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# Morphological brain changes associated with Schneider's first-rank symptoms in schizophrenia: a MRI study

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## ABSTRACT

**Background.** Schneider's first-rank symptoms involve an alienated feature of the sense of one's own mental or physical activity. To clarify the brain morphological basis for the production of these symptoms, volumes of the frontal and medial temporal regions and their clinical correlates were examined in patients with schizophrenia.

**Method.** Twenty-two patients with schizophrenia and 44 age- and gender-matched healthy control subjects were included. All patients were in their psychotic episodes with definite Schneiderian symptoms, rated by using the Scale for Assessment of Positive Symptoms. Volumetric measurements of high-resolution magnetic resonance imaging were performed in the prefrontal area, cingulate gyrus, and precentral gyrus, and the medial temporal structures such as the amygdala, hippocampus, and parahippocampal gyrus.

**Results.** Patients had significantly decreased volumes in the cingulate gray matter and the amygdala compared to controls. In the patient group, Schneiderian symptom severity showed significant inverse correlations with volumes of the right posterior cingulate gray matter and of the left anterior parahippocampal gyrus.

**Conclusions.** Schneiderian symptoms may be associated with morphological abnormalities in the limbic-paralimbic regions such as the cingulate gyrus and parahippocampal gyrus, which possibly serve the self-monitoring function and the coherent storage and reactivation of information.

## INTRODUCTION

First-rank symptoms, identified by K. Schneider as a set of phenomena indicative of schizophrenia (Schneider, 1959), have played a critical role in concepts of schizophrenia, despite the lack of consistent empirical support for their diagnostic significance (Goldman *et al.* 1992; Peralta & Cuesta, 1999). Based on the analysis of symptom clusters in schizophrenia, these symptoms have been suggested to represent a clinical syndrome distinct from other types of positive psychotic symptoms (Gur *et al.* 1994; Yuasa *et al.* 1995). Although Schneider himself avoided speculating on the theoretical implications of these phenomena, it is notable that almost all of them involve an alienated feature of the sense of one's own mental or physical activity (Liddle, 2000; Kurachi, 2003*a*). A failure of the central monitoring system has been hypothesized for the explanation of these symptoms (Frith, 1987; Frith & Done, 1988), and this hypothesis has been supported by psychological evidence in studies of schizophrenia patients with such symptoms (Frith & Done, 1989; Mlakar *et al.* 1994; Keefe *et al.*

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1999; Brebion *et al*. 2000). It has been proposed that self-monitoring involves a network of areas linking the prefrontal cortex and the hippocampus via the parahippocampal gyrus and the cingulate cortex (Frith & Done, 1988; Gray *et al*. 1991).

With regard to the neuroanatomical regions involved in Schneiderian symptoms in schizophrenia, functional neuroimaging studies have suggested that auditory hallucinations are related to abnormalities in brain regions such as the left inferior frontal, temporal, and parahippocampal cortices (Friston *et al*. 1992; Liddle *et al*. 1992; Suzuki *et al*. 1993; McGuire *et al*. 1995; Silbersweig *et al*. 1995; Shergill *et al*. 2000). In our previous study (Yuasa *et al*. 1995), the severity of auditory hallucinations and disturbance of the self (designated as 'alienation' syndrome) were related to increased blood flow in the right parietal and inferior frontal regions. Schizophrenia patients predominantly with Schneiderian delusions and hallucinations were reported to have increased glucose metabolism in the mid-temporal region (Gur *et al*. 1995). Hyperactivation of the right inferior parietal lobule and cingulate gyrus was observed during voluntary movement in schizophrenia patients experiencing delusions of control (Spence *et al*. 1997). The severity of Schneiderian first-rank symptoms was correlated with increased blood flow in the right superior parietal cortex and decreased blood flow in the left posterior cingulate and lingual cortex (Franck *et al*. 2002). Frith *et al*. (2000) have speculated that, at the physiological level, the fundamental abnormality associated with delusions of control may be found in the system which generates an inhibitory signal, such as the prefrontal cortex and/or anterior cingulate cortex, and that a failure to suppress activity in the parietal cortex would lead to delusions of control, while a failure to suppress activity in the temporal cortex would lead to hallucinations or thought insertion.

