECT, respectively.

3. Results

3.1. Clinical characteristics

Table 3 presents the clinical data in the five cases with simple schizophrenia. Clinical information was obtained from the case notes and detailed interviews of the patients and their relatives. Family histories of psychiatric disorder were found in two of the five cases. The mother of case 1 was withdrawn and considered to suffer from mental illness, although no formal psychiatric diagnosis was made. The younger brother of case 3 was suffering from schizophrenia and had experienced a psychotic episode. None of the patients had a history of obstetric complications, except case 5, who had a history of difficult labor. Early development and childhood were unremarkable in all patients. Three of the five patients had a medical history of physical illness that was considered irrelevant to the psychiatric disorder. Cases 1–3 and 5 were university graduates and case 4 was a college graduate. Cases 1, 2, and 4 had fairly good premorbid adjustments as employees of a company or a kindergarten teacher. In case 3, social function had gradually declined after the beginning of behavioral change observed at university. Although case 5's records at university were excellent, social deterioration began soon after she became a high school teacher. Approximate age at onset ranged from early twenties to mid-thirties. All patients showed prominent negative symptoms and marked deterioration in functioning from the preestablished baseline. In cases 1, 2, and 5, repeated interviews with the patients and their relatives failed to reveal any evidence of positive psychotic symp-

Table 3
Clinical and demographic characteristics of five patients with simple schizophrenia

Case no.	Age	Sex	Age at onset	Family history	OCs	Development	Medical history	Educational level	Marital status	Highest occupational function	Social function before admission
1.	43	M	Early 30s	Unspecified mental disorder (mother)	None	Not remarkable	Seborrheic dermatitis (36 years old)	University graduate	Single	Working in construction company	Unemployed, sitting in wheelchair all day
2.	32	M	Late 20s	None	None	Not remarkable	None	University graduate	Single	Working in consulting company	Unemployed, living with parents
3.	38	M	Early 20s	Schizophrenia (younger brother)	None	Not remarkable	Azoospermia (34 years old)	University graduate	Married (31 years old)	Changing work frequently	Unemployed, living with wife
4.	44	F	Mid 30s	None	None	Not remarkable	Appendectomy (14 years old), urethral stone (26 years old)	College graduate	Married (23 years old)	Kindergarten teacher	In and out of hospital, living in family
5.	36	F	Mid 20s	Unknown (adopted)	Hard labor	Not remarkable	None	University graduate	Single	High school teacher	Suspended from work

M, male; F, female; OCs, obstetric complications.

toms either currently or previously. Case 3 experienced a brief period when he complained that he felt possessed with something spiritual, but this was not preoccupying. Case 4 had a brief transient episode when she complained that "they were talking about her". Table 4 presents estimates of general intellectual functions based on the WAIS-R.

Table 2 shows the results of current symptom ratings on the SAPS and SANS. In general, the positive symptoms were very few and the negative symptoms were prominent in the patients with simple schizophrenia relative to the patients with other subtypes. However, few of the between-group differences reached statistical significance due to the small number of simple schizophrenia patients as well as large standard deviations in each group. A case showing typical illness (case 1) is briefly described in the Appendix.

3.2. Structural brain imaging

3.2.1. Qualitative CT and MRI findings of individual cases

Fig. 1 presents CT and T1-weighted MRI images of all cases. In case 1, CT and MRI revealed widening of the anterior longitudinal fissure and sulci in the bilateral frontal lobes, suggesting significant frontal cortical atrophy for a patient of the subject's age. However, enlargement of the anterior horns of the lateral ventricle was not remarkable. In cases 2 and 3, the frontal lobes appeared more atrophic than expected for age, and mild dilatation of the bilateral anterior horns of the lateral ventricle was also observed. In cases 4 and 5, neither CT nor MRI was remarkable. None of the cases showed significant dilatation of the inferior horns of the lateral ventricle or atrophic appearance of the medial temporal lobe structures.

3.2.2. Voxel-based morphometry

Compared with 20 normal controls, four patients with simple schizophrenia had decreased gray matter in the inferior frontal gyrus and the frontal pole of the left hemisphere. The patients had no more gray matter than the controls. Table 5 presents the peak SPM coordinates of the significant voxels. Fig. 2 presents SPM maps showing regional gray matter in the patients in which the presetting of height threshold, $P<0.001$ (uncorrected), was adopted, for illustrative purposes only, to demonstrate tendencies toward reductions in gray matter. Voxel-based comparison between four patients with simple schizophrenia and

Table 4
Current IQs and scaled scores of WAIS-R subtests in each patient with simple schizophrenia

