Eur Arch Psychiatry Clin Neurosci (1992) 241:195–200

European Archives of Psychiatry and Clinical Neuroscience



*Original Articles*

# Regional Cerebral Blood Flow in Patients with Schizophrenia

## A Preliminary Report

**Yasuhiro Kawasaki[1], Michio Suzuki[1], Yoshiki Maeda[1], Katsumi Urata[1], Nariyoshi Yamaguchi[1], Hiroshi Matsuda[2], Kinichi Hisada[2], Masayuki Suzuki[3], and Tsutomu Takashima[3]**

[1]Departments of Neuropsychiatry, [2]Nuclear Medicine, and [3]Radiology, Kanazawa University School of Medicine, 13-1 Takaramachi, Kanazawa 920, Japan

Received June 13, 1991

**Summary.** Regional cerebral blood flow was evaluated using Tc99m-HMPAO SPECT in 10 medicated patients with schizophrenia and 9 healthy volunteers. There were no prefrontal regions in the patient group with lower regional indices than in the control group. However, in the left hippocampal region, relative blood flow was significantly increased in the patient group compared with the control group. Furthermore, there was a relative increase in blood flow in the left basal ganglia of the patient group. A negative correlation coefficient was calculated between the relative blood flow in the left middle prefrontal cortex and the severity of the blunted affect, as well as between the relative blood flow in the left basal ganglia and the severity of the anhedonia-asociality. These findings indicate that prefrontal hypoactivity is not invariably present in all schizophrenics and that left basal ganglial hyperactivity may be associated with the effects of antipsychotic treatment and clinical improvement. Moreover, the left hippocampal hyperactivity may correspond to left limbic dysfunction in schizophrenia.

**Key words:** Regional cerebral blood flow – Tc99m-HMPAO SPECT – Schizophrenia

### Introduction

Regional cerebral blood flow (rCBF) represents a regional functional activity in the central nervous system (Sokoloff 1981). Studies of rCBF have attempted to identify regional functional abnormalities in patients with schizophrenia. Ingvar and Franzén (1974) first demonstrated an abnormal distribution of blood flow in the left hemisphere of schizophrenics. In our previous studies on the two-dimensional assessment of rCBF using 133Xe inhalation technique (Kurachi et al. 1985, 1987; Suzuki 1988), the relative frontal blood flow in schizophrenics was decreased in the left hemisphere as compared with normal controls, with this "hypofrontal" pattern being associated with high scores on several clinical rating items. These items included emotional withdrawal and blunted affect on the Brief Psychiatric Rating Scale (BPRS) of Overall and Gorham (1962), and avolition-apathy and attentional deficit on the Scale for the Assessment of Negative Symptoms (SANS) of Andreasen (1983).

Single photon emission computed tomography (SPECT) for imaging of rCBF has made the three-dimensional assessment of rCBF possible. Technetium-99m hexamethyl propyleneamine oxime (Tc99m-HMPAO) is a recently synthesized radiopharmaceutical that distributes in the brain to reflect rCBF. Current studies have confirmed that Tc99m-HMPAO readily crosses the blood-brain barrier and retains a fixed distribution for at least 5–8 hours (Neirinckx et al. 1987; Matsuda et al. 1988; Andersen 1989).

This article describes our initial experience with Tc99m-HMPAO SPECT brain scanning in schizophrenics and healthy controls. We measured rCBF in 39 brain regions of each subject. In addition, we analyzed the relationship between rCBF and clinical symptoms in the patients.

### Subjects and Methods

Ten right-handed male patients were recruited from the inpatient and outpatient facilities of the Department of Neuropsychiatry, Kanazawa University Hospital. General characteristics of the patients are listed in Table 1. The mean age of the patients was 30.6, 5.2 years (mean, SD) and the mean education level was 14.2, SD 1.7 years. All of the patients satisfied DSM-III-R criteria for schizophrenia (American Psychiatric Association 1987). Nine patients were in a chronic state of illness, and one was in a residual state after an acute psychotic period. Their mean age at the time of their initial psychopathology was 21.9, SD 4.4 years, and the mean du-