Schizophrenia patients demonstrate subtle morphological abnormalities principally in fronto-temporo-limbic-paralimbic structures (Shenton *et al*. 2001; Suzuki *et al*. 2002). There have been several structural magnetic resonance imaging (MRI) studies of the volume changes in regions which take part in manifestation of the positive psychotic symptoms. Positive formal thought disorder has been shown to relate to volume loss in the left posterior superior temporal gyrus (Shenton *et al*. 1992; Menon *et al*. 1995; Vita *et al*. 1995; Rajarethinam *et al*. 2000). Auditory hallucinations have been related to the left anterior superior temporal gyrus (Barta *et al*. 1990; Levitan *et al*. 1999) and the insula (Shapleske *et al*. 2002). Other studies revealed an inverse relationship between delusions and the left superior temporal gyrus (Menon *et al*. 1995), or overall positive psychotic symptoms and the left superior temporal gyrus (Flaum *et al*. 1995; Kim *et al*. 2003), the insula (Crespo-Facorro *et al*. 2000) or the medial temporal structures (Bogerts *et al*. 1993). However, most of the studies cited did not specifically focus on the alienated feature of psychotic symptoms. In an earlier MRI study, patients with predominantly Schneiderian delusions and hallucinations were reported to have increased ventricle–brain ratios and reduced cranial and brain volumes (Gur *et al*. 1994), but subsequent studies failed to find the association between Schneiderian symptoms and frontal or temporal lobe volume (Turetsky *et al*. 1995; Cowell *et al*. 1996). Thus, the structural brain changes underlying Schneiderian symptoms and/or self-monitoring deficits in schizophrenia remain elusive.

In the present study, we employed high-resolution MRI and attempted to clarify the common morphological substrates of the schizophrenic syndrome characterized by an alienated feature. Only patients in active psychotic episodes with definite Schneiderian symptoms were included. We performed volumetric assessments of the frontal and medial temporal lobe structures. These MRI measures were compared to those of age- and gender-matched healthy comparison subjects, and, in the patient group, correlation analyses were conducted between volume measures and the severity of Schneiderian symptoms.

We hypothesized the following: (i) schizophrenia patients with Schneiderian symptoms would have volume deficits in frontal and medial temporal structures; and (ii) Schneiderian symptoms could be related to morphological abnormalities in components of a distributed network of prefronto-limbic-paralimbic structures, which have been implicated in the self-monitoring function.

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## METHOD

### Subjects

Patients with schizophrenia who met ICD-10 diagnostic criteria for research (WHO, 1993) were recruited from the in-patient and out-patient clinics of the Department of Neuropsychiatry, Toyama Medical and Pharmaceutical University Hospital, Japan. Diagnoses were made following structured clinical interviews by psychiatrists with the Comprehensive Assessment of Symptoms and History (CASH; Andreasen *et al*. 1992*a*). Clinical symptoms were rated using the Scale for Assessment of Positive Symptoms (SAPS; Andreasen, 1984) and the Scale for Assessment of Negative Symptoms (SANS; Andreasen, 1983). A Schneiderian score was calculated by summing the seven items (described below) of the first-rank symptoms in the SAPS (Franck *et al*. 2002). Right-handed patients who underwent brain MRI scan were screened for study eligibility by an experienced psychiatrist (M.S.) on the basis of structured clinical interview data and exhaustive review of the clinical records. Inclusion criteria were:

(1) young patients aged less than 40 years who were in active psychotic episode at the time of symptom rating;

(2) psychotic symptoms were assessed, if possible, when the patients were maximally psychotic, or as soon as possible once they had become cooperative by the initial treatment for the psychotic episode;

(3) patients had definite Schneider's first-rank symptoms according to the criteria that a score was more than 3 (moderate) in any of the following seven items in the SAPS: item 2 (voices commenting); item 3 (voices conversing); item 15 (delusions of being controlled); item 16 (delusions of mind reading); item 17 (thought broadcasting); item 18 (thought insertion); and item 19 (thought withdrawal);

(4) brain MRI scan was performed within 1 month of the symptom ratings.

Among the initial total of 63 patients, 22 patients remained eligible. All patients were receiving neuroleptic medication. They were physically healthy, and none had a history of head trauma, neurological illness, serious medical or surgical illness, or substance abuse disorder. Demographic and clinical data are presented in Table 1.

Table 1. *Demographic and clinical characteristics of schizophrenia patients with Schneiderian symptoms and healthy comparison subjects*

| | Schizophrenia patients ($n=22$) | Healthy comparison subjects ($n=44$) |
|---|---|---|
| Male/female | 9/13 | 18/26 |
| Age (years) | 25·4±5·5 (range, 19–36) | 25·4±5·1 (range, 19–38) |
| Height (cm) | 162·5±8·1 | 165·1±7·5 |
| Weight (kg) | 56·9±10·8 | 57·0±9·2 |
| Education (years) | 13·1±1·7** | 16·4±2·5 |
| Parental education (years) | 12·0±2·6 | 12·8±2·5 |
| Age at onset (years) | 21·8±4·5 | — |
| Duration of illness (years) | 3·9±3·9 | — |
| Schneiderian score | 13·8±7·3 | — |
| Total SAPS score | 42·6±20·0 | — |
| Total SANS score | 52·6±23·9 | — |
| Drug dose (mg/day, haloperidol equivalent) | 14·4±10·8 | — |
| Duration of medication (years) | 2·5±2·7 | — |

Values represent mean±S.D.