	Case 1	Case 2	Case 3	Case 4	Case 5	Mean (S.D.)**
Full scale IQ	85	92	98	77*	99	93.5 (6.5)
Verbal tests						
Information	10	11	9	N.E.	12	10.5 (1.3)
Digit span	9	6	7	N.E.	8	7.5 (1.3)
Vocabulary	11	13	13	7	11	12 (1.2)
Arithmetic	8	9	10	N.E.	12	9.8 (1.7)
Comprehension	4	13	9	N.E.	10	9.0 (3.7)
Similarity	10	15	10	N.E.	13	12.0 (2.5)
Verbal IQ	92	108	98	–	107	101.3 (7.6)
Perfomance tests						
Picture completion	9	9	10	N.E.	10	9.5 (0.6)
Picture arrangement	9	6	10	N.E.	10	8.8 (1.9)
Block design	6	7	13	4	11	9.3 (3.3)
Object assembly	5	3	8	N.E.	7	5.8 (2.2)
Digit symbol	6	7	8	N.E.	5	6.5 (1.3)
Performance IQ	79	72	97	–	89	84.3 (11.0)

WAIS-R, Wechsler Adult Intelligence Scale-Revised; N.E., not examined.
*Full scale IQ was estimated using Vocabulary and Block Design as a two-subtest short form of the WAIS-R (Silverstein, 1982).
**Mean scores were calculated from values of four cases except case 4.

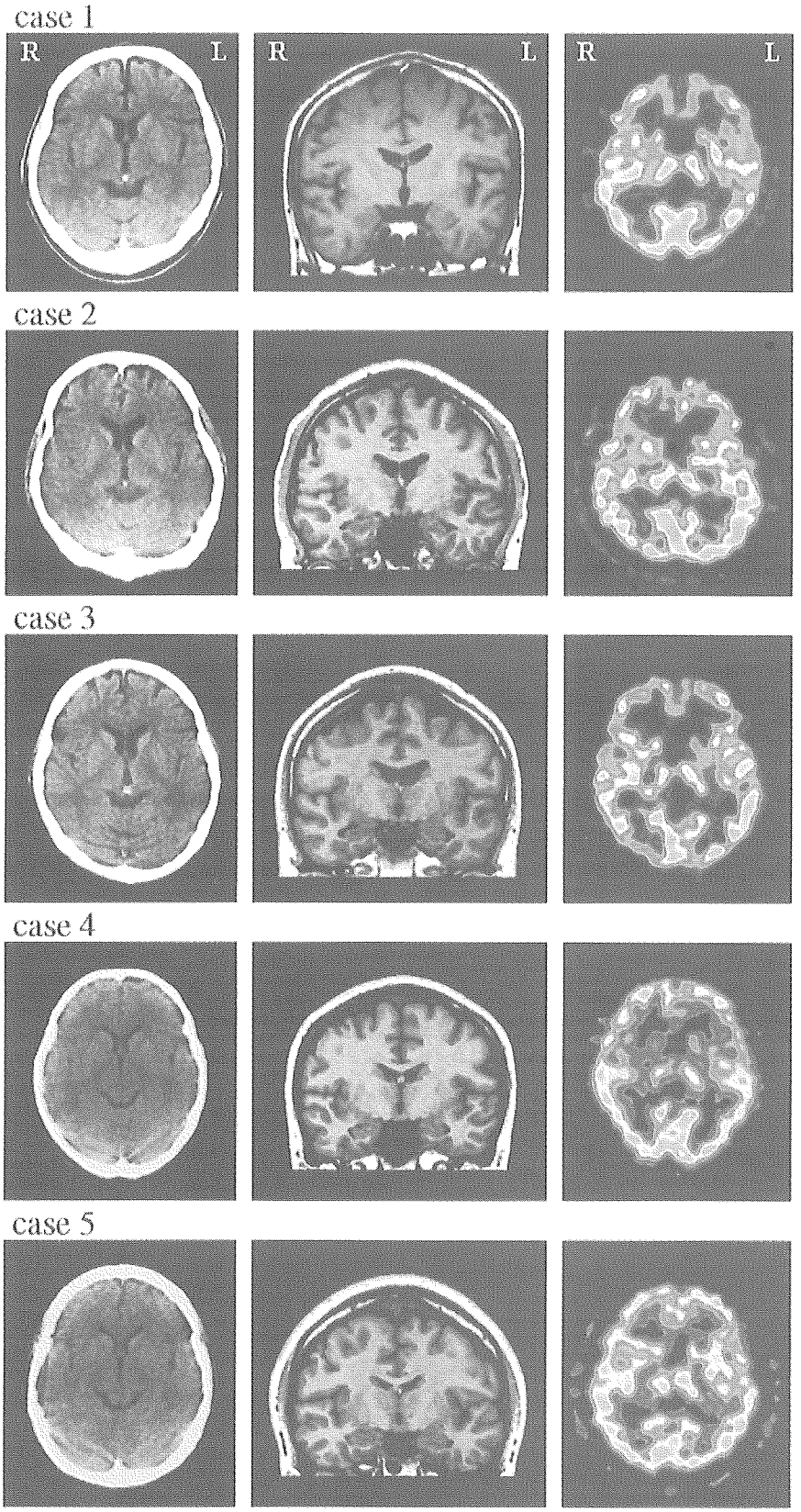

Fig. 1. Computed tomography images (left column), T1-weighted coronal magnetic resonance images through the mammillary body (middle column), and single photon emission computed tomography images (right column) in each patient with simple schizophrenia. Findings are described in the text.

