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Satoru Yuasa · Masayoshi Kurachi · Michio Suzuki
Youichi Kadono · Mié Matsui · Osamu Saitoh · Hikaru Seto

Clinical symptoms and regional cerebral blood flow in schizophrenia

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Abstract This study examined the relationship between clinical symptoms and regional cerebral blood flow (rCBF) in schizophrenic patients using single photon emission computed tomography (SPECT). The subjects were 26 medicated schizophrenic patients diagnosed according to DSM-III-R criteria. Clinical symptoms were assessed using the Scale for the Assessment of Negative Symptoms (SANS), selected items for the Positive and Negative Syndrome Scale (PANSS), and the scale for Schneider's first rank symptoms. Resting rCBF was measured using N-isopropyl-p-[I-123] iodoamphetamine (I-123 IMP) SPECT, and relative rCBF distribution was evaluated in nine regions of interest in each hemisphere. Factor analysis of symptom ratings indicated four separate syndromes: psychomotor poverty, alienation (hallucination and disturbance of the self), delusion, and disorganization. Stepwise multiple regression analysis showed the psychomotor poverty syndrome to be correlated with decreased rCBF in bilateral superior frontal areas and increased rCBF in the left thalamus and right basal ganglia. The disorganization syndrome was correlated with increased rCBF in bilateral anterior cingulates and decreased rCBF in bilateral middle frontal areas. The alienation syndrome was shown related to increased rCBF in the right inferior frontal area and parietal area. Dysfunction in distinctive neural networks involving various prefrontal areas would thus appear to underlie these syndromes in schizophrenia.

Key words SPECT · Regional cerebral blood flow · Clinical symptoms · Stepwise multiple regression · Schizophrenia

Satoru Yuasa (✉) · Masayoshi Kurachi · Michio Suzuki
Youichi Kadono · Mié Matsui · Osamu Saitoh
Department of Neuropsychiatry,
Toyama Medical and Pharmaceutical University,
2630 Sugitani, Toyama 930-01, Japan

Hikaru Seto
Department of Radiology,
Toyama Medical and Pharmaceutical University,
2630 Sugitani, Toyama 930-01, Japan

Introduction

Schizophrenia is characterized by a variety of symptoms. Kraepelin (1913) regarded disturbances of emotional activities and volition as important features of dementia praecox (schizophrenia). On the other hand, Schneider (1962) described first-rank symptoms, which consist of auditory hallucinations of particular types, several symptoms such as delusion of control and thought diffusion that have been referred to as "ego-boundary disturbance," and delusional perception (Crow 1979). Crow (1980, 1985) proposed two syndromes of schizophrenia possibly associated with specific pathological processes, i.e., type I syndrome, characterized by positive symptoms, and type II syndrome, characterized by negative symptoms. This dichotomy is widely accepted and has substantially facilitated research on schizophrenia. Recent studies based on the data of statistical analysis, however, indicate that schizophrenic symptoms are classified into three or more syndromes (Liddle 1987; Arndt et al. 1991; Peralta et al. 1992, Kawasaki et al. 1994).

As to the underlying neural mechanisms of the symptoms, Ingvar and Franzen (1974) first demonstrated by the Xe-133 clearance method the abnormal distribution of regional cerebral blood flow (rCBF) in schizophrenics; that is, the lower the flow in the left frontal region, the more striking the symptoms of indifference, inactivity, and autism. Subsequent studies using functional neuroimaging techniques such as the Xe-133 clearance method, single photon emission computed tomography (SPECT) and positron emission tomography (PET; Kurachi et al. 1987; Suzuki et al. 1992; Andreasen et al. 1992) confirm that decreased rCBF in the frontal region (hypofrontality) is associated with negative symptoms. Regarding positive symptoms, increased rCBF in the left temporal area or Broca's area has been shown in patients with persistent auditory hallucination (Kurachi et al. 1985; Matsuda et al. 1989; Yuasa et al. 1990; Suzuki et al. 1993; McGuire et al. 1993). Decreased glucose metabolism in the parietal region has been observed in patients predominantly with

delusions (Kishimoto et al. 1987). In these studies examination was made of the relationship between clinical symptom and functional state in discrete brain regions. A more adequate approach, however, would appear to be the categorization of various symptoms into several syndromes by statistical analysis followed by demonstrating correlations among syndromes and functional states in brain regions as reported by Liddle et al. (1992).

