Multiple Structural Brain Measures Obtained by Three-Dimensional Magnetic Resonance Imaging To Distinguish Between Schizophrenia Patients and Normal Subjects

by Kazue Nakamura, Yasuhiro Kawasaki, Michio Suzuki, Hirofumi Hagino, Kenzo Kurokawa, Tsutomu Takahashi, Lisha Niu, Mie Matsui, Hikaru Seto, and Masayoshi Kurachi

Abstract

This study was designed to investigate the extent to which schizophrenia patients can be differentiated from normal subjects by structural brain measures. High-resolution magnetic resonance imaging scans were performed on 57 schizophrenia patients (30 males, 27 females) and 47 normal controls (25 males, 22 females). Significant enlargements of the left and right body of the lateral ventricle, the left and right sylvian fissure, and the third ventricle were observed in the male patients. Significant enlargements of the left inferior horn, and the left and right sylvian fissure, and a significant volume reduction of the right temporal lobe were observed in the female patients. Discriminant function analysis using brain anatomical measures as variables allowed correct classification of 80.0 percent of the male patients, 80.0 percent of the male controls, 77.8 percent of the female patients, and 86.4 percent of the female controls. These findings support the view that schizophrenia patients have structural deviations in multiple brain areas and that a combination of structural brain measures can distinguish between patients and controls.

Keywords: Schizophrenia, magnetic resonance imaging, discriminant function analysis, diagnosis.


Structural brain abnormalities have been widely demonstrated in schizophrenia. With a high image resolution and a defined tissue contrast, magnetic resonance imaging (MRI) allows for detailed noninvasive morphological studies. Morphological assessments using MRI have demonstrated a variety of structural brain abnormalities in schizophrenia (Lawrie and Abukmeil 1998; McCarley et al. 1999; Wright et al. 2000), including ventricular enlargement (Degreif et al. 1992; Kawasaki et al. 1993; Sanfilipo et al. 2000a), dilatation of the Sylvian fissure (Schwartz et al. 1992; Aso et al. 2001), dilatation of the third ventricle (Suddath et al. 1990), and modest reduction in volume of the left superior temporal gyrus (Barta et al. 1990; Shenton et al. 1992), left planum temporale (Kwon et al. 1999), medial temporal lobe structures (Bogerts et al. 1993; Fukuzako et al. 1996; Pearlson et al. 1997; Whitworth et al. 1998), frontal lobe (Buchanan et al. 1998; Sanfilipo et al. 2000b), total brain gray matter (Gur et al. 1999), and total brain size (Ward et al. 1996). Despite the sufficient reproducibility of the evidence, no structural brain changes specific for schizophrenia have ever been confirmed. One would expect that the structural abnormalities of schizophrenia are not limited to just one or a few clearly delimited brain regions.

Although MRI has brought about increasing understanding of pathophysiology, little if any progress has been made in the clinical application of structural neuroimaging methods, especially in the diagnosis of schizophrenia. Because ventricular enlargement has been the most often replicated morphological finding in schizophrenia, some studies (Daniel et al. 1991; Vita et al. 2000) have evaluated the distribution of ventricular size. These studies showed considerable overlap in the ventricular size of schizophrenia patients and normal controls. The degree of differentiation based on this parameter was only very partial, and far from allowing ventricular size to be used as a distinguishing factor.
Several investigators have been studying the possibility that structural brain imaging can be used clinically as a diagnostic and/or prognostic tool. In a study of the computed tomography (CT) scans of 22 patients with a first episode acute schizophreniform disorder, Vita et al. (1991) reported that all 7 found to have ventricular enlargement at the initial evaluation (ventricle-to-brain ratio more than two standard deviations [SDs] above the mean in the controls) developed schizophrenia during follow-up periods of 2 to 10 years. Uchino et al. (1988) reported being able to correctly classify 90 percent of schizophrenia patients and 100 percent of normal controls by discriminant function analysis using two variables measured on the brain CT images: dimension of the anterior horn of the left lateral ventricle and the left Sylvian fissure. After the advent of MRI, Delisi et al. (1992) found that patients with schizophreniform disorder who had a larger ventricle-to-brain ratio tended to have a poor outcome, and Suddath et al. (1990) reported being able to identify the affected twin by visual inspection of the MRI images alone in 12 of 15 sets of monozygotic twins discordant for schizophrenia. Our preliminary study (Kurokawa et al. 2000) suggested the usefulness of reconstructed coronal slices of three-dimensional MRI images for distinguishing patients with schizophrenia spectrum disorders manifesting symptoms of obsessive-compulsive disorder (OCD) from nonpsychotic OCD patients. Another study (Leonard et al. 1999) of only male subjects reported that a combination of ten anatomical variables on MRI images enabled reliable classification of 76 percent of schizophrenia patients and 79 percent of controls.