Table 5
Location and stereotactic coordinates of the maxima demonstrated significant regional gray matter reduction in patients with simple schizophrenia compared with normal controls and corresponding *P* and *T* values

Location (Brodmann area)	Voxel level	*T*	Coordinates*		
	P value (corrected)		*x*	*y*	*z*
Left inferior frontal gyrus (47)	0.033	6.84	−45	28	−14
Left frontal pole (10)	0.046	6.64	−24	64	−1

*The coordinates refer to position within the stereotactic space according to the atlas of Talairach and Tournoux (1988).

22 schizophrenic patients of other subtypes did not reveal any significant difference.

None of the symptom scores or WAIS-R scores were significantly correlated with regional gray matter in the patients with simple schizophrenia.

3.3. Functional brain imaging

3.3.1. Qualitative SPECT findings of individual cases

Fig. 1 presents representative transaxial SPECT images in each case. The ^{99m}Tc-HMPAO SPECT scans of all five cases were reported to be abnormal. In cases 1 and 2, SPECT revealed decreased perfusion in the anterior and medial parts of bilateral frontal regions. In case 1, a mild reduction in left temporo-parietal perfusion was also observed. Case 3 had reduced perfusion in the frontal areas, more predominantly in the right hemisphere. In case 4, hypoperfusion in the bilateral frontal and left superior temporal regions was noted. Case 5 showed hypoperfusion in the middle and inferior frontal regions of both hemispheres.

3.3.2. SPM analysis of SPECT

Compared with findings in 21 normal controls, the adjusted rCBF in five patients with simple schizophrenia was decreased in frontal regions of both hemispheres including lateral, medial, and orbital aspects of the prefrontal area (Fig. 3A). In comparison with 25 schizophrenia patients of other subtypes, simple schizophrenia patients had less rCBF in the anterior part of the left superior and middle frontal region (Fig. 3B). Table 6 presents the peak SPM coordinates of the significant clusters. The simple schizophrenia patients did not show significantly increased rCBF in any region compared with the controls or schizophrenic patients of other subtypes.

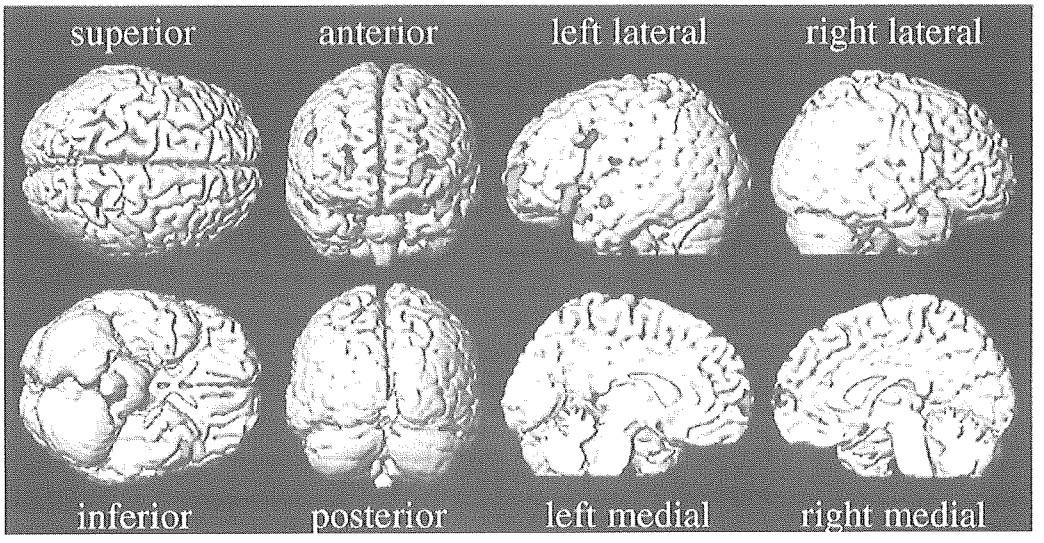

Fig. 2. Areas with gray matter reduction in four patients with simple schizophrenia compared with 20 normal controls are illustrated in red. The presetting of height threshold, $P<0.001$ (uncorrected), was adopted for illustrative purposes only.

