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Frontality, Laterality, and Cortical-Subcortical Gradient of Cerebral Blood Flow in Schizophrenia: Relationship to Symptoms and Neuropsychological Functions

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Abstract. According to the three hypotheses on the regional brain dysfunction in schizophrenia that have received some support in studies of cerebral blood flow (CBF) and cerebral metabolic rate, we calculated eight CBF measurement indices in 59 schizophrenic patients; frontality, laterality, cortical to subcortical gradients and superior to inferior difference. Four factors were selected from these eight indices, treated by principal component factor analysis (factor 1: cortical to subcortical gradient; factor 2: inferior frontality; factor 3: superior frontality; factor 4: laterality). We investigated their correlations with clinical and demographic characteristics. Factor 1 correlated with duration of illnes. Factor 2 related most highly to numbers of perseverative errors on the Wisconsin Card Sorting Test and moderately to anhedonia. Factor 4 related to attentional impairment score of the Scale for the Assessment of Negative Symptoms. The schizophrenia specific symptom score calculated from the Brief Psychiatric Rating Scale did not relate to any of these factors. It seemed that there were various dimensions of neural deficits in schizophrenia, corresponding to various aspects of symptomatology or neuropsychological functions.

Advances in neuroimaging techiques have made it possible to test hypotheses about major dimensions of regional brain dysfunction in schizophrenic patients. As Gur et al. [1] cited, there are two hypotheses on pathogenesis in schizophrenic patients. The first is the laterality hypothesis which was confirmed by regional cerebral blood flow (rCBF) measurement or positron emission tomography (PET) study. This hypothesis of cerebral hemispheric disturbance in schizophrenia [2], as modified by Gur [3], stipulates left hemispheric dysfunction and relative overactivation of the dysfunctional left hemisphere. Gur et al. [4, 5] illustrated this finding by using cerebral metabolic rate (CMR) measurement and rCBF measurement during performance of verbal and spatial tasks: cognitive challenges designed to activate left and right hemispheric processing, respectively. Schizophrenic patients failed to activate the left hemisphere for the verbal task and showed relative overactivation of the left hemisphere for the spatial task. Recently, they suggested that resting laterality measurement, CBF and CMR related to specific symptoms of schizophrenia and the frontality measurement did not [1].

Weinberger et al. [6] presented a failure to activate the prefrontal region during the performance of the Wisconsin Card Sorting Test (WCST) (prefrontal task) in schizophrenic patients. These lines of evidence have been called 'hypofrontality' [7, 8, 11, 12, 27–33].

Since single photon emission tomography (SPECT) or PET could obtain subcortical rCBF or CMR, some investigators reported that cortical-subcortical CMR dif-

ference could distinguish schizophrenic patients from normal subjects [9, 10]. This finding is of interest because the dopaminergic hypothesis is still valid as a pathogenic theory on schizophrenia.

From the viewpoint of these findings, we calculated three major dimensional indices (frontality, laterality and cortical-subcortical – basal ganglia – gradients) from rCBF data measured by the xenon-133 inhalation method and investigated the relationships between these CBF indices and demographic features, symptoms and neuropsychological functions. These three hypotheses are not mutually exclusive. We hypothesized that they relate in different ways to some aspects of demographic features, phenomenological symptoms and cognitive function examined by neuropsychological tests.

Methods

Subjects

The sample of medicated schizophrenic patients (n = 59) from Sagawa [11] were selected randomly for this study. All met the criteria of DSM-III-R [13] schizophrenic disorder, judged to be in the chronic state, and were under medication, mainly antipsychotic drugs (total chlorpromazine equivalent dose [14]; 419.0 ± (SD) 475.0). However, they were not receiving other drugs such as antihypertensives and anticonvulsants. All but 1 patient were right-handed. The control sample consisted of 36 normal volunteers. Both patients and controls were not allowed to smoke or take caffeine for 1 h prior to rCBF measurement.

Psychiatric Rating Scales and Neuropsychological Tests

The 18-item version of the Brief Psychiatric Rating Scale (BPRS) [15] and the Scale for the Assessment of Negative Symptoms (SANS) [16] were completed and three neuropsychological tests – WCST [17], Maze Test (MAZE) (WISC-R) and Word Fluency Test (WFT) [18] – were used as described in Sagawa et al. [12], within 2 weeks after the rCBF measurement.