SAPS, Scale for the Assessment of Positive Symptoms; SANS, Scale for the Assessment of Negative Symptoms.

** $p<0·01$, Student's $t$ test.

Forty-four control subjects were healthy volunteers recruited from among the community, hospital staff, and university students. They matched the patients for age, gender, handedness, and parental education. They were interviewed by psychiatrists using a questionnaire concerning their family and past histories, and present illness. Subjects were excluded if they had a history of psychiatric illness, head trauma, neurological illness, serious medical or surgical illness, or substance abuse disorder. They were also screened for history of psychiatric disorders in their first-degree relatives. All control subjects were given the Minnesota Multiphasic Personality Inventory (MMPI), and were excluded if they had abnormal profiles with any $T$ score exceeding 70.

Written informed consent was obtained from all subjects. This study was approved by the Committee on Medical Ethics of Toyama Medical and Pharmaceutical University, Japan.

### MRI acquisition

MRI scans were acquired with a 1.5 T scanner (Vision, Siemens Medical System, Inc., Erlangen, Germany). A three-dimensional $T_1$-weighted gradient-echo sequence FLASH (fast

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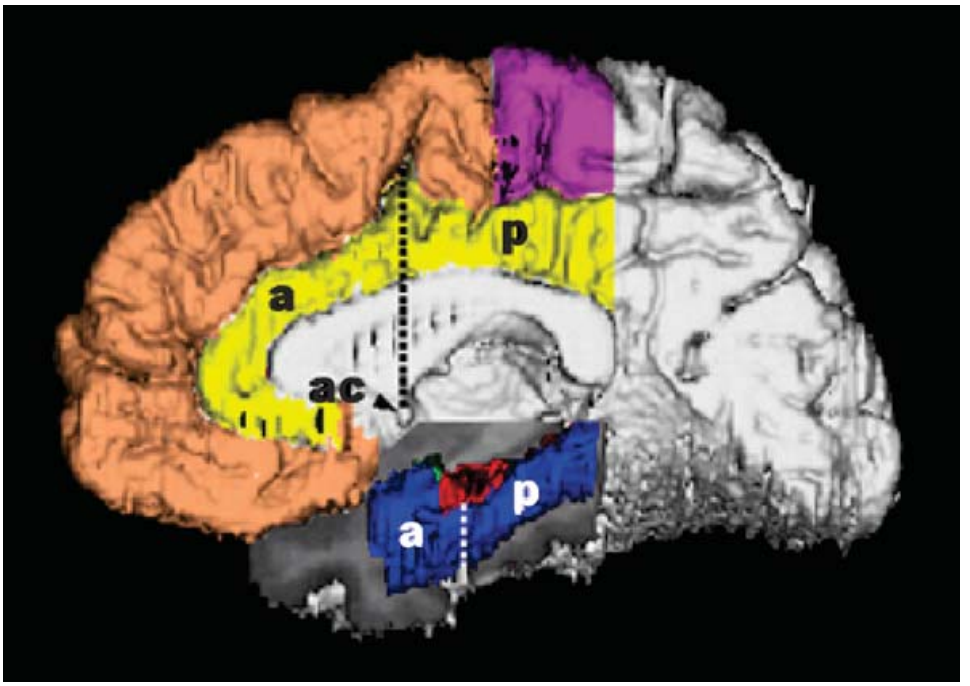



FIG. 1. Midsagittal view of a three-dimensional reconstructed image of the right hemisphere showing the regions of interest (ROIs), each of which is differentially colored: cingulate cortex (yellow), prefrontal cortex (orange), precentral cortex (purple), amygdala (green), hippocampus (red), and parahippocampal gyrus (blue). Part of the temporal lobe was removed to disclose the ROIs of the medial temporal lobe structures. The amygdala is only seen as a small piece in this aspect. The dotted lines (black, and white) indicate the level of the center of the anterior commissure and that of the posterior edge of mammillary body, respectively. a, anterior part; ac, anterior commissure; p, posterior part.

low-angle shots) with $1 \times 1 \times 1$ mm voxels was used. Imaging parameters were: TE = 5 ms; TR = 24 ms; flip angle = 40°; field of view = 256 mm; matrix size = $256 \times 256$.

## Image processing

Image processing for volumetric region-of-interest (ROI) analysis has been described in detail previously (Takahashi *et al*. 2002). Briefly, on a Unix workstation (Silicon Graphics, Inc., Mountain View, CA, USA), the image data were processed with the software package Dr. View 5.0 (Asahi Kasei Joho System Co. Ltd, Tokyo, Japan). Brain images were realigned in three dimensions and reconstructed into entire contiguous coronal slices, with a 1-mm thickness, perpendicular to the anterior commissure–posterior commissure (AC–PC) line. The whole cerebrum was separated from the brainstem and cerebellum. The signal-intensity histogram distributions across the whole cerebrum were used to segment the voxels semi-automatically into gray matter, white matter, and cerebrospinal fluid. Intracranial volume (ICV) was measured as described previously (Zhou *et al*. 2003).

