# Regional Cerebral Blood Flow and Negative/Positive Symptoms in 24 Drug-Naive Schizophrenics

O. Sabri, R. Erkwoh, M. Schreckenberger, U. Cremerius, G. Schulz, C. Dickmann, H.J. Kaiser, E.M. Steinmeyer, H. Sass and U. Buell

*Departments of Nuclear Medicine and Psychiatry, Technical University of Aachen, Germany*

SPECT/PET studies in schizophrenia revealed inconsistent changes of regional cerebral blood flow (rCBF). Frontal hyperperfusion as well as hypoperfusion are described. This study was undertaken to investigate the relations between rCBF, psychopathology according to PANSS and effects of neuroleptic therapy. **Methods:** Twenty-four drug-naive acute patients with a first manifestation of schizophrenia were examined with $^{99m}$Tc-HMPAO brain SPECT and assessed according to PANSS. Of these, 22 were controlled again after neuroleptic treatment. Following attenuation correction, region-to-cerebellar count ratios were obtained from 98 irregular regions of interest drawn in all slices (6.25 mm). The ratios were compared to 20 control subjects, and changes lying outside of 2 s.d. were considered abnormal. **Results:** In different drug-naive patients, hyperperfusion as well as hypoperfused patterns were found. In drug-naive patients, the seven subscores of positive symptoms (pos 1–7) in PANSS showed different correlations to rCBF: Formal thought disorders (pos 2) and grandiosity (pos 5) were positively correlated to bifrontal and bitemporal rCBF (r = +0.59 to +0.70). Delusional ideas (pos 1), hallucinatory behavior (pos 3) and suspiciousness (pos 6) demonstrated a negative correlation to bifrontal, cingulate, left temporal and left thalamic rCBF (r = -0.59 to -0.66). Stereotyped ideas (neg 7) as a negative symptom showed a negative correlation to left frontal, left temporal and left parietal rCBF (r = -0.59 to -0.65). No correlations were found between residual positive symptoms and rCBF after neuroleptic treatment and clinical improvement, but all negative symptoms (neg 1–7) had a negative correlation to bifrontal, bitemporal, cingulate, basal ganglia and thalamic rCBF (r = -0.59 to -0.74). **Conclusion:** Our results illustrate that different positive symptoms are accompanied by different rCBF values: some induce hyperperfusion, others hypoperfusion. After therapy (and reduction of positive symptoms), only negative symptoms correlate exclusively to hypoperfusion. This may be the crucial factor in explaining inconsistencies of past results in perfusion pattern in drug-naive schizophrenic patients.

**Key Words:** schizophrenia; technetium-99m-HMPAO; SPECT; neuroleptic treatment

R ecent SPECT/PET studies in schizophrenic patients have shown inconsistent findings of regional cerebral blood flow (rCBF) and glucose consumption (rMRGlu): Impairment of frontal rCBF or rMRGlu, so-called hypofrontality, was described predominantly in medicated patients with chronic disease (1–7). Hyperfrontality was found mainly in unmedicated patients with acute disease (8–12). Some groups exhibited increased metabolism in the basal ganglia (1,7), while others showed reduced metabolism in the basal ganglia (13). Moreover, temporal rCBF abnormalities have also been reported in schizophrenia (8,14–16). One crucial drawback to assessing relations between schizophrenic symptoms and altered rCBF may be the lack of large groups of patients examined. Studies

on rCBF in acute and never-treated ("neuroleptic-naive") schizophrenic patients are particularly rare in medical literature.

The aim of this study was to evaluate the relationship between altered rCBF values as well as negative and positive symptoms in acute and neuroleptic-naive, schizophrenic patients and to determine the influence of neuroleptic treatment to brain perfusion and negative or positive symptoms, respectively. Since not only frontal or temporal rCBF abnormalities were found, several regions of interest (ROIs) were quantified, including frontal, parietal, temporal, occipital, cingulate, basal ganglia and thalamic areas.