Thus, in this study a factor analysis of clinical symptoms was carried out and rCBF was measured using N-isopropyl-p-[I-123] iodoamphetamine (I-123 IMP) SPECT in 26 schizophrenic patients. Stepwise multiple regression analysis was conducted to determine the relationship between syndrome score and relative rCBF values.

Subjects and methods

A total of 26 patients (13 males and 13 females) from the inpatient and outpatient clinics of Toyama Medical and Pharmaceutical University Hospital participated in this study. all the patients fulfilled DSM-III-R criteria for schizophrenia (American Psychiatric Association 1987). Mean age was 23.2 ± 6.9 (SD) years. All patients were right-handed and under neuroleptic medication (mean chlorpromazine equivalent dose, 239 ± 180 mg/day). In addition, all patients were being given anticholinergic drug administration (biperiden hydrochloride, 4.2 ± 2.1 mg/day), and 9 patients antihistamines (promethazine hydrochloride, 48.9 ± 40.7 mg/day). The mean duration of illness was 3.8 ± 4.0 years. The control subjects consisted of 12 healthy volunteers (6 males and 6 females) with mean age of 25.1 ± 2.2 years. No subjects with a history of alcohol or other durg abuse, brain injury, or any other neurological disease were included. The purpose and procedures of the study were explained to the subjects and informed consent was obtained.

Assessment of clinical symptoms

Clinical symptoms were evaluated using the Scale for the Assessment of Negative Symptoms (SANS; Andreasen 1984), three items (delusion, conceptual disorganization, and hallucinatory behavior) in the Positive and Negative Syndrome Scale (PANSS; Kay et al. 1987), and the scale for Schneider's first rank symptoms (FRS; Schneider 1976) which were selected and modified from the Present State Examination (PSE; Wing et al. 1974). The FRS consists of three groups: auditory hallucinations (thoughts spoken aloud; voices discussing a subject in third person; voices commenting on thoughts or actions), disturbance of the self (thought diffusion; thought withdrawal, intrusion, or commentary; delusion of control; delusion of alien penetration), and delusional perception. Each of