## Volumetric analysis of ROIs

ROIs for volumetric measurements were placed on the frontal and medial temporal structures as presented in Fig. 1.

### *Frontal lobe*

Delineation of the frontal lobe was partially based on the works of Rademacher *et al*. (1992) and Crespo-Facorro *et al*. (1999). First, the whole frontal lobe was separated from the rest of the brain. Taking account of the intrinsic anatomical landmarks (sulci/gyri), the whole frontal lobe was subdivided into three large functional parts: the precentral gyrus, the cingulate gyrus, and the prefrontal area. The prefrontal area was defined as the part of the whole frontal lobe from which the precentral gyrus and cingulate gyrus were excluded. With the

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availability of synchronous-orthogonal views in three dimensions in conjunction with the context of gyri/sulci on successive coronal slices, decisions of anatomical landmarks (e.g. central sulcus, precentral sulcus, and cingulate sulcus) to separate and subdivide the frontal lobe could be readily made. The cingulate gyrus was further subdivided into the anterior part and the posterior part at the level of the center of anterior commissure (Fig. 1). The anterior and posterior parts approximately corresponded to Brodmann's area (BA) 24 and BA 23/31, respectively (Talairach & Tournoux, 1988). The procedure of the present study did not allow us to include part of the posterior cingulate gyrus and the retrosplenial cortex (Fig. 1). All the volumetric measurements were performed in reformatted consecutive 1-mm coronal slices (voxel size = $1 \times 1 \times 1$ mm) by manual outlining. Gray-matter volumes of the regional cortices were calculated by applying the segmentation procedure described previously.

*Medial temporal lobe structures*

The amygdala, the hippocampus and the parahippocampal gyrus were manually outlined on consecutive coronal 1-mm slices, from anterior to posterior, with the corresponding sagittal and axial planes simultaneously presented for reference. Volumes of gray and white matter in each of these structures were measured together. The detailed procedures for delineations of these structures have been described previously (Niu *et al*. in press; Suzuki *et al*. in press).

*Amygdala*: The most anterior slice of the amygdala was that on which the amygdala just appeared as oval-shaped gray matter. As the slices proceed posteriorly, the rounded cortical nucleus of the amygdala transitions to a thin strip of gray matter, known as the hippocampal-amygdala transitional area. This area was included in the amygdala ROI. Thus the most posterior slice of the amygdala was the plane where the transitional area disappeared. The inferior border of the amygdala in contact with the hippocampal head was determined by reference to the sagittal plane since the boundary between the hippocampus and the amygdala is more readily identified on the sagittal plane (Convit *et al*. 1999). The alveus was used to differentiate the hippocampal head from the amygdala. The amygdala was separated by thin strips of white matter from the entorhinal cortex medially, and from the claustrum and tail of the caudate nucleus superio-laterally. The inferiolateral boundary of the amygdala was the temporal lobe white matter and the extension of the temporal horn.

*Hippocampus and parahippocampal gyrus*: The alveus served as the superior boundary of the whole hippocampus. The inferior boundary was the white matter of the parahippocampal gyrus. The lateral and medial boundaries were the inferior horn of the lateral ventricle and the mesial edge of the temporal lobe respectively. For the parahippocampal gyrus, the most anterior slice was defined by the appearance of the white-matter tract (temporal stem) linking the temporal lobe with the rest of the brain. The parahippocampal gyrus was separated laterally by using a line drawn from the most lateral border of the hippocampal flexure to the collateral sulcus, and superiorly by the inferior gray border of the hippocampal formation. The most posterior slice for both the hippocampus and the parahippocampal gyrus was at the level of the last appearance of the fiber of the fornix. The parahippocampal gyrus was further subdivided into the anterior part and the posterior part at the level of the posterior edge of mammillary body (Fig. 1).

Three trained raters (S.Z., L.N. and H.H.), who were blinded to the subjects' identity, measured the volumes of the frontal lobe regions, the amygdala, and the hippocampus and parahippocampal gyrus respectively. Inter- and intra-rater intra-class correlation coefficients in five randomly selected brains were over 0·92 for the frontal ROIs and over 0·93 for the medial temporal ROIs.

## Statistical analysis

Statistical analyses were performed using repeated-measures multivariate analysis of variance with age and ICV as covariates (MANCOVA) for each region, with group (patients, control subjects) and gender (male, female) as between-subject factors, and hemisphere (right, left) as a within-subject factor. *Post-hoc* Tukey's honestly significant difference tests modified for unequal sample sizes were employed to follow up the significant main effects or interactions yielded by MANCOVA.