*Offprint requests to:* Y. Kawasaki

**Table 1.** General characteristics of each schizophrenic case

| Case | Age (years) | Education level (years) | Age at onset (years) | Duration of illness (years) | Neuroleptic treatment[a] (mg/day) | In-/Outpatient | Psychiatric findings during the study | Subtypes of diagnosis |
|---|---|---|---|---|---|---|---|---|
| 1 | 31 | 16 | 23.1 | 7.8 | 850 | in | Chronic delusion and social withdrawal | Paranoid |
| 2 | 28 | 12 | 23.9 | 4.1 | 850 | in | Chronic hallucination and delusion | Paranoid |
| 3 | 36 | 16 | 23.8 | 11.2 | 3600 | out | Chronic hallucination and social withdrawal | Paranoid |
| 4 | 35 | 16 | 26 | 10 | 200 | out | Chronic disorganization and delusion | Disorganized |
| 5 | 38 | 14 | 29.5 | 8.5 | 520 | out | Chronic social withdrawal | Residual |
| 6 | 26 | 16 | 25.1 | 0.9 | 75 | out | Residual state after psychotic episode | Residual |
| 7 | 35 | 12 | 19 | 16 | 500 | out | Chronic hallucination and deterioration | Paranoid |
| 8 | 23 | 14 | 19 | 4 | 150 | out | Violent behavior and anhedonia | Disorganized |
| 9 | 28 | 12 | 17.4 | 10.6 | 3025 | out | Chronic hallucination and social withdrawal | Paranoid |
| 10 | 24 | 12 | 14.8 | 9.3 | 1350 | in | Chonic delusion and social withdrawal | Paranoid |

[a] Chlorpromazine equivalent dose

ration of illness was 8.96, SD 4.0 years. All the patients had received neuroleptic treatment (mean chlorpromazine equivalent dose 1141.1, SD 1225.8 mg/day) during the study and had no history of previous electroconvulsive therapy. No patient with a history of alcohol or other drug abuse, or neurological disease was included in the study.

The age-matched control group consisted of nine right-handed male volunteers, who ranged in age from 25 to 37 years with a mean age of 29.0, SD 4.2 years. None had a history of serious medical, neurological, or psychiatric illness. All the patients and volunteers gave informed consent to participate in this study.

Measurements were taken in a dimly lit room with background noise from cooling fans. The subjects lay quietly with their eyes open for 5 min after intravenous injection of 740 MBq (20 mCi) Tc99m-HMPAO. SPECT was performed with a three-head rotating gamma camera system (GCA9300A; Toshiba, Tokyo, Japan) by employing general purpose fan beam collimators combined with a minicomputer (GMS550U; Toshiba, Tokyo, Japan). The resolution is 9 mm full width half maximum in the center of the reconstructed slice when the rotating radius is 13.2 cm. The computer slice width is 3.4 mm (Matsuda et al. 1990). The SPECT data were obtained in a 128 × 128 format for 30 angles in a 120° arc for each camera with 15 sec per angle. Total periods of data acquisition were 11 min. The filtered back projection method was used for SPECT image reconstruction after preprocessing projection data with a Butterworth filter. A series of slices, approximately parallel to the canthomeatal line, were obtained in each scan. Thirty-nine regions of interest (ROIs) were drawn in each hemisphere on five slices referring to the individual magnetic resonance imaging scan (Fig. 1). Each slice was selected at 20, 30, 45, 55, or 65% of the brain height (from the apex to the lowest part of the cerebellum). For evaluation of relative rCBF distribution in the brain, a regional index (percentile ratio between counts/voxel of one ROI and mean counts/voxel of all ROIs) was calculated, because absolute quantification of rCBF using Tc99m-HMPAO SPECT is not yet available.

Clinical symptoms were assessed by two psychiatrists using the Positive and Negative Syndrome Scale (PANSS) of Kay and Opler (1987) and SANS within 1 week of the SPECT study, with each mean score adopted.

For statistical analysis, the Mann-Whitney U test was applied between the patient and control groups. Spearman's rank correlation coefficient was used between rCBF and general characteristics or clinical symptoms. Bonferroni-adjustment of alpha-error required $P < 0.0013$ (0.05:39 regions) as the level of statistical significance. The Bonferroni-adjustment assumes that variables are independent, but rCBF variables may be dependent on one another. We therefore adjusted the criterion of significance to $P < 0.002$ and of indicating trends to $P < 0.02$.