## METHODS

### Patients

This study was performed using a protocol approved by the local ethics committee. Schizophrenic patients meeting the criteria for the Diagnostic and Statistical Manual of Mental Disorders (third revised edition, DSM-III-R) diagnosis of schizophrenia (17) were included if they were neuroleptic-naive and actively psychotic at presentation. Patients with schizophreniform disorders, schizoaffective disorders and bipolar mood disorders were excluded from the study. Twenty-four patients [16 men, 8 women; mean age 32.3 yr (s.d. 9.7)] were recruited, all of them with a first episode of schizophrenic psychosis (11 paranoid, 10 paranoid hallucinatory, 3 undifferentiated). Paranoid and undifferentiated subtypes were defined according to DSM-III-R 295.3 and 295.9 (17). The paranoid-hallucinatory subtype was used to identify patients suffering from delusions and hallucinations of varying contents not included in the paranoid subtype of DSM-III-R. Average age at illness onset was 29.6 yr (s.d. 7.2), resulting in a mean duration of 2.7 yr (s.d. 6.3) of illness before the first SPECT/PANSS (Postive and Negative Syndrome Scale of Schizophrenia) examinations were performed. Because they came from the rural area around Aachen, some patients had been ill for a long time but still had adapted to family life in the countryside. These circumstances might account for a somewhat higher average age at onset of illness than that given by DSM-III-R.

The initial examinations (SPECT, CT, psychopathology) were performed on neuroleptic-naive patients in an acute, psychotic state. Clinical assessment was done using the PANSS on the day of the SPECT study or one day earlier (Table 1). The PANSS for typological and dimensional assessment of schizophrenic phenomena has been well validated (18) and represents a continued development of two common tests, the Brief Psychiatric Rating Scale (BPRS) and the Psychopathology Rating Schedule (19). The PANSS was evaluated by a formalized, semistructured interview. There are 33 items on a scale from 1 (normal) to 7 points (extremely abnormal). The PANSS comprises subscores for 7 positive, 7 negative, 16 global psychopathological and 3 aggression risk symptoms. Evaluated subscores were expressed as percentages of the maximum points possible, subscore magnitude indicating severity of illness.

The second examinations (SPECT and PANSS) were performed

**TABLE 1**
Characteristics of Neuroleptic-Naive Schizophrenic Patients before and after Treatment

| Characteristic | Value in acute state* | Significance | Value after treatment* |
|---|---|---|---|
| Age (yr) | 32.3 ± 9.7 | ns | 32.3 ± 9.8 |
| Years of illness | 2.7 ± 6.3 | ns | 2.9 ± 6.1 |
| Pos sum | 42.5 ± 13.4 | § | 10.0 ± 9.5 |
| Pos 1 | 5.2 ± 1.6 | § | 2.0 ± 1.6 |
| Pos 2 | 3.8 ± 1.6 | § | 1.7 ± 0.8 |
| Pos 3 | 3.5 ± 1.9 | § | 1.2 ± 0.5 |
| Pos 4 | 2.9 ± 1.3 | § | 1.3 ± 0.6 |
| Pos 5 | 2.3 ± 1.6 | † | 1.5 ± 1.0 |
| Pos 6 | 4.7 ± 1.9 | § | 2.1 ± 1.5 |
| Pos 7 | 2.5 ± 1.4 | ‡ | 1.4 ± 0.7 |
| Neg sum | 16.0 ± 10.2 | ns | 16.5 ± 12.5 |
| Neg 1 | 1.8 ± 1.2 | ns | 2.2 ± 1.4 |
| Neg 2 | 2.1 ± 1.3 | ns | 2.4 ± 1.2 |
| Neg 3 | 2.3 ± 1.3 | ns | 2.1 ± 1.2 |
| Neg 4 | 2.0 ± 1.2 | ns | 1.9 ± 1.1 |
| Neg 5 | 2.1 ± 1.2 | ns | 2.0 ± 1.1 |
| Neg 6 | 1.6 ± 1.1 | ns | 1.6 ± 1.0 |
| Neg 7 | 1.8 ± 1.4 | ns | 1.6 ± 1.1 |

*All values are means ± s.d.: †p < 0.05; ‡p < 0.01; §p < 0.0005.