Because the magnitude of a single brain abnormality is so slight (Lawrie and Abukmeil 1998), we assumed that a single brain anatomical variable would be quite limited in its ability to differentiate. We hypothesized that a combination of brain anatomical variables would be effective in differentiating between schizophrenia patients and normal subjects. To test our hypothesis, we measured several brain regions on reconstructed coronal slices obtained by three-dimensional MRI and applied discriminant function analysis to assess the ability of combinations of brain anatomical variables to differentiate between patients and control subjects.

**Methods**

**Subjects.** Fifty-seven patients (30 males, 27 females) who fulfilled ICD-10 diagnostic criteria for research on schizophrenia (WHO 1993) were recruited from the inpatient and outpatient clinics of the Department of Neuropsychiatry, Toyama Medical and Pharmaceutical University Hospital. All but four (three males, one female) were right-handed. The average age of the male patients was 26.2 ± 5.6 (SD) years (range: 15–36), and the average age of the female patients was 29.3 ± 7.6 years (range: 15–45). One patient (1 male) was neuroleptic-naive, and three patients (two males, one female) were neuroleptic-free for at least 1 month before the study. The other 53 patients were on neuroleptic medication. The mean chlorpromazine-equivalent neuroleptic dose was 423.4 ± 374.2 mg/day in the male patients and 557.4 ± 508.5 mg/day in the female patients (Pakes 1982; APA 1997). Forty-one patients (24 males, 17 females) were receiving typical neuroleptics, 7 patients (4 males, 3 females) were being treated with atypical neuroleptics, such as risperidone, and 5 patients (1 male, 4 females) were being treated with a combination of atypical and typical neuroleptics. The mean age of the male patients at the onset of schizophrenia was 21.2 ± 4.5 years, and the mean age of the female patients at the onset was 23.1 ± 5.5 years. The mean interval between the onset of illness and this study was 68.8 ± 53.3 months among the male patients and 77.0 ± 62.5 months among the female patients. Patients with a lifetime history of organic brain disease, head injury, neurological illness, or significant substance abuse were excluded.

The normal controls consisted of 47 healthy volunteers (25 males, 22 females) recruited from hospital staff, medical students, pharmaceutical students, and their relatives. All of the controls but one female were right-handed. The mean age of the male control subjects was 25.1 ± 5.5 years (range: 18–38), and the mean age of the female control subjects was 26.3 ± 7.1 years (range: 20–41). Subjects were excluded if they had a lifetime history of psychiatric illness, organic brain disease, head injury, or significant substance abuse, or a family history of psychiatric illness. All normal controls took the Minnesota Multiphasic Personality Inventory (MMPI; New Japanese MMPI Committee 1997), and subjects were excluded if any of the t scores for the validity scales or clinical scales exceeded 70.

The clinical status of all patients was stable. The purpose and procedures of the present study were explained to all subjects, and their informed consent was obtained. This study was approved by the Committee on Medical Ethics of Toyama Medical and Pharmaceutical University.