## Results

### *Comparison of Schizophrenics versus Controls*

Regional indices in 39 discrete brain regions of the schizophrenics and controls are provided in Table 2. There were no prefrontal regions in the patient group showing lower regional indices than in the control group. However, in the left hippocampal region, the patient group had significantly higher regional indices ($P = 0.001$) than the control group. Furthermore, a relative rCBF increase could be estimated in the left basal ganglia ($P = 0.007$) of the patient group, but was not significant.

### *Correlation between rCBFs and general characteristics or clinical symptoms*

In the patient group, relative rCBF did not correlate with age, education level, age at the onset of illness, duration of illness, or chlorpromazine equivalent dose. The clinical symptom scores in each patient are shown in Table 3. There were only two non-significant trends between rCBFs and clinical symptoms. A negative correlation coefficient was obtained between the affective flattening or blunting score on SANS and the relative rCBF in the left middle prefrontal cortex ($r = -0.784$, $P = 0.018$). In the left basal ganglia, a negative correlation coefficient was also calculated between the relative rCBF and the anhedonia-asociality score on SANS ($r = -0.790$, $P = 0.017$).

## Discussion

In recent years, several authors have proposed that schizophrenia comprises (at least in part) positive and negative syndromes (Crow 1980; Andreasen and Olsen 1982). Clinical assessment by means of PANSS yields separate scores along a positive syndrome scale, negative syndrome scale, composite index, and general psychopathology scale. Sigh et al. (1987) suggested that this composite