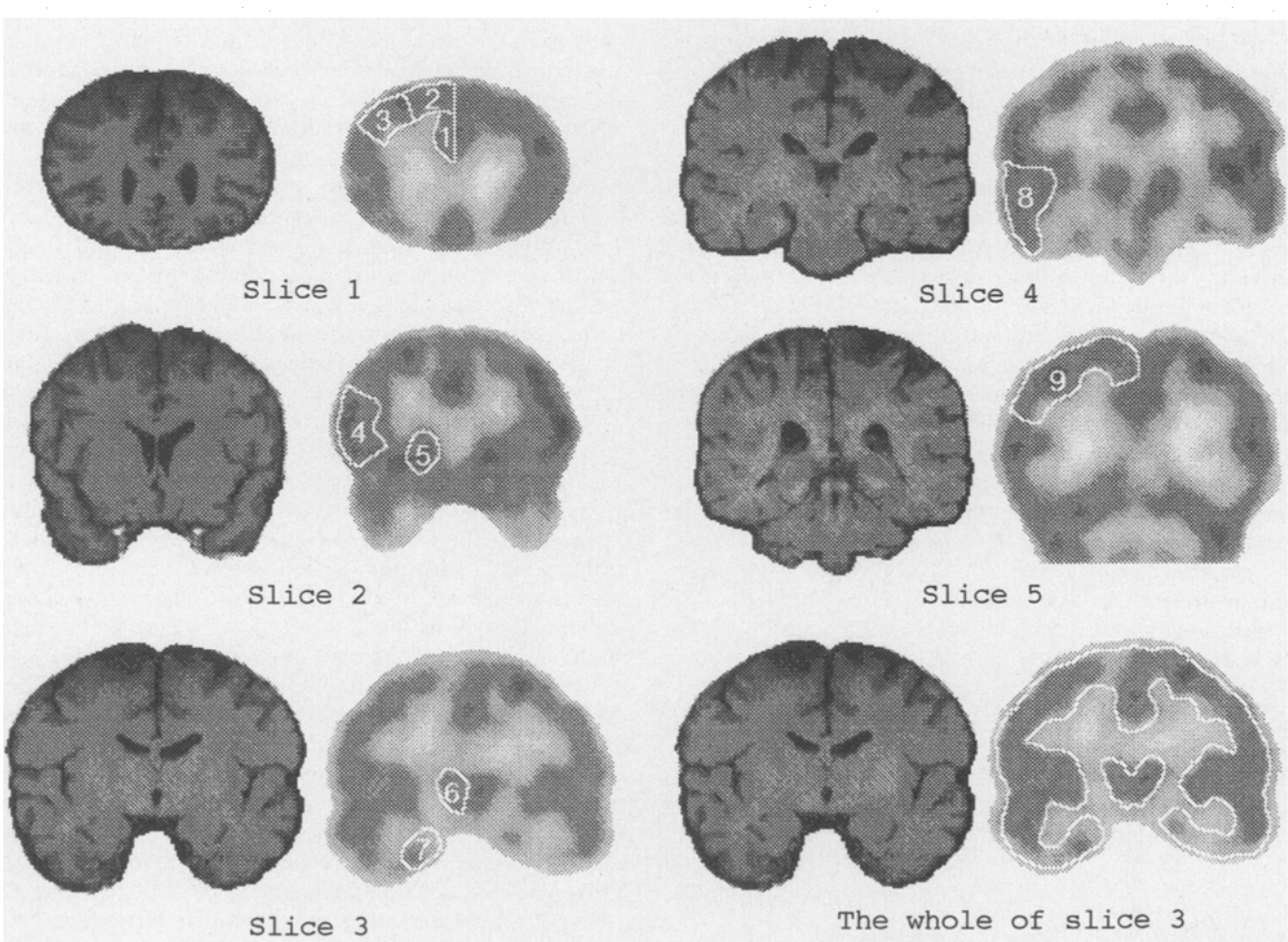

Fig. 1 Locations of regions of interest (ROIs). MR images (*left*) and SPECT images (*right*) of a patient. *1* anterior cingulate; *2* superior frontal area; *3* middle frontal area; *4* inferior frontal area; *5* basal ganglia; *6* thalamus; *7* limbic area; *8* temporal area; *9* parietal area. To assess CBF of the whole brain, all gray matter areas were delineated in the five slices. An example of slice 3 appears bottom right

these is rated on a scale of 0–2 (0, absent; 1, likely present; and 2, definitely present). The patients were assessed by two psychiatrists within 2 weeks of SPECT and each mean score was used.

SPECT procedure

Measurements were taken in a dimly lit room with background noise from cooling fans. The subjects sat quietly with their eyes open for 15 min after intravenous injection of 111 MBq (3 mCi) I-123 IMP. SPECT was performed with a three-head rotating gamma camera system (GCA9300A; Toshiba, Tokyo, Japan), using high resolution fan beam collimators provided with a minicomputer (GMS550U; Toshiba, Tokyo, Japan). The resolution was 7 mm full width at half maximum in the center of the reconstructed slice with the rotating radius at 13.2 cm. The computer slice width was 6.8 mm. The SPECT data were obtained in a 128 × 128 format for 30 angles in a 120° arc for each camera at 60 s per angle. The total period of data acquisition was 30 min. The filtered-back projection method was used for SPECT image reconstruction after preprocessing projection data with a Butterworth filter. A series of 5.1-mm-thick coronal slices, approximately vertical to the orbitomeatal line (OM line), were obtained by each scan. Nine regions of interest (ROIs) were drawn in each hemisphere on five slices, referring to individual magnetic resonance imaging with 5.0-mm-thick slices separated by 0.1 mm (Fig. 1). The slice through the temporal pole and head of the caudate was taken as the baseline splice (slice 2). Slice 1 was selected approximately 15.3 mm anterior to the baseline slice. Slice 3, 25.5 mm posterior to slice 2, best represented the thalamus and limbic area. Slice 4 was approximately 35.7 mm posterior to slice 2 and presented the temporal lobe. Slice 5 was approximately 56.1 mm posterior to slice 2 and showed the parietal lobe. To assess CBF of whole brain, all cortical and subcortical gray matter areas were delineated in these five slices and the values were averaged. To determine relative rCBF distribution in the brain, the ratio of counts/voxel of each ROI to averaged counts/voxel of the whole brain was calculated.

Data analysis

Statistical analysis was carried out using the program, Stat View II, for the Macintosh (Abacus Concepts, Inc., Berkeley). Eleven of the symptoms in SANS, PANSS, and FRS were subjected to factor analysis. The method of principal component analysis was used to extract initial factors, which were subjected to varimax rotation. Factor scores were calculated by the regression method.