**MRI Procedure.** MR images were obtained with a 1.5-T Magnetom Vision machine (Siemens Medical System, Inc., Erlangen, Germany). A three-dimensional fast low angle shot (FLASH) imaging sequence was used to obtain T1-weighted images with a slice thickness of 1.0 mm in the sagittal plane. Imaging parameters were time to repetition (TR) = 24 ms, time to echo (TE) = 5 ms, flip angle = 40°, matrix 256 × 256, number of excitations = 1, and field of view = 25.6 cm. Voxel size was 1.0 × 1.0 × 1.0 mm.
The MRI data were transferred to a Unix workstation (Silicon Graphics, Inc., Mountain View, CA) and were randomly coded and analyzed with Dr. View 5.0 software (Asahi Kasei Joho System Co., Ltd., Tokyo, Japan). Before reconstruction of the MR images, they were realigned in three dimensions to standardize for differences in head tilt during MR image acquisition. Head tilt in the sagittal plane was corrected by aligning the anterior commissure–posterior commissure (AC–PC) plane. Correction in the axial and coronal planes was achieved by aligning the longitudinal third ventricle and the interhemispheric fissure by reference to the symmetry of the eyeballs and the optic nerves. After correction, entire contiguous coronal images were reconstructed with 1-mm-thick slices vertical to the AC–PC line. The three contiguous coronal slices in which the mammillary body was most clearly seen were chosen for measurement. There were two reasons for using the mammillary body as the guideline for the MRI measurements. First, the fact that the mammillary body is a small, discrete structure makes selection of the slices precise and easy to reproduce. Second, these slices include several important brain regions in which structural abnormalities have been repeatedly reported in schizophrenia, such as the lateral and third ventricles, the Sylvian fissure, the superior temporal gyrus, and the medial temporal lobe structures. Not single but three contiguous slices were used to reduce the variability of region of interest (ROI) volume that accompanies slice selection.

The volume of the following ROIs was measured: the body and inferior horn of the lateral ventricle, the third ventricle, the Sylvian fissure, the interhemispheric fissure, the temporal lobe, and the gray matter and white matter of the superior temporal gyrus (figure 1). We also measured volumes of the left and right cerebral hemispheres for further regression procedure. The temporal lobe was demarcated by drawing a line perpendicular to the axis of the temporal stem from the inferior aspect of the insula. The medial boundary of the superior temporal gyrus was defined by a line connecting the superior temporal sulcus with the circular sulcus, the superior boundary by the Sylvian fissure, and the inferior boundary by the superior temporal sulcus (Bryant et al. 1999). The lateral boundary of the Sylvian fissure was defined by a line connecting the outer limb of the postcentral gyrus with the outer limb of the superior temporal gyrus. The superior boundary of the interhemispheric fissure was defined by a line connecting the outer limb of the left superior frontal gyrus with the right one. The hippocampus and the amygdala, important because of their theoretical relevance to schizophrenia, were also visible on the images, but because the study slices were taken at the transition between the regions, each image showed either the amygdala or the hippocampus. Because this might confound the interpretation of the results, we excluded the medial temporal lobe structures from the evaluated regions.

The signal-intensity distributions of the voxels were calculated from all T1-weighted images of each subject according to the Alpert algorithm (Alpert et al. 1996), and the results were displayed in histograms. Histograms of gray levels were computed and used to select minimal intensity points between the gray matter and cerebrospinal fluid (CSF) peaks (lower intensity threshold) and between the gray and white matter peaks (upper intensity threshold). These thresholds were used to segment the voxels into gray matter, white matter, and CSF. The cerebral hemisphere was distinguished from the sulcal and ventricular CSF by using a lower intensity threshold, and its surface was outlined manually with a cursor and demarcated from other tissue (i.e., skull, scalp, and neck tissue). The body and inferior horn of the lateral ventricle, the third ventricle, the Sylvian fissure, and the interhemispheric fissure were recognized by voxels with signal intensity corresponding to the CSF level in every slice, and these voxels were colored to measure ROI volumes. In other regions, after brain tissue was separated from sulcal CSF by using a lower intensity threshold, each anatomical region was outlined manually with a cursor, and the voxels of the delineated region were colored. In the superior temporal gyrus, gray matter and white matter were measured separately by using the upper intensity threshold. Colored voxels were counted in each slice, and the voxels in three slices were summed and divided by three (i.e., number of slices) to obtain the actual volume of each region. Obtained left and right cerebral hemispheric volumes added up to the cerebral volume for the further regression procedure.

All measurements were carried out by one rater (K.N.) who was blinded to individuals' sex and diagnosis. The intraclass correlation coefficient for intrarater reliability was determined to be 0.95 for the white matter of the left superior temporal gyrus; 0.97 for the left and right cerebral hemispheres and the white matter of the left superior temporal gyrus; 0.98 for the interhemispheric fissure, the left inferior horn, the third ventricle, and the body of the right lateral ventricle; and 0.99 for all other regions. To evaluate the reliability of the measurements, a second rater (Y.K.) blinded to the diagnoses measured all regions in five cases. The intraclass correlation coefficient for interrater reliability was determined to be 0.97 for the third ventricle and the white matter of the right superior temporal gyrus, 0.98 for the interhemispheric fissure, and 0.99 for all other regions.