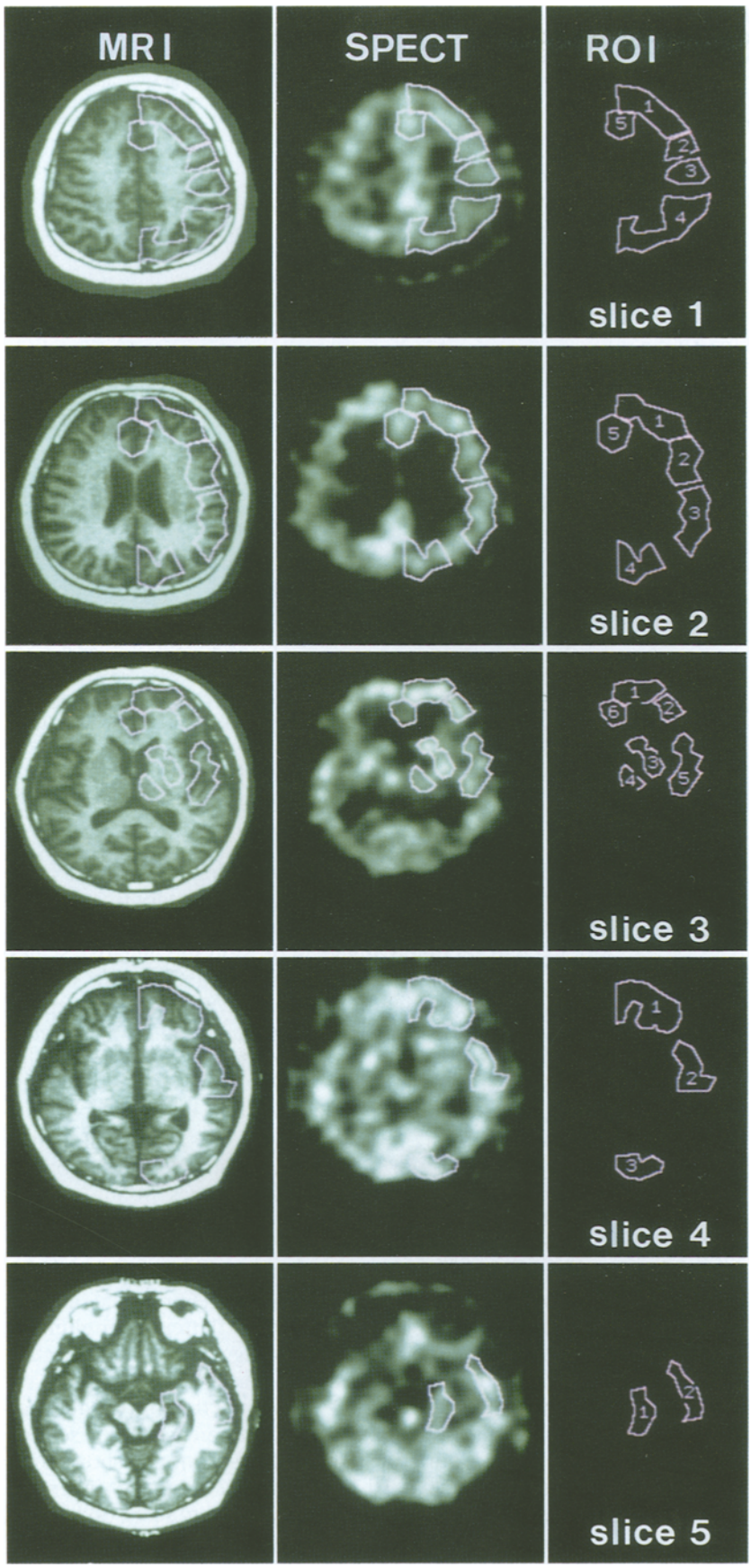


**Fig. 1.** Placement of regions of interest (ROIs). The first column shows a MR image of a patient. A SPECT study of the same patients in the second column. The third column indicates a regional schema of each ROI. Abbreviations used *Slice 1:* 1, superior prefrontal cortex; 2, premotor cortex; 3, primary motor cortex; 4, superior parietal cortex; 5, superior medial prefrontal cortex. *Slice 2:* 1, middle prefrontal cortex; 2, middle frontal cortex; 3, inferior parietal cortex; 4, superior occipital cortex; 5, middle medial prefrontal cortex. *Slice 3:* 1, inferior prefrontal cortex; 2, inferior frontal cortex; 3, basal ganglia, 4, thalamus; 5, superior temporal cortex; 6, inferior medial prefrontal cortex. *Slice 4:* 1, orbitofrontal cortex; 2, middle temporal cortex; 3, inferior occipital cortex. *Slice 5:* 1, hippocampal region; 2, inferior temporal cortex

**Table 2.** Comparison of regional indices between schizophrenics and controls

| Regions | Schizophrenics Mean ± SD | Controls Mean ± SD |
|---|---|---|
| *Slice 1* | | |
| Superior prefrontal cortex | | |
| Lt. | 94.7 ± 9.8 | 99.3 ± 3.2 |
| Rt. | 95.2 ± 2.0 | 98.5 ± 3.6 |
| Premotor cortex | | |
| Lt. | 97.2 ± 3.5 | 98.7 ± 3.5 |
| Rt. | 98.7 ± 2.3 | 100.4 ± 3.2 |
| Primary motor cortex | | |
| Lt. | 98.6 ± 3.3 | 96.0 ± 3.9 |
| Rt. | 99.7 ± 3.9 | 97.7 ± 2.6 |
| Superior parietal cortex | | |
| Lt. | 95.7 ± 3.8 | 96.4 ± 3.8 |
| Rt. | 97.4 ± 3.1 | 97.2 ± 3.8 |
| Superior medial prefrontal cortex | 96.5 ± 5.4 | 97.9 ± 3.7 |
| *Slice 2* | | |
| Middle prefrontal cortex | | |
| Lt. | 97.4 ± 4.4 | 100.3 ± 2.5 |
| Rt. | 99.7 ± 3.9 | 99.3 ± 2.4 |
| Middle frontal cortex | | |
| Lt. | 99.1 ± 1.7 | 98.6 ± 1.8 |
| Rt. | 97.9 ± 3.0 | 99.3 ± 3.6 |
| Inferior parietal cortex | | |
| Lt. | 98.9 ± 3.5 | 99.2 ± 3.1 |
| Rt. | 98.0 ± 2.8 | 100.0 ± 2.6 |
| Superior occipital cortex | | |
| Lt. | 102.1 ± 2.3 | 100.2 ± 3.4 |
| Rt. | 102.0 ± 3.7 | 99.8 ± 3.4 |
| Middle medial prefrontal cortex | 95.6 ± 3.7 | 99.9 ± 2.3 |
| *Slice 3* | | |
| Inferior prefrontal cortex | | |
| Lt. | 103.8 ± 2.9 | 104.3 ± 2.2 |
| Rt. | 101.6 ± 3.2 | 105.0 ± 4.8 |
| Inferior frontal cortex | | |
| Lt. | 98.9 ± 1.8 | 102.6 ± 3.5 |
| Rt. | 101.0 ± 2.9 | 105.1 ± 4.5 |
| Basal ganglia | | |
| Lt. | 108.2 ± 2.7[a] | 103.5 ± 2.6 |
| Rt. | 106.6 ± 4.7 | 102.2 ± 3.4 |
| Thalamus | | |
| Lt. | 104.6 ± 4.2 | 104.0 ± 3.0 |
| Rt. | 106.2 ± 5.3 | 103.2 ± 2.5 |
| Superior temporal cortex | | |
| Lt. | 103.4 ± 3.5 | 102.3 ± 3.0 |
| Rt. | 104.5 ± 2.5 | 103.1 ± 1.7 |
| Inferior medial prefrontal cortex | 99.4 ± 4.0 | 103.0 ± 4.1 |
| *Slice 4* | | |
| Orbitofrontal cortex | | |
| Lt. | 100.9 ± 1.9 | 99.8 ± 2.9 |
| Rt. | 99.1 ± 2.7 | 101.7 ± 3.2 |
| Middle temporal cortex | | |
| Lt. | 100.4 ± 2.6 | 101.9 ± 3.6 |
| Rt. | 100.7 ± 2.8 | 100.2 ± 4.6 |
| Inferior occipital cortex | | |
| Lt. | 108.9 ± 3.4 | 105.7 ± 6.7 |
| Rt. | 107.2 ± 5.3 | 105.4 ± 7.3 |
| *Slice 5* | | |
| Hippocampal region | | |
| Lt. | 92.7 ± 4.2[b] | 86.2 ± 2.1 |
| Rt. | 88.1 ± 3.5 | 88.0 ± 4.5 |
| Inferior temporal cortex | | |
| Lt. | 98.9 ± 3.0 | 96.1 ± 5.0 |
| Rt. | 98.7 ± 2.6 | 95.2 ± 4.2 |