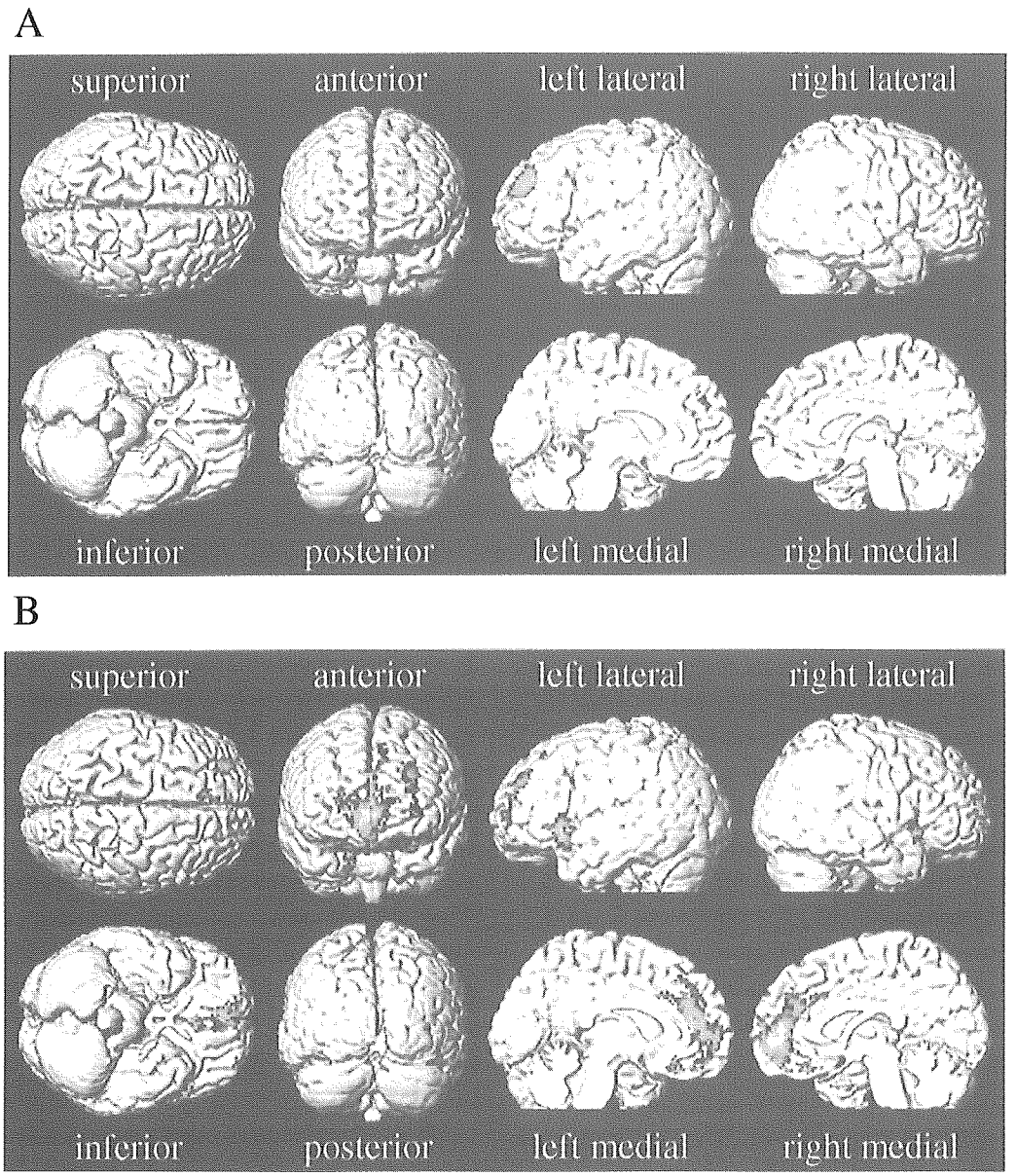

Fig. 3. Areas with significantly reduced perfusion in five patients with simple schizophrenia are illustrated in red, compared with 21 normal controls (A) or 25 schizophrenia patients with subtype diagnoses other than simple schizophrenia (B).

Correlation analyses revealed no significant correlation between any of the symptom scores or WAIS-R scores and rCBF.

4. Discussion

The present study included five patients who fulfilled the criteria for both simple deteriorative disorder in DSM-IV and simple schizophrenia in ICD-10. Such patients are so rare that we were able to collect only five cases from patients consecutively admitted to our department during the last 10 years.

This study was clearly limited by the small sample size of the patients with simple schizophrenia, and all findings should be considered preliminary. Voxel-based analyses of brain-imaging data with a small number of patients were undertaken not to draw conclusions but to look for a guide for further study of this uncommon disorder. Another limitation is related to the clinical diagnosis of the patients. Although the diagnoses were carefully made according to detailed premorbid and morbid information, because of the

Table 6
Location and stereotactic coordinates of the maxima demonstrated significant regional hypoperfusion in patients with simple schizophrenia compared with normal controls or other schizophrenia subtype patients and corresponding P and T values