To obrain an index of symptom specificity for schizophrenia, we calculated the average scores for specific (SP) and nonspecific (NS) symptoms form the BPRS items as described in Gur et al. [1]. We also determined that the dependent measure of symptom specificity was SP-NS. This index was considered to highlight specific symptoms in relation to nonspecific symptoms.

We examined the correlations among the specificity index, the SP and NS scores and the total BPRS score. Furthermore, the relationships among the specificity index, subscores on SANS, and the total SANS score were also examined. No specific index correlated with the total BPRS score which was considered to represent the overall severity of the illness. But moderate correlations were noted with the BPRS positive symptoms [19] ($r = 0.53$, $p < 0.001$) and the total SANS score ($r = 0.42$, $p < 0.01$). It seemed that the specificity index was not associated with the overall severity of illness. We also ensured that the specificity index could contribute unique information on the relationship between clinical symptomatology and rCBF distribution patterns as cited in Gur et al. [1]. Clinical and demographic characteristics of the patients of the present study are shown in table 1.

CBF Measurement

CBF was determined by the xenon-133 inhalation technique using SPECT (ring-type detection, SET-021, HEADTOME system, Shimazu, Japan). Trace amounts of xenon-133 in air (30 mCi/l) were inhaled through a mouthpiece for approximately 1 min. The uptake and clearance of isotope from the brain were monitored by collimated sodium iodide crystal detectors. The rCBF values were computed from the clearance rates as described by Kanno and Lassen [20] at two planes (35 and 70 mm above the orbito-meatal line; OM+35, 70). The integrity of the rCBF measurements was evaluated as described in Komatani et al. [21], which also includes an illustration of regions of interests. It is known that the rCBF values were affected by the arterial blood carbon dioxide concentration ($PaCO_2$). In a previous study we found that the arterial blood carbon dioxide concentration highly correlated with the end-tidal carbon dioxide concentration, therefore the data were adjusted by the end-tidal carbon dioxide concentration [22]. Studies were conducted with initial respiration training, eyes closed and ears uncovered. Here we reported data on 'the resting baseline condition' only. We described 'the resting condition' as exclusion of any mental activations. However, it seemed to us that 'the resting condition' does not signify no mental activities during rCBF measurement, because it requires some effort for most subjects to breathe in xenon-133 and an air mixture through a mouthpiece.

The resting measurement of rCBF was used to calculate the frontality, laterality, and gradient of cortical-subcortical (basal ganglionic) rCBF. As described by Gur et al. [1], we calculated four parameters such as the frontality scores at the inferior plane (frontal-temporal; F1) and superior plane (frontal-parietal; F2) and the laterality scores at the inferior plane (left-right mean CBF; L1) and superior plane (left-right mean CBF; L2). Furthermore we also calculated the gradient scores which were defined as the differences between cortical rCBF (inferior frontal, superior frontal and temporal) and subcortical (basal ganglionic) rCBF (G1, G2 and G3). The reasons for the inclusion of these gradient scores are given in the following; first, cortical-subcortical metabolic difference differentiate schizophrenic patients from normal controls as reported by Volkow et al. [9], second, these three cortical regions and basal ganglia appear to be connected with dopaminergic neurons. The disturbance of dopaminergic neurons in these regions is considered to be an important etiological mechanism in schizophrenia. In addition, we calculated an S-I score (superior mean CBF – inferior mean CBF). Eight CBF measurement scores were defined as above. Table 2 shows each CBF measurement score (mean ± SD, range).

Statistical Analysis

To show the relationships among scores of two symptom rating scales and also between those scores and rCBF indices, Pearson's product-moment correlation coefficients were computed. In consideration of 'multiple comparison problem' in the univariate tests and the multiplicity of coefficients on the Pearson correlation analyses, we adjusted the criterion of significance to $p < 0.01$, using Bonferroni's inequality [23]. To get reduced testable independent variables, eight rCBF indices were subjected to factor analysis with Varimax rotation and four factors were obtained. To investigate further relationships between these four factors and clinical characteristics

Table 1. Clinical and demographic characteristics of study patients (mean ± SD)