Wilcoxon test (s.d. is not needed for this test, but included to show comparable deviations of individual values): Pos sum = sum score of all positive symptoms in PANSS in percentage of maximal possible points; Neg sum = sum score of all negative symptoms in percentage of maximal possible points; Pos 1–7 = scores of each single positive symptom; Neg 1–7 = scores of each single negative symptom.

after neuroleptic treatment and clinical improvement. Choice of neuroleptics and dosage depended exclusively on the individual target syndrome, with the aim of achieving a psychopathological remission. The neuroleptics given were haloperidol, bromperidol, sulpiride, clozapine, thioridazine or levomepromazine, dosed individually according to each patient. Neuroleptic dosages were expressed as chlorpromazine units per day (CU/day). Before the second examination, patients received 848.7 CU/day over an average of 96.8 days (range: 17–405 days).

## Control Patients

For ethical reasons, control patients were comprised of 12 women and 8 men patients (n = 20) with unspecific headache or recent small meningioma (<1 ml) without neurological and psychiatric abnormalities and without morphological alterations of the brain, especially without medium or severe atrophy in CT. The mean age (54.2 ± 14.1 yr) was significantly higher than the average age of schizophrenic patients (32 ± 9.7 yr, p < 0.01, U-test). Regression analysis, however, showed no linear correlation between the rCBF equivalent (rCBF normalized to cerebellum: cerebral-to-cerebellar ratio) and age in any of the cortical ROIs investigated, p > 0.05. By dividing control subjects into two subgroups—(a) age-matched to schizophrenic patients (n = 6, 36.0 ± 10 yr) and (b) older control patients (n = 14, 61.5 ± 9.8 yr) and performing U-tests to both groups—revealed no significant differences in rCBF ratios (p > 0.05). Therefore, all control patients were pooled for comparable group sizes (Table 2).

## Imaging Protocol

Control subjects and patients were examined as follows: Subjects underwent cannulation of an arm vein and were allowed to rest for at least 10 min before injection of 740 MBq $^{99m}$Tc-HMPAO. During the injection, subjects were lying comfortably with their eyes closed, ears unplugged and environmental noises kept to a minimum for 5 min after start of the injection. They were scanned 15 min after injection using a special headholder (for canthomeatal positioning) (20) and a double-head ROTA gamma camera to collect 60 30-sec frames in 3° angular steps during a 180° rotation for each head in a 128 × 128 matrix with a zoom of 1.0, resulting in a pixel size of 6.25 mm. Restless patients received up to 15 mg diazepam intravenously 10 min after the radiotracer injection to avoid interactions between diazepam and rCBF, as well as motion artifacts during the long scanning period (40 min). During radiotracer injection (without applicating diazepam) up to 5 min, we ensured no patient movement by providing a comfortable and known environment (patients had enough time to get accustomed to the room before the examinations started). All neuroleptic-naive patients could be examined without exhibiting motor activity during radiotracer injection, and (if required after injection of diazepam) without motion artifacts during the scanning period. After unproblematic injection of the radiotracer in one patient, however, scanning was performed 2 hr postinjection without diazepam administration and no motion artifacts, since 15 min postinjection the patient did not feel capable of tolerating the scanning procedure and refused to receive diazepam.

**TABLE 2**
Mean rCBF (Normalization-to-Cerebellum) in Schizophrenic Subjects before and after Treatment and in Control Subjects*