Regional index indicates percentile ratio between counts/voxel of one region of interest and mean counts/voxel of all regions of interest

SD, standard deviation; Lt., left side; Rt., right side

[a] $P<0.02$, [b] $P<0.002$ compared to controls by Mann-Whitney U test

index, which is obtained by subtracting the negative from positive score, reflects the degree of predominance of a positive or negative syndrome. Many of the present patients had relatively higher scores on the negative scales than on the positive scales. Therefore, the patients studied here had predominantly negative symptoms and experienced chronic social impairment due to auditory hallucinations and/or affective flattening and avolition despite neuroleptic treatment.

A series of reports (Weinberger et al. 1986; Buchsbaum et al. 1987; Paulman et al. 1990), as well as our own previous reports, have demonstrated "hypofrontality" in some schizophrenics. In the present study using Tc99m-HMPAO SPECT, we could not replicate a direct finding of this hypofrontality. Our results, however, indicated that the patients with relative left prefrontal hypoactivity were characterized by the presence of clinical impairment such as the affective flattening or blunting score on SANS. These findings suggest that hypofrontality is not an invariable finding in schizophrenics.

Buchsbaum et al. (1987) reported that the basal ganglia metabolic rates are increased with medication in schizophrenics. In our study, the left basal ganglia showed increased relative rCBF, and this increase was inversely correlated with the anhedonia-asociality score on SANS. Compared with our experimental study on chronic haloperidol effects in rat brain using N-Isopropyl-p-[125I] iodo-amphetamine (Kawasaki 1990), the striatum, a region where we observed a relative rCBF increase in this

**Table 3.** Score on clinical symptoms in each schizophrenic case

| Case | PANSS | | | SANS | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Positive scale (7–49)[a] | Negative scale (7–49)[a] | General scale (16–112)[a] | Affective flattening or blunting (0–45)[a] | Alogia (0–30)[a] | Avolition apathy (0–25)[a] | Anhedonia asociality (0–30)[a] | Inattention (0–20)[a] | Summary score (0–15)[a] |
| 1 | 14 | 20 | 35 | 18.5 | 7.5 | 13 | 10 | 3 | 10.5 |
| 2 | 22 | 21 | 35 | 17.5 | 11 | 16 | 16.5 | 10 | 12 |
| 3 | 27.5 | 17 | 37 | 2 | 10 | 13.5 | 7 | 9 | 11 |
| 4 | 11 | 25 | 32 | 20 | 13 | 15 | 7 | 9 | 14 |
| 5 | 7 | 20 | 26 | 17 | 9 | 14 | 16 | 6 | 12 |
| 6 | 7 | 14.5 | 29 | 17 | 3 | 11 | 6 | 8 | 8 |
| 7 | 17 | 23 | 36 | 13 | 8 | 11 | 15 | 9 | 12 |
| 8 | 24 | 29.5 | 46 | 15 | 12 | 11 | 13 | 5 | 14 |
| 9 | 15 | 20.5 | 31 | 23 | 11 | 13 | 13 | 4 | 11 |
| 10 | 27 | 23 | 54 | 19.5 | 15 | 16 | 13 | 12.5 | 14 |
| Mean ± SD | 17.1 ± 7.3 | 21.3 ± 3.9 | 36.0 ± 7.8 | 16.2 ± 5.4 | 9.9 ± 3.1 | 13.4 ± 1.8 | 11.7 ± 3.7 | 7.5 ± 2.8 | 11.8 ± 1.7 |