Variable	Patients	Controls
Age, years	31.7 ± 8.7	32.3 ± 6.7
Duration, years	8.8 ± 7.1	–
Total dose, mg/day[a]	419.0 ± 475.0	–
Total SANS	60.6 ± 19.9	–
Total BPRS	54.9 ± 9.7	–
Positive symptoms[b]	18.5 ± 5.1	–
SP	3.5 ± 0.7	–
NS	2.6 ± 0.7	–
SP-NS[c]	0.9 ± 0.9	–
WFT	20.5 ± 7.7**	31.1 ± 4.0
MAZE, s	117.7 ± 71.1*	49.7 ± 12.3
CA on WCST	2.3 ± 1.9**	4.9 ± 0.5
PE on WCST	20.3 ± 18.9*	2.5 ± 1.9
TE on WCST	28.3 ± 17.5**	8.4 ± 3.1
Sex		
Female	20 (34%)	11 (31%)
Male	39 (66%)	25 (69%)

Comparisons were made with analysis of variance, * $p < 0.005$, ** $p < 0.001$.

[a] Chlorpromazine equivalent dose.

[b] Positive symptoms composed from 18-item BPRS defined by Kitamura et al. [19].

[c] Schizophrenia-specific symptoms composed from BPRS defined by Gur et al. [1].

Table 2. rCBF measurement indices (mean ± SD)

Index	Patients ml/100 g/min	Controls ml/100 g/min
F1	−1.8 ± 4.3***	3.8 ± 3.4
F2	2.4 ± 4.7	4.0 ± 4.6
L1	0.7 ± 2.0*	−0.3 ± 2.3
L2	−0.6 ± 1.9	−1.8 ± 2.1
G1	−9.1 ± 5.7***	−0.4 ± 12.0
G2	−7.5 ± 5.5***	−1.6 ± 4.6
G3	−7.6 ± 5.3	−6.0 ± 4.4
S-I	−2.4 ± 2.2**	−0.9 ± 2.9

Comparisons were made with ANOVA, * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

in schizophrenic patients, a multiple regression analysis was conducted. For the analysis, stepwise methods with Akaike's information constant [24] were employed. The 'HALBAU' program from Gendai Suugakusha-Shuppan [25] was used. The significance level for a multiple regression analysis was 0.05.

Results

Demographic and Physiological Variables of Patients and Controls

The demographic and clinical characteristics of patients and controls are given in table 1. There were no statistically significant differences between the patients and controls as regards age (analysis of variance) or sex (χ^2). There were statistically significant differences between the patients and controls on five rCBF measurement indices: F1, L1, G1, G2 and S-I. These findings seemed to reflect mainly the hypofrontal pattern of the rCBF in schizophrenic patients. Laterality indices of the patients differed from those of the controls slightly, but not evidently (table 2). These rCBF measurement indices separated two groups as significantly more different than could be expected by chance ($\chi^2 = 36.4$, $p < 0.01$), and the percentage of subjects correctly classified was 82.1%. G1, G3, L2, and G2 made a significant contribution to discrimination ($F = 40.7$, d.f. = 1, 93, $p < 0.001$; $F = 11.0$, d.f. = 1, 92, $p < 0.005$; $F = 6.6$, d.f. = 1, 91, $p < 0.05$, and $F = 4.4$, d.f. = 1, 90, $p < 0.05$, respectively).

Relationships between CBF Measurement Scores and Scores of Rating Scales or Neuropsychological Tests

Only correlation between the SP-NS score and G3 reached a trend level ($r = -0.26$, d.f. = 57, $p < 0.05$). Since this correlation can be explained by chance, the interpretation should be made with care. No significant correlation was found between any other rCBF measurement scores and scores of symptom rating scales (table 3).

We could not replicate the correlation between the laterality score and the specificity index as reported by Gur et al. [1]. Table 4 shows correlations among eight rCBF measurement indices. Three gradient indices showed high correlations ($r \geq 0.65$). Two frontality indices showed independent correlation to each gradient index. The inferior frontal index (F1) was moderately correlated with the gradient index (G1; $r = 0.49$). The superior frontal index (F2) was moderately correlated with the gradient (G2; $r = 0.53$). Two laterality indices (L1, L2) were slightly correlated, and the superior lateral index was slightly correlated with the S-I index.

The eight rCBF measurements were reduced via a principal components factor analysis followed by Vari-

Table 3. Correlations between rCBF measurement indices and BPRS indices

	SP	NS	SP-NS
F1	–	–	–
F2	–	–	–
L1	–	–	–
L2	–	–	–
G1	–	–	–
G2	–	–	–
G3	–	–	−0.26*
S-I	–	–	–

* $p < 0.05$.