Location (Brodmann area)	Voxel level	T	Cluster level	Coordinates*		
	P value (uncorrected)		P value (corrected)	x	y	z
Compared with normal controls						
Left medial frontal gyrus (8)	<0.001	5.91	<0.001	−10	42	16
Straight gyrus (11)	<0.001	5.70	<0.001	0	28	−22
Left inferior frontal gyrus (47)	<0.001	5.32	<0.001	−50	20	−4
Right inferior frontal gyrus (47)	<0.001	4.84	0.001	46	16	−4
Left superior and middle frontal gyrus (9)	<0.001	4.81	<0.001	−28	50	34
Compared with other schizophrenia subtypes						
Left superior and middle frontal gyrus (9)	<0.001	5.29	0.042	−28	48	32

*The coordinates refer to position within stereotactic space according to the atlas of Talairach and Tournoux (1988).

problems inherent in the diagnosis of simple schizophrenia, they may well be changed in the future if prominent delusions or hallucinations develop after long-lasting negative symptoms. However, for further understanding of this uncommon disorder, it is thought important to collect patients currently conforming to the strict operational diagnostic criteria and to accumulate our knowledge of the neurobiological features of such patients.

The major findings in this study were that some of the patients with simple schizophrenia had an apparent atrophic appearance and all had reduced cerebral perfusion in the frontal lobe. To our knowledge, there have been two studies that examined brain abnormalities in patients with simple schizophrenia employing modern brain-imaging techniques (Galderisi et al., 1999; Serra-Mestres et al., 2000). Galderisi et al. (1999) compared MRI scans of patients fulfilling ICD-8/9 criteria for simple schizophrenia as well as DSM-IV criteria for simple deteriorative disorder with scans of other schizophrenic subtype patients and neurological controls. Although simple schizophrenia patients had greater ventricle and subarachnoid space volumes than the controls, they did not find any major differences between the patients with simple schizophrenia and those with other subtypes. Serra-Mestres et al. (2000) performed CT and SPECT scans in patients with simple schizophrenia meeting Black and Boffeli's criteria (Black and Boffeli, 1989). Of the nine patients, three had a minor degree of cortical atrophy, whereas all patients showed SPECT abnormalities, with a pattern of frontal and/or temporal perfusion deficits. Compared with the results of these earlier studies, some of our patients revealed more remarkable atrophic changes in the frontal lobe on CT and MRI scans. In accordance with the study by Serra-Mestres et al. (2000), the SPECT scans in the present study showed brain perfusion deficits in all the patients examined. It should be noted that our schizophrenia comparison group consisted of several different subtypes. It is, however, unlikely that this factor significantly affected the results because the imaging characteristics of the simple schizophrenia patients were rather robust even in each single case. It might be reasonable to predict that these features would be even stronger if we were able to collect a larger number of patients with simple schizophrenia. Our results and those of Serra-Mestres et al. (2000) suggest that brain-imaging techniques may play a supplementary but important role in the clinical diagnosis of simple schizophrenia.

Convergent evidence suggests that the pathological process in schizophrenia predominantly affects the fronto–temporolimbic–paralimbic regions (Shenton et al., 2001; Suzuki et al., 2002). Structural abnormalities in the frontal lobe have been demonstrated in many volumetric (Andreasen et al., 1994; Buchanan et al., 1998; Sullivan et al., 1998; Crespo-Facorro et al., 2000; Mitelman et al., 2003; also see reviews by Shenton et al., 2001) and voxel-based morphometric studies of MRI (Wright et al., 1999; Paillère-Martinot et al., 2001; Sigmundsson et al., 2001; Wilke et al., 2001; Ananth et al., 2002; Suzuki et al., 2002; Kawasaki et al., 2004). Post-mortem brain studies have also revealed prefrontal abnormalities in neuronal number (Benes et al., 1991), size (Rajkowska et al., 1998), and

density (Benes et al., 1986; Selemon et al., 1995). Reduced metabolic activity or reduced task-related activation in the frontal lobe (so-called "hypofrontality") is one of the best established findings reported in functional imaging studies of schizophrenia (Ingvar and Franzén, 1974; Weinberger et al., 1986; Buchsbaum et al., 1992; Taylor, 1996), although it is normally detected statistically as a group difference from comparison subjects. Hypofrontality has been correlated with the severity of negative symptoms or psychomotor poverty syndrome and cognitive impairments (Wolkin et al., 1992; Liddle et al., 1992; Yuasa et al., 1995; Andreasen et al., 1996; Nohara et al., 2000). A recent positron emission tomography study has shown that schizophrenia patients of the Kraepelinian type, characterized by an unremitting course and poor outcome, have lower frontal glucose metabolism (Buchsbaum et al., 2002). MRI studies have also shown a relationship between volume reduction in the frontal lobe and psychomotor poverty syndrome or social dysfunction (Chua et al., 1997; Chemerinski et al., 2002).