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Table 2. *Volumes of the regions of interest in schizophrenia patients with Schneiderian symptoms and healthy comparison subjects*

| Regions of interest | Schizophrenia patients ($n=22$) | Healthy comparison subjects ($n=44$) | Diagnosis effect | | |
|---|---|---|---|---|---|
| | | | $F$ | df | $p$ |
| Intracranial volume | 1480±178 | 1483±136 | <0·01 | 1, 61 | 0·987 |
| Prefrontal gray matter[a] | | | 0·72 | 1, 60 | 0·396 |
| Left | 91·55±11·25 | 94·57±8·75 | | | |
| Right | 88·37±11·23 | 89·57±7·66 | | | |
| Cingulate gyrus gray matter[b,c] | | | 9·47 | 1, 60 | 0·003 |
| Left | 7·81±1·87 | 8·77±2·25 | | | |
| Right | 9·43±2·31 | 10·82±1·80 | | | |
| Anterior part[c] | | | 4·17 | 1, 60 | 0·045 |
| Left | 3·69±1·46 | 4·16±1·69 | | | |
| Right | 5·14±1·84 | 5·88±1·59 | | | |
| Posterior part[b] | | | 10·17 | 1, 60 | 0·002 |
| Left | 4·12±0·80 | 4·61±0·94 | | | |
| Right | 4·29±1·23 | 4·94±0·67 | | | |
| Precentral gyrus gray matter[a] | | | 2·05 | 1, 60 | 0·157 |
| Left | 18·60±2·90 | 19·34±2·02 | | | |
| Right | 17·44±2·51 | 18·21±2·09 | | | |
| Amygdala[b,c] | | | 13·75 | 1, 60 | <0·001 |
| Left | 0·99±0·13 | 1·11±0·14 | | | |
| Right | 1·05±0·15 | 1·14±0·13 | | | |
| Hippocampus[c] | | | 1·50 | 1, 60 | 0·225 |
| Left | 3·02±0·44 | 2·89±0·40 | | | |
| Right | 3·20±0·52 | 3·15±0·36 | | | |
| Parahippocampal gyrus | | | 1·41 | 1, 60 | 0·239 |
| Left | 7·28±0·83 | 7·07±0·84 | | | |
| Right | 7·38±0·93 | 7·24±0·78 | | | |
| Anterior part[c] | | | 1·97 | 1, 60 | 0·164 |
| Left | 2·58±0·43 | 2·41±0·60 | | | |
| Right | 2·88±0·56 | 2·74±0·55 | | | |
| Posterior part[a] | | | <0·01 | 1, 60 | 0·970 |
| Left | 4·70±0·61 | 4·69±0·49 | | | |
| Right | 4·50±0·60 | 4·54±0·48 | | | |

Values are mean±S.D. of measured volume ($cm^3$).

*Post-hoc* comparisons followed multivariate analysis of variance with age and intracranial volume as covariates (MANCOVA) revealed: [a] Volume is larger on left hemisphere than on right hemisphere ($p<0·001$ for prefrontal area and precentral gyrus; $p=0·003$ for posterior parahippocampal gyrus). [b] Volume is smaller in patients than in controls ($p=0·009$ for whole cingulate gyrus; $p=0·007$ for posterior cingulate gyrus; $p=0·002$ for amygdala). [c] Volume is larger on right hemisphere than on left hemisphere ($p<0·001$ for whole cingulate gyrus, anterior cingulate gyrus, hippocampus, and anterior parahippocampal gyrus; $p=0·003$ for amygdala).

In the patient group, Pearson's correlation coefficients were calculated to examine relationships between the ROI volumes relative to ICV ($100 \times$ ROI volume/ICV) and the Schneiderian score. The Schneiderian score was log-transformed in order to remove skewness. To prevent a possible Type I error due to multiple comparisons, we limited the correlation analysis to the relative ROI volumes and the Schneiderian score. When significant correlations were obtained, they were also examined by partial correlation coefficients controlling for potential confounders such as duration of illness, duration of medication, dose of neuroleptics, or age. Further, the specificity of such correlations to the Schneiderian symptoms was examined by partial correlation coefficients controlling for the overall severity of symptoms assessed by total scores of the SAPS and SANS. Statistical significance was defined as $p<0·05$ (two-tailed).

## RESULTS

### Comparisons of volume measures between patients and controls

Volumes of intracranial cavity, gray matter of the frontal lobe regions, amygdala, hippocampus, and parahippocampal gyrus are presented in Table 2.