Table 4. Correlations among eight rCBF measurements

Variable	1	2	3	4	5	6	7	8
1 F1		–	–	–	0.49**	–	−0.27*	–
2 F2			–	–	–	0.53**	–	–
3 L1				0.26*	–	–	–	–
4 L2					–	–	–	0.36
5 G1						0.65***	0.71***	–
6 G2							0.66***	–
7 G3								–
8 S-I								

* $p < 0.05$; ** $p < 0.001$; *** $p < 0.001$.

Table 5. Principal component factor analysis of eight rCBF measurements

Factor	Factor 1	Factor 2	Factor 3	Factor 4
F1	−0.00	−0.99	0.06	−0.04
F2	0.09	−0.10	0.81	−0.04
L1	−0.10	−0.30	0.22	0.29
L2	0.06	0.08	0.09	0.56
G1	0.86	−0.49	0.03	0.01
G2	0.72	−0.05	0.50	0.10
G3	0.95	0.26	−0.01	0.05
S-I	0.22	0.11	−0.21	0.55
Percentage of variance	28.0	16.6	12.6	8.9
Cumulative percentage of variance	28.0	44.6	57.2	66.1

Table 6. Correlations between four rCBF measurement factors and predictors

	Factor 1	Factor 2	Factor 3	Factor 4
Age	–	0.33**	–	–
Duration	−0.28*	0.29*	–	–
Total dose	–	–	–	–
Total SANS	–	–	–	–
Total BPRS	–	–	–	–
Positive symptoms	–	–	–	–
SP	–	–	–	–
NS	–	–	–	–
SP-NS	−0.26*	–	–	–
WFT	–	−0.28*	–	–
MAZE	–	–	–	–
CA on WCST	–	–	–	–
PE on WCST	–	0.31*	–	–
TE on WCST	–	0.31*	–	–

* $p < 0.05$; ** $p < 0.01$.

max rotation. Table 5 presents the results of the principal component factor analysis. Principal component factor analysis of these eight rCBF measurements produced four factors with eigenvalues greater than 0.7. Although eigenvalue of the fourth factor was less than 1.0, this factor seemed to represent the laterality score, as we expected that the laterality factor might emerge in this three-dimensional model. These factors accounted for 28.0, 16.6, 12.6 and 8.9% of variance, respectively. The rCBF measurements are applied to these four factors in table 5. As evident from this table, the first factor appears to represent cortical-subcortical rCBF gradients; the second factor, inferior hypofrontality; the third factor, superior hypofrontality; and the fourth factor, the information on laterality at the superior plane and the difference between superior mean CBF and inferior mean CBF. We found that the same four factors were selected in normal subjects. To determine which, if any, of these factors are related to symptomatology and neuropsychological functions, correlation coefficients were calculated for each factor score of symptom rating scales and scores on neuropsychological tests. The results are summarized in table 6. Both first and second factors exhibited a mild but not significant relationship with the duration of illness; and the second factor exhibited a significant relationship with age and trend level relation-

Table 7. Predictor and partial correlation of clinical variables for factor scores analyzed by multiple regression in schizophrenic patients

Dependent variable:	R^2	AIC	F (d.f.)
Independent variables:	β (SE)	partial correlation	partial F
Factor 1	0.38	131.2	3.79 (2, 43)*
Duration	0.39 (0.02)	−0.31	4.59*
NS	0.37 (0.20)	0.27	3.25
Constant	−0.54		
Factor 2	0.68	118.3	4.55 (7, 38)***
Anhedonia	0.18 (0.05)	0.49	12.00**
PE on WCST	0.03 (0.01)	0.46	10.5**
Age	0.04 (0.01)	0.37	6.1*
WFT	−0.03 (0.01)	−0.33	4.5*
Alogia	−0.09 (0.05)	−0.26	2.7
Total SANS	−0.02 (0.02)	−0.23	2.0
Positive symptoms	−0.04 (0.03)	−0.21	1.7
Constant	−0.31		
Factor 3	0.47	137.4	3.93 (3, 43)*
Sex	1.0 (−0.3)	0.43	9.32*
CA on WCST	0.16 (0.09)	0.27	3.32
SP-NS	0.28 (0.16)	0.25	2.87
Constant	−2.00		
Factor 4	0.48	146.4	4.16 (3, 42)*
Attentional impairment	−0.20 (0.06)	−0.43	9.55**
TE on WCST	0.02 (0.01)	0.30	4.06
Sex	0.51 (0.36)	0.21	1.98
Constant	0.23		

AIC: Akaike's information constant.