In the present study, the patients with simple schizophrenia showed relatively severe functional abnormalities in the prefrontal regions. Some of the patients also revealed atrophic appearance of the frontal lobes. These prefrontal abnormalities may underlie severe and persistent negative symptoms in our patients, although correlation analyses failed to demonstrate such relationships probably due to the small sample size. The prefrontal association cortices are known as regions where myelogenesis occurs latest and maturation is the most protracted in the human brain (Yakovlev and Lecours, 1967; Fuster, 1997; Sowell et al., 2001, 2003). Insults to the pre- or post-natal myelination process in the prefrontal areas might be involved in the prominent negative symptoms enduring after the onset without remission in simple schizophrenia. However, these abnormalities appear not to be specific to simple schizophrenia, but to be more severe in simple schizophrenia than in other subtypes.

Previous volumetric MRI studies have repeatedly revealed enlargement of the inferior horn of the lateral ventricle (Degreef et al., 1992; Yotsutsuji et al., 2002) or volume reductions in medial temporal structures such as the hippocampus, amygdala, and parahippocampal gyrus in patients with schizophrenia other than simple subtype (see reviews by Lawrie and Abukmeil, 1998; Wright et al., 2000; Shenton et al., 2001). Some of these studies have reported associations between the enlarged inferior horn or reduced medial temporal volume and positive psychotic symptoms in schizophrenia (Degreef et al., 1992; Kawasaki et al., 1993; Bogerts et al., 1993). In this context, it may be of interest to note that none of the five cases with simple schizophrenia had obvious atrophic features of the medial temporal lobes by visual inspection of CT or MRI. Nor did voxel-based analysis of MRI reveal any gray matter reductions in the medial temporal structures, which have been rather consistently reported in previous voxel-based morphometric studies in schizophrenia (Wright et al., 1999; Paillère-Martinot et al., 2001; Sigmundsson et al., 2001; Kubicki et al., 2002; Suzuki et al., 2002; Kawasaki et al., 2004). A speculative interpretation is that the lack of morphological changes in the medial temporal lobes or deviant involvement of the prefrontal areas relative to the medial temporal structures might be related to brain mechanisms that suppress the clear manifestation of positive symptoms in simple schizophrenia.

Taken together, our five cases may occupy an extreme position on the schizophrenic continuum where the prefrontal deficits/negative symptoms are most purely manifested as a phenotype. Chronicity of illness and putatively severe cognitive impairments may also be associated with prefrontal abnormalities. Further functional imaging studies should be performed to test the task-related prefrontal activation that may reflect a functional reserve of the prefrontal cortex in patients with simple schizophrenia.

It is known that schizophrenia is often associated with impairment in general intellectual functioning (IQ) and, among schizophrenia patients, verbal IQ is generally higher than performance IQ (Aylward et al., 1984). In the present study, we did not apply a measure of premorbid intellectual functioning such as the National Adult Reading Test. However, compared with performance on the Vocabulary subtest, which has been thought to be a good indicator of original intellectual ability (Russell et al., 2000), performance on other subtests in our patients with simple schizophrenia was worse in general. Also considering the educational levels and premorbid occupational functioning of the patients, their current IQs may have

considerably deteriorated from the baseline. Although the WAIS-R was not designed to provide specific information to separate frontal lobe from more widespread disturbance, several subtests may reflect frontal lobe malfunction: sustained attention measured by the Digit Span or Digit Symbol subtest may be impaired by frontal lobe damage and, depending on the size and location of the lesion within the frontal lobe, constructional abilities assessed by the Object Assembly or Block Design subtest may be affected (Stuss and Benson, 1986). It is of interest to note that the simple schizophrenia patients in the current study had lower scores on the Digit Span, Object Assembly, and Digit Symbol subtests than on other subtests (Table 4). Systematic neuropsychological investigations including tests specific to frontal lobe functions may also help to determine the nature of the prefrontal disorders in simple schizophrenia patients (such a study is currently being performed).

In conclusion, the present study suggests that simple schizophrenia, or at least a subpopulation, may have rather homogeneous features of brain morphological and functional abnormalities affecting the prefrontal area. In further studies, larger samples and/or longitudinal courses of patients with simple schizophrenia should be investigated using quantitative brain-imaging techniques as well as neuropsychological batteries.

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Appendix A. Case 1

A 43-year-old single man. His birth, early development, and childhood were unremarkable. He achieved average performance at school. He went on to work between the age of 23 and 32 after graduation from university, but changed several jobs for ambiguous reasons. At the age of 28 after his father died, he returned home and started to live with his mother. His mother had been socially withdrawn and was said to suffer from psychiatric disorder. After he stopped working, he was also totally socially withdrawn and spent all day sitting with a foot warmer and watching TV. At the age of 41, he felt numbness in his extremities and difficulties in walking. Soon after this, his feet became immobile in "talipes equinus" due to disuse atrophy of the Achilles tendons. He could not walk and began to sit in a wheelchair. His mother took meals to him and helped him to excrete. He was sitting in a room full of trash and did not take a bath for more than a year. A nurse in the public health center and his cousin took him to the hospital.