**Statistical Analysis.** All statistical analyses were performed using the software package STATISTICA 4.1J for
Figure 1. Regions measured and analyzed in this study

Note.—All regions were measured in the three consecutive reconstructed coronal slices, 1 mm thick, in which the mammillary body was most clearly seen.

Macintosh (Statsoft, Tulsa, OK). Demographic and clinical variables were compared across the four groups by analysis of variance (ANOVA). Post hoc Scheffé tests were carried out to follow up the significant main effects and interactions yielded by ANOVA.

Because the actual volumes of each ROI did not take into account normal variation associated with differences in cerebral volume and age, the raw data of the actual volumes were corrected by regression analyses for subject-to-subject variations in cerebral volume and age estimated from the normal controls in each gender. We followed this approach as outlined by Pfefferbaum et al. (1993) and Sullivan et al. (2000). In brief, brain measures for the control subjects were regressed against cerebral volume and age, yielding a residual value for each normal control that was independent of an estimate of brain size and normal aging (Zipursky et al. 1992). After calculation of the control group regression, the ROI value for the patients was entered into the same equation as for the normal controls to calculate residual values independent of normal aging and brain size effects. All regional volumes were expressed as $z$ scores. For the normal controls, the expected mean $z$ score was 0 with an SD of 1. The use of standardized $z$ scores allows analysis of disease-related changes independent of the effects of head size and normal aging (Mathalon et al. 1993). Lower $z$ scores for tissue volume and higher $z$ scores for CSF volume are in the direction of greater abnormality. Group differences in each ROI volume and discriminant function analysis were examined using $z$ scores.

A series of analyses of covariance (ANCOVAs) were carried out to evaluate differences in each ROI volume across the diagnostic groups for each gender separately. Diagnosis (i.e., schizophrenia or control) was used as a between-group factor, and laterality (i.e., left or right cerebral hemisphere) was used as a within-group factor. Educational level was treated as a covariate. One-way ANCOVAs for the third ventricle and the interhemispheric fissure were carried out without using laterality as the within-group factor (Strakowski et al. 1999). To compare the groups in terms of each ROI volume, post hoc Scheffé tests were conducted to follow up the significant main effect or interaction.
Discriminant function analyses were conducted to assess the ability of a combination of brain anatomical variables to distinguish between schizophrenia patients and normal controls. The independent variables were z scores for each ROI volume. Discriminant functions were derived by stepwise methods using Wilks method. Variables were selected for each gender separately according to stepwise selection criteria. The stepwise selection criteria were decided by the overall multivariate F value of each variable to test differences between the two diagnostic groups and to maximize the discriminant function between groups. Variables were entered by stepwise selection, with a minimum F value of 1.00 required to enter (Carter et al. 1999). No independent variables were intentionally forced into the discriminant function. The probability level adopted for statistical significance in all of the analyses was \( p < 0.05 \).

Results

Demographic and Clinical Characteristics. Table 1 summarizes the demographic and clinical characteristics of the schizophrenia patients and normal controls. There were no significant differences in age across the four groups. There was a significant main effect of sex for height (ANOVA, \( F = 181.0, df = 1,100, p < 0.001 \)). The post hoc Scheffé test showed that the male subjects were taller than the female subjects (\( p < 0.001 \)), but there were no significant differences between the patients and the normal controls within each gender group. There were significant main effects of sex (ANOVA, \( F = 10.23, df = 1,100, p < 0.001 \)), diagnosis (ANOVA, \( F = 27.71, df = 1,100, p < 0.001 \)), and the sex \( \times \) diagnosis interaction (ANOVA, \( F = 7.90, df = 1,100, p = 0.006 \)) for educational level across the four groups. The post hoc Scheffé test showed that the male control subjects had a higher educational level than the male patients (\( p < 0.001 \)), the female control subjects (\( p < 0.001 \)), and the female patients (\( p < 0.001 \)). There were no significant differences between the male patients and the female patients in age at onset, duration of illness, or medication dosage.