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$, remaining values non-significant.

ship with numbers of perseverate and total errors on WCST. No significant relationship between these four factors and any other symptoms by rated BPRS and SANS or scores on neuropsychological tests were found.

Results of a Multiple Regression Analysis

To explore further the relationships between these four factors and demographic variables, symptom rating scales and neuropsychological tests assessed in this study, we performed a stepwise regression analysis, with these four factors as dependent variables and age, sex, duration of illness, total dosage, scores of symptom rating scales and scores on neuropsychological tests as independent variables (table 7).

The first factor was related only to the duration of illness, respectively (partial correlation coefficient: $r = -0.31$, $F = 4.59$, $p < 0.05$). The second factor was related to numbers of perseverate errors on WCST (partial correlation coefficient: $r = 0.46$, $F = 10.5$, $p < 0.01$), age (partial correlation coefficient: $r = 0.37$, $F = 6.1$, $p < 0.05$), score on WFT (partial correlation coefficient: $r = -0.33$, $F = 4.5$, $p < 0.05$) and the subscore of SANS (anhedonia; partial correlation coefficient: $r = 0.49$, $F = 12.0$, $p < 0.01$). The third factor was significantly associated only with sex difference (partial correlation coefficient: $r = 0.43$, $F = 9.32$, $p < 0.05$). The fourth factor was associated with the subscore of SANS (attentional impairment; partial correlation coefficient: $r = -0.43$, $F = 9.55$, $p < 0.01$).

Discussion

Recent brain imaging studies have suggested that there may be various regional brain dysfunctions in schizophrenia. Utena [26] proposed a theoretical brain dysfunction model in schizophrenia called 'cubic theory', describing a possible functional disconnection between anterior and posterior, left hemisphere and right hemisphere, and cortical and subcortical in the brain of schizophrenics.

Our attempt, in this study, was to integrate data from an rCBF study of schizophrenic patients by using a strategy of neurophysiological gradient measures and examining their correlations with psychopathology rated by BPRS and SANS, and with neuropsychological functions measured by WCST, MAZE and WFT.

In this study, the frontality measure was associated with perseverate errors on WCST and also related to negative symptoms such as anhedonia. These lines of evidence have been reported by several investigators [6–8, 11, 12, 27–33].

We could not replicate the correlation between greater relative left hemispheric activity and the severity of schizophrenia-specific symptoms which was described by Gur et al. [1], whereas partial correlation coefficient between the laterality measure (factor 4) and attentional impairment achieved slight significance. In addition, no correlation was found for the frontality gradient. However, cortical-subcortical gradient (G3) was associated

slightly with the severity of schizophrenia-specific symptoms (SP-NS). This result should be interpreted with caution because factor 1, which represented cortical-subcortical rCBF gradients, was not related to the severity of schizophrenia-specific symptoms after being adjusted for the duration of illness using a multiple regression analysis. Therefore, G3 seemed to be associated more closely with the duration of illness than with SP-NS.

The failure of the frontality and laterality measures to correlate with symptom specificity in our sample suggests that both the measures might not be associated with symptom specificity in a simple fashion such as a linear relationship. Another reason for the failure may be that there were many types of severity in our sample and all patients were under medication. Gur et al. [5] reported that the medicated schizophrenic patients had symmetrical resting CBF, whereas the unmedicated patients with some condition showed higher left hemispheric CBF even at rest. If a sample was homogeneous in severity and the information on the total dosage was monitored, we could replicate the correlation between laterality measure of CBF and symptom specificity, as cited by Gur et al. [1]. However, it is too difficult to take account of the accurate dosage effect on CBF and to measure 'resting CBF', because the patients, and even normal subjects, had to exert much effort to breathe in a mixture of xenon-133 and air. Furthermore, during rCBF measurement, there might be some emotional problems such as anxiety, which cannot be controlled. Therefore, controlled CBF data in the same conditions should be obtained and the effect of drugs should be eliminated if possible. In addition, the data on laterality measurement shoud be interpreted with caution because these laterality measurements might change, possibly according to the mental activity when the rCBF or CMR was measured. The PET studies suggested that spatial tasks, considered to be right hemispheric tasks, failed to activate the right hemisphere in schizophrenic patients [4, 5, 28]. Berman and Weinberger [32] suggested that the left side, relative to the right side, is disturbed in the prefrontal region and the right side, relative to left side, is disturbed in the parietal region in schizophrenic patients who participated in rCBF studies coupled with various task performances. Brain imaging with high resolution, coupled with sophisticated activation conditions, has revealed more precise regional brain dysfunction in schizophrenic patients.