On admission, he was filthy and dishevelled but appeared indifferent to his physical condition and the environment. He showed obvious flattening of affect and aspontaneity. He would almost invariably lie down on the bed and stare at the ceiling. He showed a minor degree of poverty of speech, typically giving superficial answers at some length to questions. There was no evidence of formal thought disorder, and repeated interviews did not reveal any evidence of delusions or hallucinations.

Treatment with neuroleptics resulted in modest improvement. He gradually became able to walk with a physical rehabilitation program that he required great encouragement to carry out. After a 2-year admission, he was transferred to another hospital for further rehabilitation.

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Volumetric analysis of sulci/gyri-defined in vivo frontal lobe regions in schizophrenia: Precentral gyrus, cingulate gyrus, and prefrontal region

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Abstract

Methodological limitations in most previous magnetic resonance imaging (MRI)-based volumetric studies might have contributed to the inconsistent results regarding the frontal lobe regions of schizophrenia. Thus, applying the largest sample to date among those that have fully taken account of the intrinsic anatomical landmarks, this study aimed at clarifying the volumetric alterations of the frontal lobe and its subregions in schizophrenia. Participants comprised 59 patients with schizophrenia and 58 healthy controls. Measurements were performed on consecutive 1-mm-thick coronal slices reformatted from three-dimensional 1.5-T MR images. The whole frontal lobe was demarcated and then subdivided into the precentral gyrus (PCG), anterior cingulate, and posterior cingulate, and the remainder temporarily as the prefrontal region. Patients with schizophrenia had significant cortical volume reductions in the bilateral whole frontal lobe, prefrontal region, PCG, posterior cingulate, and right anterior cingulate. This study has confirmed that patients with schizophrenia do have cortical volume reductions in the whole frontal lobe and its subregions. Volume reduction in the PCG suggests that the primary motor cortex might contribute to the mechanisms of schizophrenia, considering its important role in the processing of multiple motor-related cognitive functioning suggested by the recent literature.

Keywords: Psychosis; Brain morphometry; Magnetic resonance imaging; Primary motor cortex; Mirror neuron system

1. Introduction

Although frontal lobe dysfunction has been repeatedly shown to be one of the central characteristics of

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schizophrenia, magnetic resonance imaging (MRI)-based volumetric studies attempting to determine in vivo gross structural alterations in this region have failed to provide consistent evidence, with approximately 40% reporting negative results (as reviewed by McCarley et al., 1999; Shenton et al., 2001; Wright et al., 2000 for a meta-analysis). Such inconsistency may partially result from small alterations in the frontal lobe being just at the threshold for MRI detection, but considerable methodological differences in defining boundaries for regions of interest among previous studies might have contributed more. Using arbitrary landmarks (e.g., the coronal level of the genu of the corpus callosum as the posterior boundary of the prefrontal region) (methods reviewed by Convit et al., 2001), superficially, could maintain uniform tracing procedures among subjects and achieve high intra- and inter-rater reliabilities. However, such methods might have failed to take into account the large morphological variance in the frontal lobe structures across subjects and even between the hemispheres. Furthermore, the measured volume of the (pre)frontal lobe could be affected by anatomically abnormal landmark structures. In fact, the corpus callosum has been reported to be abnormal in size or shape (Shenton et al., 2001). Thus, using different arbitrary landmarks could not only have resulted in inconsistency, but also could have made it difficult to document that the measures and the statistical results are valid. Although a number of studies have measured the whole (pre)frontal lobe based on intrinsic anatomical landmarks (Buchanan et al., 1998; Baaré et al., 1999; Crespo-Facorro et al., 2000; Convit et al., 2001; Yamasue et al., 2004), they may not be definitive because only relatively small samples (fewer than 30 patients) were used. We argue that the distributions of anatomical brain measures in schizophrenia populations often have larger variances and considerable overlap with those of the normal population, and the magnitude of the morphological alterations in the brain structures of schizophrenia patients is generally small. So results from small samples could be either unstable or insufficient to examine such small differences. Among these previous approaches, two studies (Crespo-Facorro et al., 2000; Yamasue et al., 2004) employed fairly large samples. However, as the former examined only male patients and the latter had a patient sample composed of 20 males and 7 females, both studies were inappropriate to examine gender effects. There are also two important studies on this topic that must be mentioned here (Gur et al., 2000; Hirayasu et al., 2001), although neither study traced the frontal lobe fully according to the intrinsic anatomical landmarks; one employed a carefully selected sample composed of almost 20 first-episode schizophrenia patients and demonstrated a significant reduction of the total prefrontal gray matter (Hirayasu et al., 2001), and the other had a sample even larger than ours and showed volume reductions in multiple prefrontal regions (Gur et al., 2000). Another main reason for the inconsistent frontal lobe findings in schizophrenia frontal lobe might be taking this anatomically and functionally heterogeneous large tissue as a whole. Although almost all the frontal subregions have at least once been reported to be smaller in schizophrenia (Buchanan et al., 1998; Baaré et al., 1999; Goldstein et al., 1999; Gur et al., 2000; Crespo-Facorro et al., 2000; Convit et al., 2001; Chemerinski et al., 2002; Yamasue et al., 2004), findings are not consistent across studies and rarely replicated, and the use of small samples is still a common limitation of these studies.