Pearson's correlation coefficients with Bonferroni corrections were used to assess the relationship between the actual volume of each ROI and medication dosage, age at the onset of illness, or duration of illness. No significant correlation was found between the actual volume of each ROI and any clinical features.

Comparison of the Volume of Each ROI Between Patients and Controls. Among the male subjects, the ANCOVA revealed a significant main effect of diagnosis (\( F = 6.44; df = 1,52; p = 0.014 \)) for the body of the lateral ventricle. Post hoc Scheffé tests showed that the left and right bodies of the patients were significantly larger than those of the normal controls (left: \( p < 0.001 \); right: \( p < 0.001 \)). There was a significant main effect of diagnosis for the Sylvian fissure (\( F = 6.62; df = 1,52; p = 0.012 \)). Post hoc Scheffé tests revealed that both the left and the right Sylvian fissure of the patients were significantly larger than those of the normal controls (left: \( p = 0.021 \); right: \( p = 0.039 \)). The third ventricle of the patients was significantly larger than that of the normal controls (\( F = 9.16; df = 1,52; p = 0.004 \)). There was no effect or interaction for the inferior horn of the lateral ventricle, the interhemispheric fissure, the temporal lobe, and the gray and white matters of the superior temporal gyrus (table 2, figure 2).

### Table 1. Demographics of the schizophrenia patients and normal controls

<table>
<thead>
<tr>
<th>Variable</th>
<th>Male (n = 30)</th>
<th>Male (n = 25)</th>
<th>Male (n = 27)</th>
<th>Male (n = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>26.2 ± 5.6</td>
<td>25.1 ± 5.5</td>
<td>29.3 ± 7.6</td>
<td>26.3 ± 7.1</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>170.0 ± 5.4²</td>
<td>172.1 ± 4.0²</td>
<td>158.9 ± 4.1²</td>
<td>159.8 ± 3.5²</td>
</tr>
<tr>
<td>No. (% of right-handed)</td>
<td>27 (90)</td>
<td>25 (100)</td>
<td>26 (96)</td>
<td>21 (95)</td>
</tr>
<tr>
<td>Education (yrs)</td>
<td>13.8 ± 2.0³</td>
<td>17.4 ± 3.5³</td>
<td>13.6 ± 2.1³</td>
<td>14.7 ± 1.0³</td>
</tr>
<tr>
<td>Age at onset (yrs)</td>
<td>21.2 ± 4.5</td>
<td>23.1 ± 4.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of illness (mos)</td>
<td>68.8 ± 53.3</td>
<td>77.0 ± 62.5</td>
<td>557.4 ± 508.5</td>
<td></td>
</tr>
<tr>
<td>Drug (mg/day, chlorpromazine equivalent)</td>
<td>423.4 ± 374.2</td>
<td>423.4 ± 374.2</td>
<td>423.4 ± 374.2</td>
<td>423.4 ± 374.2</td>
</tr>
</tbody>
</table>

*Note.* — ANOVA = analysis of variance; SD = standard deviation.

† Table values are mean ± SD.

² Significant main effect of sex for height (ANOVA, \( F = 181.0; df = 1,100; p < 0.001 \)). Post hoc Scheffé test showed that the male subjects were taller than the female subjects (\( p < 0.001 \)).

§ Significant main effect of sex (ANOVA, \( F = 10.23; df = 1,100; p = 0.002 \)), diagnosis (ANOVA, \( F = 27.71; df = 1,100; p < 0.001 \)), and sex \( \times \) diagnosis interaction (ANOVA, \( F = 7.90; df = 1,100; p = 0.006 \)). Post hoc Scheffé test showed that the male controls had higher education levels than the male patients (\( p < 0.001 \)), the female patients (\( p < 0.001 \)), and the female controls (\( p < 0.001 \)).
Table 2. F values of the ANCOVA main effects and interactions for all ROIs in male subjects