| ROI | Before treatment | | After treatment | | Controls (n = 20) | |
|---|---|---|---|---|---|---|
| | Left | Right | Left | Right | Left | Right |
| Superior frontal | 0.79 ± 0.06 | 0.79 ± 0.06 | 0.79 ± 0.06 | 0.79 ± 0.06 | 0.79 ± 0.05 | 0.79 ± 0.06 |
| Posterior frontal | 0.79 ± 0.06 | 0.79 ± 0.06 | 0.79 ± 0.05 | 0.79 ± 0.07 | 0.78 ± 0.04 | 0.78 ± 0.05 |
| Inferior frontal | 0.74 ± 0.06 | 0.75 ± 0.05 | 0.74 ± 0.05 | 0.75 ± 0.05 | 0.75 ± 0.03 | 0.75 ± 0.03 |
| Anterior cingulate | 0.80 ± 0.05 | 0.80 ± 0.05 | 0.81 ± 0.06 | 0.81 ± 0.06 | 0.79 ± 0.04 | 0.79 ± 0.04 |
| Parietal | 0.83 ± 0.06 | 0.80 ± 0.06 | 0.84 ± 0.06 | 0.82 ± 0.04 | 0.81 ± 0.04 | 0.79 ± 0.05 |
| Superior temporal | 0.77 ± 0.04 | 0.78 ± 0.05 | 0.79 ± 0.05 | 0.78 ± 0.04 | 0.79 ± 0.03 | 0.78 ± 0.04 |
| Inferior temporal | 0.76 ± 0.05 | 0.76 ± 0.05 | 0.77 ± 0.05 | 0.77 ± 0.04 | 0.76 ± 0.03 | 0.77 ± 0.03 |
| Mesial temporal | 0.78 ± 0.05 | 0.77 ± 0.05 | 0.79 ± 0.06 | 0.77 ± 0.05 | 0.80 ± 0.05 | 0.78 ± 0.04 |
| Occipital | 0.83 ± 0.04 | 0.82 ± 0.05 | 0.85 ± 0.06 | 0.84 ± 0.05 | 0.84 ± 0.03 | 0.84 ± 0.03 |
| Basal ganglia | 0.87 ± 0.07 | 0.89 ± 0.08 | 0.91 ± 0.07 | 0.91 ± 0.07 | 0.87 ± 0.04 | 0.88 ± 0.04 |
| Thalamus | 0.90 ± 0.04 | 0.91 ± 0.05 | 0.92 ± 0.05 | 0.94 ± 0.06 | 0.90 ± 0.07 | 0.91 ± 0.05 |

*All values are mean ± s.d.
ROI = 98 regions of interest defined in 13 canthomeatal slices and summed up to 11 ROIs on each hemisphere; after treatment = ROI values after application of neuroleptics (848.7 CU/day for 96.8 days) and clinical improvement.

**TABLE 3**

Correlation between rCBF (Normalized-to-Cerebellum) and Single Positive (Pos 1–7)* and Negative (Neg 1–7)* Symptoms in Neuroleptic-Naive Patients (n = 24) during the Acute Phase

| ROI | Pos 1 | Pos 2 | Pos 3 | Pos 5 | Pos 6 | Neg 7 |
|---|---|---|---|---|---|---|
| Frontal left | | +0.69‡ | | +0.63† | −0.60† | −0.60† |
| Frontal right | | +0.68‡ | | +0.59† | | |
| Superior frontal left | | +0.59† | | +0.62† | | |
| Superior frontal right | | +0.63† | | | | |
| Posterior frontal left | | | | | | |
| Posterior frontal right | | | | | | |
| Inferior frontal left | | +0.70‡ | | | −0.61† | −0.61† |
| Inferior frontal right | | +0.67‡ | | | −0.61† | |
| Anterior cingulate | −0.60† | +0.59† | | | | −0.59† |
| Parietal left | | | | | | −0.59† |
| Parietal right | | | | | | |
| Temporal left | | +0.62† | | +0.59† | | −0.59† |
| Temporal right | | +0.66‡ | | +0.65‡ | | |
| Superior temporal left | | +0.69‡ | | +0.62† | −0.61† | −0.65‡ |
| Superior temporal right | | +0.69‡ | | | | |
| Inferior temporal left | | | | | | |
| Inferior temporal right | | +0.59† | | +0.70‡ | | |
| Mesial temporal left | | +0.59† | | | | |
| Mesial temporal right | | | | | | |
| Occipital left | | | | | | |
| Occipital right | | | | | | |
| Basal ganglia left | | | | | | |
| Basal ganglia right | | | | | | |
| Thalamus left | | | −0.66‡ | | | |
| Thalamus right | | | | | | |

*Spearman correlation coefficients with r.

†p < 0.001; ‡p < 0.0005, two-tailed significance level.

Only correlation coefficients |x| > 0.58 are shown. Pos sum (subscore of all positive symptoms), neg sum, pos 4, pos 5 and neg 1–6 did not show correlation coefficients >0.58.