The present study has attempted to overcome these various methodological limitations. First, we set up feasible gyri/sulci-based methods for MRI-based parcellation of the frontal lobe, largely following the guidelines of Rademacher et al. (1992) and Crespo-Facorro et al. (1999). With the availability of synchronous–orthogonal views in three dimensions, in conjunction with the context of gyri/sulci on successive coronal slices, decisions of necessary anatomical landmarks could be readily made. Regional white matter was also defined by using the main landmarks. Second, the whole frontal lobe was ultimately subdivided into multiple functionally homogeneous subregions similar to those defined by the Iowa group (Crespo-Facorro et al., 1999). For the first phase of this study, the whole frontal lobe was separated from the rest of the cerebrum and then subdivided into the precentral gyrus (PCG, the primary motor area [M1]), cingulate gyrus (the limbic area), and the remainder temporarily as the prefrontal area (the cognitive area). In contrast to the prefrontal cortex and anterior cingulate gyrus, little attention has been paid to volumetric alteration of the PCG and posterior cingulate in schizophrenia. However, M1 has recently been suggested to play an important role in the processing of motor-related cognitive informa-

tion as a node of the human mirror–neuron system (reviewed by Georgopoulos, 2000), and the posterior cingulate has also been suggested to subserve a variety of cognitive functions (e.g., long-term memory and working memory) (reviewed by Maddock, 1999; Kobayashi, 2001). Third, we performed the measurements in the largest sample to date among those that have fully taken account of the intrinsic anatomical landmarks of the frontal lobe and its subregions in schizophrenia. This sample was composed of roughly equal numbers of male and female patients (about 30 of each) and matched control subjects, thus allowing an observation of gender effects. We expected that patients with schizophrenia would show volume reductions in the whole frontal lobe and some of the subregions (e.g., prefrontal region and cingulate gyrus); as for the PCG, it was difficult to make a special hypothesis because of the background that this region had been rarely mentioned in previous studies. However, given the potential importance of the PCG in cognitive processing, it would be of interest to examine the region morphometrically in schizophrenia.

2. Methods

2.1. Subjects

Table 1 presents the demographic and clinical data of the subjects. All subjects were right-handed. The groups were matched for age, gender, and parental education.

Fifty-nine medicated patients with DSM-IV schizophrenia were recruited from both inpatient and outpatient clinics. Diagnoses were made based on the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1997). Clinical symptoms were rated within 1 month of scanning using the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984a) and the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1984b). Fifty-eight control subjects were healthy volunteers recruited from among the community, hospital staff, and medical students. They were interviewed by psychiatrists using a questionnaire concerning their families, histories, and present illness. Subjects were excluded if they had a history of head trauma, neurological illness, serious medical or surgical illness, or substance abuse disorder. Control subjects with a personal or family history of psychiatric disorder or any T-score of the Minnesota Multiphasic Personality Inventory (MMPI) exceeding 70 were also excluded.

After complete description of the study to the subjects, written informed consent was obtained. This study was approved by the Committee on Medical Ethics of the Toyama Medical and Pharmaceutical University.

2.2. Magnetic resonance image acquisition and processing

Magnetic resonance images (MRI) were obtained using a 1.5-T Magnetom Vision (Siemens Medical

Table 1
Demographic and clinical characteristics of the subjects

Characteristics	Schizophrenia patients		Normal control subjects	
	Male ($n=31$)	Female ($n=28$)	Male ($n=30$)	Female ($n=28$)
Age (years)	25.4 ± 4.9	25.7 ± 5.1	24.9 ± 5.1	24.8 ± 5.9
Education (years)	13.5 ± 1.96*	13.3 ± 2.0*	17.1 ± 2.7	15.0 ± 1.7**
Parental education (years)	12.4 ± 1.8	12.0 ± 2.4	13.0 ± 2.5	12.6 ± 2.5
Age at onset of illness (years)	21.9 ± 4.5	22.0 ± 4.4	–	–
Duration of illness (years)	3.6 ± 4.0	4.1 ± 4.3	–	–
Duration of medication (years)	2.4 ± 2.9	3.1 ± 3.6	–	–
Dose of drug (mg/day; HPD equivalent)	11.9 ± 8.6	10.5 ± 10.7	–	–
Total SAPS score	23.1 ± 21.4	27.1 ± 20.5	–	–
Total SANS score	49.8 ± 22.8	44.2 ± 24.1	–	–

Values represent mean ± S.D.
HPD, haloperidol; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms.
* Significantly different from the same-gender control subjects ($P<0.02$).
** Significantly different from male control subjects ($P<001$).