<table>
<thead>
<tr>
<th>ROI</th>
<th>Diagnosis (D)</th>
<th>Laterality (L)</th>
<th>D × L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body of lateral ventricle</td>
<td>6.44*</td>
<td>0.75</td>
<td>0.75</td>
</tr>
<tr>
<td>Inferior horn of lateral ventricle</td>
<td>0.01</td>
<td>1.01</td>
<td>1.01</td>
</tr>
<tr>
<td>Sylvian fissure</td>
<td>6.62*</td>
<td>0.03</td>
<td>0.03</td>
</tr>
<tr>
<td>Temporal lobe</td>
<td>0.02</td>
<td>0.02</td>
<td>0.02</td>
</tr>
<tr>
<td>White matter of superior temporal gyrus</td>
<td>0.76</td>
<td>0.31</td>
<td>0.31</td>
</tr>
<tr>
<td>Gray matter of superior temporal gyrus</td>
<td>0.04</td>
<td>0.76</td>
<td>0.76</td>
</tr>
<tr>
<td>Interhemispheric fissure</td>
<td>0.81</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Third ventricle</td>
<td>9.16**</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Cerebral volume</td>
<td>0.86</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Note.—ANCOVA = analysis of covariance; D × L = diagnosis by laterality interaction; ROI = region of interest.

1 F values for each region are from a D × L ANCOVA design with education as covariate, except for the 1-way ANCOVA for the interhemispheric fissure and third ventricle.

2 For the cerebral volume, 1-way ANCOVA with education as covariate was performed using raw data in each subject.

* p < 0.05; ** p < 0.01

Among the female subjects, ANCOVA revealed a significant main effect of diagnosis (F = 5.67; df = 1,46; p = 0.021) for the inferior horn. Post hoc Scheffé tests showed that the left inferior horn of the patients was significantly larger than that of the normal controls (p = 0.016). There was also a significant main effect of diagnosis on the Sylvian fissure (F = 8.39; df = 1,47; p = 0.005). Post hoc Scheffé tests revealed that both the left and right Sylvian fissure of the patients was significantly larger than in the normal controls (left: p < 0.001; right: p < 0.001). A significant main effect of laterality (F = 10.59; df = 1,47; p = 0.002) and a significant diagnosis × laterality interaction (F = 10.59; df = 1,47; p = 0.002) for the temporal lobe existed. Post hoc Scheffé tests revealed that the right temporal lobe of the patients was significantly smaller than that of the normal controls (p = 0.004) and that the temporal lobe of the patients was significantly smaller on the right side than that on the left (p = 0.004). There was no effect and interaction for the body of the lateral ventricle, the third ventricle, the interhemispheric fissure, and the gray and white matters of the superior temporal gyrus (table 3, figure 3).

Discriminant Function Analysis. Among the male subjects, the following variables were considered in the discriminant function analysis after the stepwise procedure: the third ventricle, the white matter of the left superior temporal gyrus, the right body of the lateral ventricle, the interhemispheric fissure, the left Sylvian fissure, the left body of the lateral ventricle, and the white matter of the right superior temporal gyrus (F = 3.96; df = 7,47; p = 0.002, Wilks lambda = 0.62). Use of these variables to reclassify the schizophrenia patients and normal controls resulted in correct classification of 80 percent of the
### Table 3. F values of the ANCOVA main effects and interactions for all ROIs in female subjects

<table>
<thead>
<tr>
<th>ROI</th>
<th>Diagnosis (D)</th>
<th>Laterality (L)</th>
<th>D × L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body of lateral ventricle</td>
<td>1.27</td>
<td>0.06</td>
<td>0.06</td>
</tr>
<tr>
<td>Inferior horn of lateral ventricle</td>
<td>5.67*</td>
<td>2.56</td>
<td>2.56</td>
</tr>
<tr>
<td>Sylvian fissure</td>
<td>8.39**</td>
<td>0.04</td>
<td>0.04</td>
</tr>
<tr>
<td>Temporal lobe</td>
<td>0.69</td>
<td>10.59**</td>
<td>10.59**</td>
</tr>
<tr>
<td>White matter of superior temporal gyrus</td>
<td>0.001</td>
<td>2.02</td>
<td>2.02</td>
</tr>
<tr>
<td>Gray matter of superior temporal gyrus</td>
<td>0.21</td>
<td>0.12</td>
<td>0.12</td>
</tr>
<tr>
<td>Interhemispheric fissure</td>
<td>0.01</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Third ventricle</td>
<td>3.01</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Cerebral volume</td>
<td>8.05**</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

**Note.**—ANCOVA = analysis of covariance; D × L = diagnosis by laterality interaction; ROI = region of interest.

1 F values for each region are from a D × L ANCOVA design with education as covariate, except for the 1-way ANCOVA for the interhemispheric fissure and third ventricle.