For clarification of multiple correlations between clinical symptoms and rCBF, stepwise multiple regression was conducted using factor scores of the clinical symptoms as dependent variables and relative rCBF values calculated from nine ROIs in each hemisphere as independent variables. In the calculations, 2.00 was used for F-to-enter and remove. For comparison of rCBF in the schizophrenic patients and controls, the Student's *t*-test was used, and the correlation of rCBF and neuroleptic dosage and other drugs, was determined based on Pearson's correlation. The value $P < 0.01$ was considered statistically significant and $0.01 \leq P < 0.05$ as a tendency.

Results

Factor analysis of clinical symptoms

As shown in Table 1, the factor analysis of SANS and six positive symptom ratings indicated four factors. The first factor loads heavily in hallucinatory behavior, auditory hallucination, disturbance of the self, and attentional impairment. These symptoms are designated the alienation syndrome for convenience.

The second factor has heavy loadings in affective flattening, avolition, and anhedonia. These symptoms are designated the psychomotor poverty syndrome according to Liddle (1987).

The third factor has heavy loadings in delusion and delusional perception. This group is designated the delusion syndrome.

The fourth factor has loading in conceptual disorganization and is designated the disorganization syndrome.

Multiple correlations among factor scores and regional cerebral blood flow

The data for this parameter are shown in Table 2.

Factor 1 (alienation)

In the right hemisphere, relative rCBF in the parietal area entered the equation on the first step and accounted for 11% of the variance. The inferior frontal area entered the equation on the second step, predicting positively and accounting for an additional 18% of the variance. No other effects were significant. These two predictors as the optimal combination with factor 1 explained 29% of outcome variance ($F = 4.69$; $P < 0.05$).

Table 1 Factor analysis of clinical symptoms of patients with schizophrenia

Symptom[a]	Factor 1	Factor 2	Factor 3	Factor 4
Hallucinatory behavior	0.776	–0.181	0.170	0.270
Auditory hallucination	0.904	–0.042	0.085	–0.010
Disturbance of self	0.555	0.107	0.381	0.360
Attentional impairment	0.684	0.265	–0.039	–0.105
Affective flattening	0.146	0.855	–0.010	–0.118
Avolition	–0.106	0.921	0.003	0.170
Anhedonia	0.014	0.909	0.072	–0.052
Delusion	0.097	0.023	0.902	0.158
Delusional perception	0.076	–0.001	0.869	–0.232
Conceptual disorganization	0.098	–0.012	–0.054	0.917
Alogia	0.455	0.479	–0.129	0.374

[a] Clinical symptoms were assessed with the Scale for the Assessment of Negative Symptoms (SANS) and six positive symptom ratings

Table 2 Correlations between clinical factor scores and regional cerebral blood flow by multiple regression analysis. Std coeff standard partial regression coefficient; R multiple correlation coefficient; Cumulative R^2 proportion of total variance accounted for at each step in hierarchical multiple regression analysis. Factor 1 alienation syndrome; Factor 2 psychomotor poverty syndrome; Factor 4 disorganization syndrome

Dependent variables	Predictor	Std coeff	R	Cumulative R^2
Left hemisphere				
Factor 2	Superior frontal area	–0.47	0.44	0.19
	Thalamus	0.46	0.63	0.40
Factor 4	Parietal area	0.34	0.35	0.12
	Anterior cingulate	0.37	0.51	0.26
	Middle frontal area	–0.29	0.59	0.34
Right hemisphere				
Factor 1	Pariental area	0.45	0.33	0.11
	Inferior frontal area	0.45	0.54	0.29
Factor 2	Basal ganglia	0.50	0.42	0.18
	Superior frontal area	–0.37	0.55	0.31
Factor 4	Middle frontal area	–0.52	0.36	0.13
	Anterior cingulate	0.40	0.52	0.27

Table 3 Comparison of regional cerebral blood flow in control and schizophrenic patients (mean ± SD)