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*Frontal lobe regions*

MANCOVA revealed a significant main effect of diagnosis in gray matter of the cingulate gyrus ($F=9{\cdot}47$, df $=1, 60$, $p=0{\cdot}003$). When its anterior and posterior parts were compared separately, there were also significant main effects of diagnosis ($F=4{\cdot}17$, df $=1, 60$, $p=0{\cdot}045$ for the anterior part; $F=10{\cdot}17$, df $=1, 60$, $p=0{\cdot}002$ for the posterior part). *Post-hoc* analyses showed significant gray-matter reductions of the whole cingulate gyrus ($p=0{\cdot}009$) and posterior part of the cingulate gyrus ($p=0{\cdot}007$) in the patients. There was no significant main effect of diagnosis in MANCOVA for gray matter of the precentral gyrus or prefrontal area. Significant main effects of hemisphere were observed in gray matter of the whole cingulate gyrus ($F=37{\cdot}32$, df $=1, 62$, $p<0{\cdot}001$), anterior part of the cingulate gyrus ($F=35{\cdot}36$, df $=1, 62$, $p<0{\cdot}001$), precentral gyrus ($F=24{\cdot}29$, df $=1, 62$, $p<0{\cdot}001$), and prefrontal area ($F=68{\cdot}00$, df $=1, 62$, $p<0{\cdot}001$). *Post-hoc* analyses revealed that the whole cingulate gyrus and the anterior part of the cingulate gyrus were larger on the right than on the left, whereas the precentral gyrus and prefrontal area were larger on the left than on the right (all $p<0{\cdot}001$). A significant interaction of gender by hemisphere was observed in the prefrontal area ($F=8{\cdot}81$, df $=1, 62$, $p=0{\cdot}004$). *Post-hoc* analyses revealed that the bilateral prefrontal area volumes were larger in males than in females ($p<0{\cdot}001$ for both hemispheres).

*Medial temporal lobe*

MANCOVA revealed a significant main effect of diagnosis in the amygdala ($F=13{\cdot}75$, df $=1, 60$, $p<0{\cdot}001$). *Post-hoc* analysis showed significant volume reduction in the patients ($p=0{\cdot}002$). There was no significant main effect of diagnosis in the hippocampus or parahippocampal gyrus. Nor was a significant diagnosis effect observed when the parahippocampal gyrus was subdivided into the anterior and posterior parts. There were significant main effects of hemisphere for the amygdala ($F=8{\cdot}57$, df $=1, 62$, $p=0{\cdot}005$), hippocampus ($F=47{\cdot}64$, df $=1, 62$, $p<0{\cdot}001$), anterior parahippocampal gyrus ($F=28{\cdot}54$, df $=1, 62$, $p<0{\cdot}001$), and posterior parahippocampal gyrus ($F=8{\cdot}33$, df $=1, 62$, $p=0{\cdot}005$). *Post-hoc* tests revealed that the amygdala ($p=0{\cdot}003$), hippocampus ($p<0{\cdot}001$), and anterior parahippocampal gyrus ($p<0{\cdot}001$) in the right hemisphere were larger than those in the left, while the posterior parahippocampal gyrus ($p=0{\cdot}003$) showed an asymmetry of left larger than right.

### Correlations between volume measures and Schneiderian symptom severity

The Schneiderian score showed a trend toward a significant inverse correlation with the relative volume of gray matter of the right cingulate gyrus ($r=-0{\cdot}45$, $p=0{\cdot}051$). When the cingulate gyrus was subdivided into anterior and posterior parts, the Schneiderian score was significantly correlated with the relative volume of the right posterior cingulate cortex ($r=-0{\cdot}59$, $p=0{\cdot}004$) (Fig. 2*a*), but not with that of the anterior cingulate cortex ($r=-0{\cdot}09$, $p=0{\cdot}693$). This correlation between the Schneiderian score and the right posterior cingulate volume remained significant even after excluding a single subject with the lowest posterior cingulate volume ($r=-0{\cdot}52$, $p=0{\cdot}017$). There was also a significant inverse correlation between the Schneiderian score and the relative volume of the left anterior parahippocampal gyrus ($r=-0{\cdot}46$, $p=0{\cdot}032$) (Fig. 2*b*).

In this study, the illness duration in the patients varied among individuals, even though only young patients with relatively short duration were included. It was possible that progressive morphological changes, which have been suggested to occur in schizophrenia (Shenton *et al*. 2001), may have confounded the correlation results. In order to eliminate such effects, we conducted a partial correlation analysis controlling for the illness duration. The correlations between the Schneiderian score and the right posterior cingulate or the left anterior parahippocampal gyrus remained significant. Similarly these correlations controlling for duration of medication, dose of neuroleptic drugs, age, or the total scores of the SAPS and SANS also remained significant.