2 For the cerebral volume, 1-way ANCOVA with education as covariate was performed using raw data in each subject.

* 0.05; ** 0.01

### Figure 3. Standardized z scores for each region of interest for female patients with schizophrenia

![Image of standardized z scores](image)

**Note.**—GM = gray matter; WM = white matter. For the normal controls, the expected mean z score was 0 with a standard deviation of 1.

* 0.05; ** 0.01; *** 0.001

patients (empirical sensitivity) and 80 percent of the normal controls (empirical specificity) (table 4). Among the female subjects, the following variables were considered in the discriminant function analysis: the left Sylvian fissure, the left inferior horn, the right and the left temporal lobes, the white matter of the left and the right superior temporal gyrus, and the gray matter of the left superior temporal gyrus (F = 5.23; df = 7, 41; p < 0.001, Wilks lambda = 0.52), and use of these variables resulted in correct classification of 77.8 percent of the patients and 86.4 percent of the normal controls (table 5).

We also assessed the ability of single brain anatomical variables to discriminate between patients and controls by selecting the variables that had the largest F value according to the results of stepwise selection in each gender group. The third ventricle correctly classified 63.3 percent of the male patients and 64 percent of the male normal controls (F = 11.21; df = 1, 53; p = 0.002, Wilks lambda = 0.82). The left Sylvian fissure correctly classified 70.3 percent of the female patients and 72.7 percent of the female normal controls (F = 9.94; df = 1, 47; p = 0.003, Wilks lambda = 0.82).

### Discussion

We used discriminant function analysis with a combination of anatomical variables and found that it distinguished between the schizophrenia patients and normal controls with high correct classification rates. Measures of multiple brain anatomical variables enabled correct classification of 80 percent of the male and 81.6 percent of the female subjects. When only a single brain anatomical variable of the third ventricle for male or the left Sylvian...
Table 4. Classification of the male schizophrenia patients and male controls

<table>
<thead>
<tr>
<th>Actual group</th>
<th>Correct classification rate</th>
<th>Predicted Group</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia patients (n = 30)</td>
<td>80%</td>
<td>24</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Normal controls (n = 25)</td>
<td>80%</td>
<td>5</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>80%</td>
<td>29</td>
<td>26</td>
<td></td>
</tr>
</tbody>
</table>

Note.—F = 3.96; df = 7,47; p = 0.002, Wilks lambda = 0.62 for the discriminant analysis.

Table 5. Classification of the female schizophrenia patients and female controls

<table>
<thead>
<tr>
<th>Actual group</th>
<th>Correct classification rate</th>
<th>Predicted Group</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia patients (n = 27)</td>
<td>77.8%</td>
<td>21</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Normal controls (n = 22)</td>
<td>86.4%</td>
<td>3</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>81.6%</td>
<td>24</td>
<td>25</td>
<td></td>
</tr>
</tbody>
</table>

Note.—F = 5.23; df = 7,41; p < 0.001, Wilks lambda = 0.52 for the discriminant analysis.

Several studies have attempted to distinguish schizophrenia patients from normal controls by means of discriminant function analysis with variables obtained by positron emission tomography (Levy et al. 1991), neuropsychological tests (Arango et al. 1999; Evans et al. 1999), eye tracking function (Campana et al. 1999), MMPI scales (Carter et al. 1999), event-related potentials (Knott et al. 1999), and other modalities (Goldstein et al. 1999). Levy et al. (1991) used positron emission tomography and succeeded in discriminating 84 percent of patients and 91 percent of control subjects on the basis of axial brain levels corresponding to the basal ganglia. Scores of MMPI scales reclassified 65.5 percent of high-risk schizophrenia subjects and 66.2 percent of control subjects correctly (Carter et al. 1999). Arango et al. (1999) reported that 75.3 percent of schizophrenia patients and 86.1 percent of normal controls were correctly classified by the results of neuropsychological tests, and Evans et al. (1999) reported that 73 percent of schizophrenia patients and 72 percent of mood disorder patients were correctly reclassified by the results of a neuropsychological test battery. These studies succeeded in using multiple variables as predictive factors to distinguish patients from normal controls, but they used functional variables that were susceptible to the subjects’ condition. It can be assumed that variables such as brain structures have the advantage of providing more stable information.