An ideal study would be for nonmedicated patients on their first visits to be followed up prospectively by using brain imaging methods under a constant condition with control as much as possible and using valid psychometric scales for schizophrenic symptoms. In addition, new SPECT systems with high resolution and radiopharmaceuticals for rapid rCBF measurements will be available [33]. They will abet progress in schizophrenia research.

In conclusion, we observed that three-dimensional rCBF measurements were associated with different aspects of demographic features, symptomatology, and neuropsychological functions in schizophrenic patients. With some limitations such as sampling of patients, the calculation method of rCBF or controlling the condition at rCBF measurement, we found that the frontality measurement was related to negative symptoms and cognitive deficits, but the laterality measurement was not related to specific symptoms of schizophrenia as expected. To integrate various regional brain dysfunction hypotheses, further investigation should be conducted not only using the brain imaging methods but also other neuroscientific modalities currently being developed in neuropharmacology [34] or neurophysiology. In addition a more sophisticated experimental design should be developed based on more sophisticated statistical issues.

References

1 Gur, R.E.; Resnick, S.M.; Gur, R.C.: Laterality and frontality of cerebral blood flow and metabolism in schizophrenia: Relationship to symptom specificity. Psychiat. Res. *27:* 325–334 (1989).

2 Flor-Henry, P.: Lateralized temporal-limbic dysfunction and psychopathology. Ann. N.Y. Acad. Sci. *280:* 777–795 (1976).

3 Gur, R.E.: Left hemisphere dysfunction and left hemisphere overactivation in schizophrenia. J. abnorm. Psychol *87:* 226–238 (1978).

4 Gur, R.E.; Skolnik, B.E.; Gur, R.C.; et al.: Brain function in psychiatric disorders. I. Regional cerebral blood flow in medicated schizophrenics. Archs gen. Psychiat. *40:* 1250–1254 (1983).

5 Gur, R.E.; Gur, R.C.; Skolnik, B.E.; et al.: Brain function in psychiatric disorders. III. Regional cerebral blood flow in unmedicated schizophrenics. Archs gen. Psychiat. *42:* 329–334 (1985).

6 Weinberger, D.R.; Berman, K.F.; Zec, R.F.: Physiological dysfunction of dorsolateral prefrontal cortex in schizophrenia: I. Regional cerebral blood flow evidence. Archs gen. Psychiat. *43:* 114–124 (1986).

7 Ingvar, D.H.; Franzen, G.: Abnormalities of cerebral blood flow distribution in patients with chronic schizophrenia. Acta psychiat. scand. *50:* 425–462 (1974).

8 Ariel, R.N.; Berg, R.A.; Quaife, M.A.; Dirksen, J.W.; Wilson, J.; Graber, B.: Regional cerebral blood flow in schizophrenics. Test