## DISCUSSION

In the present study, the schizophrenia patients with Schneiderian symptoms had smaller volumes in the cingulate cortex and amygdala compared to the comparison subjects. The severity of Schneiderian symptoms in the patients was negatively correlated with the volumetric

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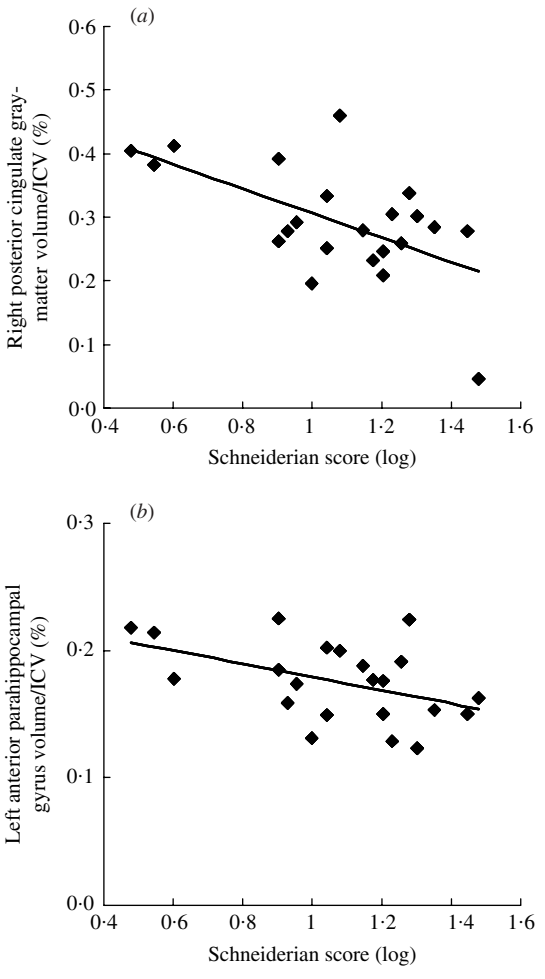



FIG. 2. (*a*) Correlations between Schneiderian score and relative right posterior cingulate gray-matter volume ($r = -0{\cdot}59$, $p = 0{\cdot}004$). (*b*) Correlations between Schneiderian score and relative left anterior parahippocampal gyrus volume ($r = -0{\cdot}46$, $p = 0{\cdot}032$).

measures of the right cingulate cortex, especially of the posterior part, and the left anterior parahippocampal gyrus. As these brain regions are intimately interconnected, our results suggest that structural abnormalities in the limbic-paralimbic neural circuit may underlie the schizophrenic syndrome with alienated features. To our knowledge, this is the first study to show the relation of overall severity of Schneiderian symptoms to the structural changes in specific brain regions in schizophrenia. In accordance with our hypothesis, these regions partly overlap with those which have been implicated in the self-monitoring function (Frith & Done, 1988; Gray *et al.* 1991).

The cingulate gyrus is a major component of the 'paralimbic belt' and has reciprocal connections with neocortical association areas as well as with the amygdala and hippocampus. The anterior and posterior parts of the cingulate cortex are differentially organized in cytoarchitecture as well as in function, although they are densely interconnected (Vogt *et al.* 1995; Devinsky *et al.* 1995). The anterior cingulate (BA 24/32) has been implicated not only in non-spatial attentional and executive functions (Pardo *et al.* 1990; Elliott & Dolan, 1998), but also in numerous other functions such as motor control, spatial working memory, selection for action, conflict monitoring, error monitoring, and performance evaluation (Paus *et al.* 1993; Carter *et al.* 1998; Botvinick *et al.* 1999; MacDonald *et al.* 2000). Posner & Rothbart (1998) proposed a broad role for the anterior cingulate in the conscious self-regulation of behavior via its reciprocal anatomical connectivity with the prefrontal and limbic regions. On the other hand, there is evidence that the posterior cingulate (BA 23/29/30) is involved in episodic memory, processing of emotionally salient stimuli, and spatial attention (Grasby *et al.* 1993; Maddock, 1999; Mesulam *et al.* 2001). Mesulam *et al.* (2001) have suggested that the posterior cingulate may enable the bias of anticipatory attention to be set in the direction of events that have intrinsic or experientially acquired significance.

In schizophrenia, functional and structural abnormalities of the anterior cingulate cortex have been reported in a large number of neuroimaging and post-mortem studies (Benes *et al.* 1991; Andreasen *et al.* 1992*b*; Carter *et al.* 1997; Takahashi *et al.* 2002, 2003), and its critical role in the pathophysiology of schizophrenia has been proposed (Benes, 1998; Tamminga *et al.* 2000). It has been suggested that impaired error monitoring in schizophrenia patients relates to dysfunction in the anterior cingulate (Carter *et al.* 2001; Alain *et al.* 2002). Laurens *et al.* (2003) recently reported decreased activity of the rostral anterior cingulate and associated limbic-paralimbic structures, including the posterior cingulate gyrus and hippocampus, during the commission of errors in schizophrenia patients. The posterior cingulate has been

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examined less extensively in structural imaging studies of schizophrenia. However, a few voxel-based morphometric studies have shown gray-matter reduction in the posterior cingulate in patients with schizophrenia (Sowell *et al.* 2000; Hulshoff Pol *et al.* 2001), and a recent longitudinal MRI study demonstrated posterior cingulate gray-matter loss in parallel with psychosis development (Pantelis *et al.* 2003). Previous functional imaging studies revealed that patients with schizophrenia showed abnormal metabolism in the posterior cingulate (Andreasen *et al.* 1997; Haznedar *et al.* 1997), and cerebral blood flow in this region was negatively correlated with Schneiderian first-rank symptoms (Franck *et al.* 2002). In addition, the cingulate gyrus has been implicated in the etiology of 'alienation' in organic brain disorders (Feinberg *et al.* 1992). Thus, considering the anatomical and functional correlates of the cingulate cortex, its structural deficits might represent the liability that internally generated thoughts or actions are imbued with abnormal perceptual qualities and misattributed to external agencies.