Enlargements of the left and right body of the lateral ventricle, the left and right Sylvian fissure, and the third ventricle were demonstrated in the male patients in comparison with the control subjects. Four of these five ROIs were included in the seven ROIs that were selected in the discriminant function analysis. Among the female subjects, enlargements of the left inferior horn and the left and right Sylvian fissure, and a volume deficit of the right temporal lobe, were demonstrated in the patients. Three of these four ROIs were included in the seven ROIs that were selected in the discriminant function analysis. It can be speculated that multiple brain regions in schizophrenia make up a distinctive pattern of structural deviation from the normal controls, irrespective of the degrees of statistical differences in each region.

The present study is clearly limited by the fact that measurements were conducted by using not all but only a small number of slices. Although we selected the slices where the structural changes are frequently seen in schizophrenia, the present findings may not strictly reflect the...
discrete brain changes in this disease. We intended to reduce the time and effort required for whole brain measurements and to acquire an adapted and simple method for clinical use. Although present slice selection might have lessened the ability to detect structural differences, our method yielded favorable discrimination rates, indicating a great potential for future clinical application. To validate our method, however, it is important to show that the ROI volume from the selected three slices adequately reflects the corresponding total volume. In our previous study, we examined the relationships between several ROI volumes in the three slices through the mamillary body and their corresponding total volumes (Kurokawa et al. 2000), and analyses confirmed significant positive correlations in the body of the lateral ventricle, the inferior horn, the third ventricle, and the cerebral hemisphere. We further measured corresponding total volumes of the temporal lobe and superior temporal gyrus following the methods developed by Shenton et al. (1992) and examined the relationship between their volumes in the three slices and their total volumes using Pearson's correlation coefficient. We found significant positive correlation for the temporal lobe \((r = 0.94, p < 0.001)\), the white matter of the superior temporal gyrus \((r = 0.90, p < 0.001)\), and the gray matter of the superior temporal gyrus \((r = 0.93, p < 0.001)\), indicating that the ROI volumes evaluated in this study adequately reflect the corresponding total volumes.

It is likely that inclusion of other brain regions increases the accuracy of discrimination. Frontal lobe volume reductions have been demonstrated in schizophrenia patients (Buchanan et al. 1998; Sanfilipo et al. 2000b), and recent voxel-based MRI analysis stressed the importance of structural abnormalities in the frontal region (Wright et al. 1995; Suzuki et al. 2002). Negative symptoms and cognitive dysfunction of schizophrenia have been linked with abnormalities in the frontal regions (Liddle et al. 1992; Cummings 1993; Baaré et al. 1999; Nohara et al. 2000). Additional inclusion of the frontal lobe measurements should make our method more precise and more applicable.

The method reported here may open new avenues for clinical application of neuroimaging methods, especially in the diagnosis of schizophrenia. Thus far, investigations have been limited to comparisons between schizophrenia patients and healthy subjects. Further studies that include other psychiatric disorders and mood disorders should be conducted to assess the specificity of the findings. A study is now under way in our department to differentiate patients in the early phase of schizophrenia from subjects with schizophrenia-related personality disorder by means of the neuroimaging method. Because there has been evidence that early therapeutic intervention with antipsychotic drugs improves the outcome of schizophrenia (Crow et al. 1986; Wyatt 1991; Loebel et al. 1992), early detection of schizophrenia using the neuroimaging method would provide a more robust basis on which early therapeutic intervention could be started with a reasonable risk-benefit ratio. In conclusion, our data suggest that a combination of brain anatomical variables is useful in distinguishing schizophrenia patients from normal controls, both male and female. Although the individual structural brain abnormalities are subtle, combining them provides more reliable power to identify schizophrenia patients.

### Reference


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Nohara, S.; Suzuki, M.; Kurachi, M.; Yamashita, I.; Matsui, M.; Seto, H.; and Saitoh, O. Neural correlates of memory organization deficits in schizophrenia: A single


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