PANSS, Positive and Negative Syndrome Scale; SANS, Scale for the Assessment of Negative Symptoms; SD, standard deviation

[a] Scale range

study, also showed an increase in absolute local cerebral blood flow. This relative rCBF increase in the left basal ganglia may reflect some effect of chronic antipsychotic drug treatment or an improvement in the clinical symptoms.

Clinical observations (Flor-Henry 1976), theoretical considerations (Torrey and Peterson 1974), and recent morphological findings (Bogerts et al. 1985; DeLisi et al. 1988) have suggested limbic system involvement in schizophrenia. In the left hippocampal region, the patient group showed a significant relative rCBF increase compared with the control group. These results are consistent with those reported by Musalek et al. (1988, 1989), who, using Tc99m-HMPAO SPECT, also assessed medicated schizophrenics with chronic auditory hallucination. DeLisi et al. (1989) showed that schizophrenics have greater metabolic activity in the left than the right anterior temporal lobe, with the extent of this lateralization proportional to the severity of the psychopathology. The hippocampal region measured here consisted of the hippocampus, amygdala, and parahippocampal formation. We could not specify which anatomical region is responsible for this rCBF increase. Nevertheless, our finding of increased relative rCBF in the left hippocampal region may correspond to left limbic dysfunction in schizophrenia.

The patients in this study tended to demonstrate negative symptoms rather than positive ones. Therefore, to evaluate a correlation between the heterogeneous collection of schizophrenic symptoms and rCBF, we are following up this question with more cases. Furthermore, we did not divide some of the neuroanatomical structures (i.e. the basal ganglia and the hippocampal formation) into more discrete regions, because only horizontal slice measurement was performed. This three-dimensional study using Tc99m-HMPAO SPECT provides finer spatial resolution, not only in horizontal but also in vertical slices. It may be possible to apply more rigorous ROI designation to identify regional abnormalities in schizophrenics.

*Acknowledgements.* This research was supported in part by Grant-in-Aid for Co-operative Research (A) 01304040 from the Ministry of Education, Science and Culture, Japan.

## References

American Psychiatric Association, Committee on Nomenclature and Statistics (1987) Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition. American Psychiatric Association, Washington, DC

Andersen AR (1989) 99mTc-D, L-Hexamethylene-propylene-amine Oxime (99mTc-HMPAO): basic kinetic studies of a tracer of cerebral blood flow. Cerebrovasc Brain Metab Rev 4: 288–318

Andreasen NC (1984) The scale for the assessment of negative symptoms (SANS). Iowa City, Iowa: University of Iowa

Andreasen NC, Olsen S (1983) Negative vs positive schizophrenia: definition and validation. Arch Gen Psychiatry 39: 789–794

Bogerts B, Meertz E, Schönfeldt-Bausch R (1985) Basal ganglia and limbic system pathology in schizophrenia. Arch Gen Psychiatry 42: 784–791

Buchsbaum MS, Wu JC, DeLisi LE, Holcomb HH, Hazlett E, Cooper-Langston K, Kessler R (1987) Positron emission tomography studies of basal ganglia and somatosensory cortex neuroleptic drug effects: differences between normal controls and schizophrenic patients. Biol Psychiatry 22: 479–494

Crow TJ (1980) Molecular pathology of schizophrenia: more than one disease process? BMJ 280: 66–68

DeLisi LE, Dauphinais D, Gershon ES (1988) Perinatal complications and reduced size of brain limbic structures in familial schizophrenia. Schizophr Bull 14: 185–191