Brain region	Left		Right	
	Patients	Controls	Patients	Controls
Anterior cingulate	100.2 ± 3.6	102.8 ± 3.6*	100.1 ± 4.4	101.2 ± 3.3
Superior frontal	99.0 ± 4.8	99.2 ± 2.5	99.0 ± 3.4	99.3 ± 3.4
Middle frontal	102.1 ± 4.3	102.0 ± 3.2	101.4 ± 4.5	101.2 ± 3.3
Inferior frontal	101.8 ± 3.5	103.2 ± 3.9	100.8 ± 4.3	101.2 ± 4.3
Basal ganglia	105.0 ± 7.9	106.0 ± 4.5	105.3 ± 7.3	103.4 ± 4.1
Thalamus	109.1 ± 6.4	109.6 ± 5.7	109.3 ± 6.1	107.0 ± 5.6
Limbic	90.7 ± 8.8	90.9 ± 6.4	90.5 ± 5.2	90.1 ± 5.2
Temporal	102.7 ± 3.9	101.6 ± 3.4	102.2 ± 3.4	100.7 ± 2.3
Parietal	101.2 ± 2.8	101.0 ± 2.2	101.6 ± 2.7	99.5 ± 4.1

For comparison of controls and patients, the two-tailed *t*-test was used. * $P < 0.05$

Factor 2 (psychomotor poverty)

In the left hemisphere the optimal combination of two predictors [superior frontal area (step 1) and thalamus (step 2)] explained 40% of outcome variance ($F = 7.70$; $P < 0.01$). The superior frontal area was a negative predictor and accounted for 19% of the variance. The thalamus was a positive predictor. In the right hemisphere the optimal combination of two predictors [basal ganglia (step 1) and superior frontal area (step 2)] explained 31% of outcome variance ($F = 5.12$; $P < 0.05$).

Factor 4 (disorganization)

In the left hemisphere the optimal combination of three predictors [parietal area (step 1), anterior cingulate (step 2), and middle frontal area (step 3)] explained 34% of outcome variance ($F = 3.84$; $P < 0.05$). The parietal area and anterior cingulate were positive predictors. The middle frontal area was a negative predictor. In the right hemisphere the optimal combination of two predictors [middle frontal area (step 1) and anterior cingulate (step 2)] explained 27% of outcome variance ($F = 4.18$; $P < 0.05$). The middle frontal area was a negative predictor and the anterior cingulate was a positive predictor.

Relationship between rCBF and neuroleptic dosage in the schizophrenic group

Relative rCBF in the patients showed no significant correlation with the chlorpromazine equivalent dosage, anticholinergic drugs, or antihistamines. Only the left superior frontal rCBF showed a tendency to correlate with the chlorpromazine equivalent dosage ($r = 0.46$, $P = 0.016$, Pearson's correlation).

Comparison of rCBF for schizophrenic patients and controls

The patient group showed a tendency toward decreased rCBF in the left anterior cingulate ($P < 0.05$) compared with controls. The rCBF in other brain regions showed no significant difference between the two groups (Table 3).

Discussion

Factor analysis of the previously mentioned 11 symptoms from SANS, PANSS, and FRS demonstrated that schizophrenic symptoms could be grouped into four syndromes (one negative and three presumably positive). The psy-

chomotor poverty syndrome (factor 2) and disorganization syndrome (factor 4) are basically the same as those specified by Liddle (1987) who sent forth a three-syndrome classification. However, the symptoms of disturbance of the self (so-called bizarre delusions) and hallucinations were classified together in factor 1 in the present study, being distinct from delusion (factor 3). Theoretically, particularly in German psychopathology, disturbance of the self, i.e., disturbance of the boundaries of the self, is separate from delusions such as delusional perception or delusional ideas (Hamilton 1974). In fact, disturbance of the self occurs in schizophrenia, but not in delusional disorders. Mayer-Gross et al. (1969) stated that "... some workers have made the weakness or loss of the self the central symptom of schizophrenia. The passivitiy phenomena in which this loss is best seen are indeed very characteristic of schizophrenia. ...There are obvious relations between passivity and hallucinations and both phenomena may be based on the same mechanisms...". Crow (1979) maintains that "the ego-boundary disturbances are not unrelated in form to the auditory hallucinations. Delusional perception by contrast seems unrelated to either of these two groups of symptoms," which is consistent with the result of factor analysis of the clinical symptoms in the present study. Factor 1 was thus designated here as the alienation syndrome, because disturbance of the self and auditory hallucination are experiences that internally generated mental activities acquire alien nature. In Liddle's study (1987), although classified as the reality distortion syndrome, the nuclear syndrome of the Present State Examination is distinct from other delusions, and this is partially in accord with the results of the present study. A limitation of the present analysis is that it is based on a relatively small sample size. Reexamination with a larger sample size (52 patients with schizophrenia) was thus conducted using SANS and the scale for the Assessment of Positive Symptoms (SAPS) and the results confirmed four-syndrome classification (Matsui et al. in preparation).