using the Xe-133 inhalation method. Archs gen. Psychiat. *40:* 258–263 (1983).
9 Volkow, N.D.; Brodie, J.D.; Wolf, A.P.; et al.: Brain organization in schizophrenia. J. cereb. Blood Flow Metab. *6:* 441–446 (1986).
10 Resnik, S.M.; Gur, R.E.: Alavi, A.; Gur, R.C.; Reivich, M.: Positron emisssion tomography and subcortical glucose metabolism in schizophrenia. Psychiat. Res. *24:* 1–11 (1988).
11 Sagawa, K.: Regional cerebral blood flow in schizophrenic patients. HEADTOME xenon 133 inhalation technique. Yamagata Med. J. *7:* 19–33 (1989).
12 Sagawa, K.; Kawakatsu, S.; Koatani, A.; et al.: Correlation of regional cerebral blood flow with performance on neuropsychological tests in schizophrenic patients. Schizophr. Res. *3:* 241–246 (1990).
13 American Psychiatric Association: Diagnostic and statistical manual of mental disorders; 3rd ed. revised. (American Psychiatric Association, Washington 1987).
14 Davis, J.M.: Dose equivalence of antipsychotic drugs. J. psychiat. Res. *11:* 65–66 (1974).
15 Overall, J.E.; Gorham, D.R.: The brief psychiatric rating scale. Psychol. Rep. *10:* 799–812 (1962).
16 Andreasen, N.C.: Negative symptoms in schizophrenia: definition and reliability. Archs gen. Psychiat. *39:* 784–788 (1982).
17 Milner, B.: Effects of different brain lesions on card sorting. Archs Neurol. *9:* 100–110 (1963).
18 Benton, A.L.: Differential behavioral effects in frontal lobe disease. Neuropsychologia *6:* 53–60 (1968).
19 Kitamura, T.; Yuzuriha, T.; Morita, M.; Itoh, J.; Suga, R.; Nakagawa, Y.: Oxford version of the BPRS: development and validation of subscales. Arch. psychiat. diagn. clin. Eval. *1:* 101–107 (1990).
20 Kanno, I.; Lassen, N.A.: Two methods for calculating regional cenrebral blood flow from emission tomography of inert gas concentrations. J. Comput. assist. Tomogr. *3:* 71–76 (1979).
21 Komatani, A.; Takanashi, K.; Yamaguchi, K.; Kera, M.; Sugai, Y.; Takahashi, K.: Factors affecting accuracy of tomographic measurement of rCBF by HEADTOME. Jap. J. Nucl. Med. *23:* 1019–1024 (1986).
22 Komatani, A.; Yamaguchi, K.; Kera, M.; et al.: Effect of breathing fluctuations on cerebral blood flow in demented patients and its correction method using end-tidal CO_2 concentration. Jap. J. Nucl. Med. *26:* 165–170 (1989).
23 Grove, W.M.; Andreasen, N.C.: Simultaneous tests of many hypotheses in exploratory research. J. nerv. ment. Dis. *170:* 3–8 (1982).
24 Akaike, H.: A new look at the statistical model identification. IEEE Trans. Automat. Contr. *19:* 716–723 (1974).
25 Takagi, H.; Yanai, H.; Hattori, Y.; Ichikawa, M.; Satoh, T.; Marui, E.: High quality Analysis Libraries for Business and Academic Users ('HALBAU') (Gendai Suugakusha-Shuppan, Kyoto 1988).
26 Utena, H.: Hysteresis and functional disconnection: update on the theory after 10 years. Seishin Igaku (Clin. Psychiat.) 1988:30: 247–254.
27 Buchsbaum, M.S.; Haier, R.J.: Functional and anatomical brain imaging: impact on schizophrenia research. Schizophr. Bull. *13:* 129–146 (1987).
28 Buchsbaum, M.S.; Nuechterlein, K.H.; Haier, R.J.; et al.: Glucose metabolic rate in normals and schizophrenics during the continuous performance test assessed by positron emission tomography. Br. J. Psychiatr. *156:* 216–227 (1990).
29 Mathew, R.J.; Wilson, W.H.; Tant, S.R.; et al.: Abnormal resting regional cerebral blood flow patterns and their correlates in schizophrenia. Archs gen. Psychiat. *45:* 542–549 (1988).
30 Mathew, R.J.; Wilson, W.H.: Chronicity and a low anteroposterior gradient of cerebral blood flow in schizophrenia. Am. J. Psychiat. *147:* 211–213 (1990).
31 Kurachi, M.; Kobayashi, K.; Matsubara, R.; et al.: Regional cerebral blood flow in schizophrenic disorders. Eur. Neurol. *24:* 176–181 (1985).
32 Berman, K.F.; Weinberger, D.R.: Lateralisation of cortical function during cognitive tasks: regional cerebral blood flow studies of normal individuals and patients with schizophrenia. J. Neurol. Neurosurg. Psychiat. *53:* 150–160 (1990).
33 Devous, M.D.: Imaging brain function by single photon emission computer tomography; in Andreasen, Brain imaging: applications in psychiatry, pp. 147–234 (American Psychiatric Press, Washington 1989).
34 Carlsson, M.; Carlsson, A.: Interaction between glutamatergic and monoaminergic systems within the basal ganglia – implications for schizophrenia and Parkinson's disease. Trends Neurosci. *13:* 272–276 (1990).

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