The anterior parahippocampal gyrus was another region implicated in the Schneiderian symptoms in the current study. Cytoarchitectonic as well as volumetric abnormalities in the entorhinal cortex (anterior part of the parahippocampal gyrus) have been demonstrated in post-mortem and MRI studies in schizophrenia (Jakob & Beckmann, 1986; Falkai *et al.* 2000; Joyal *et al.* 2002). A positron emission tomography study demonstrated that abnormal cerebral blood flow in the left parahippocampal region correlated with overall symptom severity in schizophrenia (Friston *et al.* 1992). Our findings are consistent with the notion that subtle structural abnormality of the entorhinal cortex, especially of the left side, is associated with the expression of positive symptoms in schizophrenia (Bogerts, 1997; Kurachi, 2003*b*). The hippocampo-entorhinal complex is thought to play a critical role in memory and learning by acting as a neural gateway for encoding and retrieval, and thus, possibly orchestrate the coherent storage and reactivation of information distributed widely in the brain (Mesulam, 2000). A structurally deviant parahippocampal gyrus might conduct misguiding orchestration, which could contribute, to some extent, to adding an alienated nature to the experiences of patients.

Few attempts have been made to examine specific relationships between structural deficits of the amygdala and clinical symptoms of schizophrenia using MRI, since many of the previous studies measured the amygdala and hippocampus as a single ROI (Shenton *et al.* 2001). Kurachi (2003*b*) proposed the amygdala as a principal candidate for the substrate of Schneiderian symptoms based on theoretical considerations as well as on data from experimental studies. Among a limited number of studies which specifically measured the amygdala, Gur *et al.* (2000) observed smaller volume of the amygdala only in male patients with schizophrenia. Joyal *et al.* (2003) reported bilateral volume reductions of the amygdala in first-episode patients. Reduced volume of the amygdala found in the present study is consistent with these previous studies. However the amygdala volumes were not correlated with the severity of Schneiderian symptoms. The human amygdala, in general, plays crucial roles in modulating the impact of sensory stimuli according to the emotional valence and in emotional conditioning (Mesulam, 2000). So a possible contribution of the involvement of the amygdala may at least be to exert an abnormal modulation of emotional experiences elicited by the Schneiderian symptoms, and to add further distortion of psychological reality to the patients' experiences.

The findings of the current study should be interpreted with caution for several reasons. First, the relatively small sample size of patients with Schneiderian symptoms may have limited the ability to generalize our findings. Second, although we reduced the number of correlation analyses, the possibility of a Type I error due to the multiple comparisons must be taken into account, especially for the marginally significant correlation between the Schneiderian score and the left anterior parahippocampal gyrus volume. A further study with a larger sample is needed to confirm this finding. Third, the lack of implication of the prefrontal cortex may not exclude the possible differential contributions of the prefrontal subcomponents to the formation of Schneiderian symptoms. A future study subdividing the prefrontal cortex into functionally heterogeneous subcomponents will clarify this issue. Finally, the Schneiderian symptoms consist of certain types of auditory

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hallucination and the so-called bizarre delusions (disturbance of the self), which are phenomenologically different, although all of them share an alienated feature. Thus, there should be some differences in the underlying neurobiology among these symptoms. Especially, the superior temporal gyrus has been suggested to be involved in the auditory hallucinations (Barta *et al*. 1990; Suzuki *et al*. 1993; Levitan *et al*. 1999), whereas the parietal cortex has been related to delusions of control (Spence *et al*. 1997; Blakemore *et al*. 2003). However, this point is somewhat out of the scope, since the specific aim of the current study was to find a common morphological basis (denominator) for the alienated features of schizophrenia syndrome. Involvement of additional structural deficits and/or functional changes elicited in more widespread interconnected regions may be responsible for the variety of the alienated symptoms.

In summary, the present study suggests that Schneider's first-rank symptoms are based on structural changes in the limbic-paralimbic circuit comprising the cingulate gyrus, the parahippocampal gyrus, and possibly the amygdala. Future studies should be worth being performed to confirm our findings with a larger sample and to clarify the relationships between the morphological changes in the brain and cognitive deficits possibly underlying Schneiderian symptoms, such as the self-monitoring dysfunction, in patients with a propensity for these symptoms.

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## DECLARATION OF INTEREST

None.

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