DeLisi LE, Buchsbaum MS, Holcomb HH, Langston KC, King AC, Kessler R, Picker D, Carpenter WT, Morihisa JM, Margolin R, Weinberger DR (1989) Increased temporal lobe glucose use in chronic schizophrenic patients. Biol Psychiatry 25: 835–851

Flor-Henry P (1976) Lateralized temporal-limbic dysfunction and psychopathology. Ann NY Acad Sci 280: 777–795

Ingvar DH, Franzén G (1974) Distribution of cerebral activity in chronic schizophrenia. Lancet ii:1484–1486

Kawasaki Y (1990) Effects of antipsychotic drug on the local cerebral blood flow in rats. Juzen Med Soc 99:450–462

Kay SR, Opler LA (1987) The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 13:261–275

Kurachi M, Kobayashi K, Matsubara R, Hiramatsu H, Yamaguchi N, Matsuda H, Maeda T, Hisada K (1985) Regional cerebral blood flow in schizophrenic disorders. Eur Neurol 24:176–181

Kurachi M, Suzuki M, Kawasaki Y, Kobayashi K, Shimazu A, Yamaguchi N (1987) Regional cerebral blood flow in patients with schizophrenic disorders. In: Takahashi R, Flor-Henry P, Gruzelier J, Niwa S (eds) Cerebral Dynamics, Laterality and Psychopathology. Elsevier, Amsterdam, pp 493–501

Matsuda H, Oba H, Seki H, Higashi S, Sumiya H, Terada H, Imai K, Shiba K, Mori H, Hisada K (1988) Determination of flow and rate constants in kinetic model of [99mTc]-hexamethylpropylene amine oxime in the human brain. J Cereb Blood Flow Metabol 8:S61–S68

Matsuda H, Oskoie SD, Kinuya K, Tsuji S, Sumiya H, Tonami N, Hisada K (1990) Tc-99m HMPAO brain perfusion tomography atlas using a high resolution SPECT system. Clin Nucl Med 15:428–431

Musalek M, Podreka I, Suess E, Nutzinger D, Passweg V, Strobl R, Walter H, Baumgartner C, Lesch OM (1988) Neurophysiological aspects of auditory hallucinations: 99mTc-(HMPAO)-SPECT investigation in patients with auditory hallucinations and normal controls- a preliminary report. Psychopathology 21:275–280

Musalek M, Podreka I, Walter H, Suess E, Passweg V, Nutzinger D, Strobl R, Lesch OM (1989) Regional brain function in hallucinations: a study of regional cerebral blood flow with 99m-Tc-HMPAO-SPECT in patients with auditory hallucinations, tactile hallucinations, and normal controls. Compre Psychiatry 30:99–108

Neirinckx RD, Canning LR, Piper IM, Nowotonik DP, Pickett RD, Holmes RA, Volkert WA, Forster AM, Weisner PS, Mariott JA, Chaplin SB (1987) Technetium-99m D, 1-HM-PAO: a new radiopharmaceutical for SPECT imaging of regional cerebral blood perfusion. J Nucl Med 28:191–202

Overall JR, Gorham DR (1962) The brief psychiatric rating scale. Psychol Rep 10:799–812

Paulman RG, Devous MD, Gregory RR, Herman JH, Jennings L, Bonte FJ, Nasrallah HA, Raese JD (1990) Hypofrontality and cognitive impairment in schizophrenia: dynamic single-photon tomography and neuropsychological assessment of schizophrenic brain function. Biol Psychiatry 27:377–399

Sigh MM, Kay SR, Opler LA (1987) Anticholinergic-neuroleptic antagonism in terms of positive and negative symptoms of schizophrenia: implications for psychobiological subtyping. Psychol Med 17:39–48

Sokoloff L (1981) Relationship between local functional activity, energy metabolism, and blood flow in the central nervous system. Fed Proc 40:2311–2316

Suzuki M (1988) A study on the relationship between regional cerebral blood flow and clinical symptoms in functional psychoses: (I) schizophrenic disorder. Juzen Med Soc 97:764–778

Torrey EF, Peterson MR (1974) Schizophrenia and the limbic system. Lancet ii:942–946

Weinberger DR, Berman KF, Zec RF (1986) Physiologic dysfunction of dorsolateral prefrontal cortex in schizophrenia: I. regional cerebral blood flow evidence. Arch Gen Psychiatry 43:114–124