To our knowledge, this is the first study to demonstrate the relationship between clinical syndromes identified by factor analysis and rCBF in schizophrenia using multiple regression analysis.

In the present study, psychomotor poverty syndrome scores (factor 2) were correlated with decreased relative rCBF in bilateral superior frontal areas. Many, although not all, studies demonstrate reduced activity in the frontal lobe in schizophrenic patients (Buchsbaum 1990; Andreasen et al. 1992), and the inverse correlation between the negative syndrome and rCBF in prefrontal regions is consistent with some studies (Ingvar and Franzen 1974; Kurachi et al. 1987; Volkow et al. 1987; Suzuki et al. 1992; Andreasen et al. 1992; Wolkin et al. 1992; Liddle et al. 1992). As to the site in the frontal cortex correlated with negative symptoms, the left mesial frontal cortex (Andreasen et al. 1992), as well as dorsolateral prefrontal convexity (Wolkin et al. 1992; Liddle et al. 1992) has been reported. It follows from the present results that the bilateral superior frontal areas may be most importantly involved in the psychomotor poverty syndrome. A significant correlation was also found between the psychomotor poverty syndrome and increased relative rCBF in the left thalamus and right basal ganglia. That increased rCBF in the basal ganglia is correlated with psychomotor poverty is consistent with Liddle et al. (1992). Changes in the thalamus may reflect a secondary or compensatory phenomenon following frontal lobe dysfunction. However, primary thalamic pathology is also possible, because reduction in total cell number and volume of the mediodorsal thalamic nucleus has been reported in a neuropathological study on schizophrenic patients (Pakkenberg 1992). Thalamic abnormalities in schizophrenia have been suggested by a magnetic resonance imaging study (Andreasen et al. 1994). Carlsson (1988) propose that the schizophrenic syndrome may be related to a dysregulation in cortico-striato-thalamocortical feedback loops. Dysfunction of the fronto-thalamic and fronto-basal ganglia circuit are shown by this study to possibly be associated with the psychomotor poverty syndrome.

The disorganization syndrome (factor 4) mainly represents formal thought disorder. Factor scores for this symptom were correlated with increased relative rCBF in bilateral anterior cingulate cortices and decreased relative rCBF in bilateral middle frontal areas. A positive correlation between rCBF in the anterior cingulate and disorganization syndrome is consistent with the findings of Liddle et al. (1992). The anterior cingulate is a brain region in which neuropathological abnormalities have been observed in schizophrenic subjects (Benes et al. 1991). Neuropsychological studies suggest a neural network involving the anterior cingulate in connection with the parietal and frontal cortices to modulate directed attention and possibly to be involved in schizophrenia (Mesulam 1981; Mesulam and Geschwind 1978). The present findings are in agreement with these proposals and suggest aberrant functional activity in the neural network involving the anterior cingulate to possibly underlie formal thought disorders.

Factor scores of the alienation syndrome (factor 1) positiviely correlated with relative rCBF in the right parietal and inferior frontal areas. There have been some reports (Kurachi et al. 1985; Matsuda et al. 1989; Yuasa et al. 1990; Suzuki et al. 1993) showing that increased activity in the left temporal area may be associated with auditory hallucination. Liddle et al. (1992) demonstrated the reality distortion syndrome including hallucination and disturbance of the self to be associated with increased rCBF in the left parahippocampal region, striatum and many other brain regions. However, this was not found in the present study. Additional research should be conducted to clarify the underlying mechanism of the alienation syndrome.

Two syndromes, psychomotor poverty and disorganization, were found here associated with decreased relative rCBF in distinct prefrontal areas, whereas disorganization and alienation were associated with increased rCBF in other frontal areas. Disturbed functioning of distributed neural networks involving various prefrontal areas would thus appear to underline these syndromes. Although sev-

eral authors have proposed hypotheses that could integrate frontal hypoactivity and the dopamine theory in schizophrenia (Weinberger 1987; Grace 1991), the pathogenesis of hypofrontality remains unclear (Kurachi et al. 1995; Suzuki et al. 1995). This is a preliminary study in which data for each hemisphere were examined separately due to the small sample size. Detailed study on the relationships between four clinical syndromes and dysfunction in various brain regions using functional and morphological brain imaging will contribute to clarify the underlying mechanisms of schizophrenia.

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