## SPECT Data Analysis

Reconstruction was performed by filtered backprojection using a Butterworth filter (cutoff frequency 0.48, filter order 3.0). Attenuation correction was performed according to Chang (*21*). The spatial resolution was 15 mm (FWHM) in the transaxial plane.

Semiquantitaive rCBF analysis was derived from normalization to the neocerebellum (rCBF ratio). Therefore, two identical ROIs (each 99 pixels in size) were placed in each cerebellar hemisphere (excluding the vermis). There were no significant differences between the left and right cerebellum in the control and in the patient group (t-test, p > 0.05), so that the mean value of the counting rates of both ROIs was used as reference value. Since there were no statistical differences in the mean cerebellum values of our control group and those of the schizophrenic patients group (t-test: control subjects 15125 ± 4670 counts, patients 15139 ± 3104 counts, p > 0.05), and since the neocerebellum is not involved in schizophrenia, this reference region seems to be more appropriate than a normalization to the whole slice (which contains also the areas with changed perfusion) even in the knowledge of activation studies which showed an involvement of the palaeocerebellum (*16*). There were no significant differences in cerebellum counts of drug-naive patients before and after neuroleptic treatment and clinical improvement (p > 0.05).

By using the anatomical atlasses of Talairach and Touroux and Kretschmann and Weinrich (*22,23*) and dividing the brain (cerebrum) into 13 canthomeatal slices (the most basal and the most dorsal slices were not included to minimize partial volume effects, the lowest one included counted as number 1) of 6.25 mm thickness, 98 irregular ROIs were visually defined. Corresponding ROIs of all slices were summed together and defined as follows:

superior frontal (slices 9–13), inferior frontal (slices 3–8, posterior frontal ("precentral," 10–12), frontal (mean superior, posterior and inferior frontal), parietal (slices 10–13), superior temporal (slices 5–8), inferior temporal (slices 1–4), mesial temporal (slices 1–3), temporal (mean superior, inferior and mesial temporal), occipital (slices 3–10), anterior cingulate (slices 5–10), basal ganglia (slices 4–7) and thalami (slices 4–7), each on the left and right hemisphere (Table 2). It is important to emphasize that all ROIs were larger than 2.5 × FWHM (15 mm) of our gamma camera to allow a secure quantification (*24*).

The intraobserver variability determined for every single ROI (n = 98) in the control group (n = 20) was lower than 3%, which is lower than 1 s.d. (<0.02) of the ROI values. The interobserver variability for n = 20, determined by two blinded evaluators (even with different shapes of irregular ROIs), was lower than 4%, which is also lower than 1 s.d. (<0.04).

All ROI-values were normally distributed (Shapiro-Wilks-test, Lilliefors-test, p > 0.05) so that differences of more than 2 s.d. between the patients and the control subjects were considered abnormal.

## CT

Every schizophrenic patient underwent CT to exclude medium-to-severe atrophy, which was recently shown to significantly reduce rCBF and-rMRGlu values compared to patients without or only slight atrophy (*25*).

## Statistical Analysis

For comparison of rCBF ratios between schizophrenic patients and control subjects, t-tests for independent samples were done.

**TABLE 4**
Correlation between rCBF (Normalized-to-Cerebellum), Single Negative Symptoms (Neg 1–7)* and Neg Sum* in Neuroleptic-Naive Patients after Neuroleptic Treatment and Clinical Improvement

| ROI | Neg 1 | Neg 2 | Neg 5 | Neg 6 | Neg 7 | Neg sum |
|---|---|---|---|---|---|---|
| Frontal left | −0.59† | −0.59† | | | | −0.70‡ |
| Frontal right | | | −0.59† | | | −0.65† |
| Superior frontal left | −0.59† | | | | | −0.72‡ |
| Superior frontal right | | | −0.68‡ | | | −0.67† |
| Posterior frontal left | | | | | | |
| Posterior frontal right | | | | | | |
| Inferior frontal left | −0.61† | −0.63† | | | | −0.71‡ |
| Inferior frontal right | | | −0.61† | | | −0.62† |
| Anterior cingulate | | | −0.63† | | | −0.72‡ |
| Parietal left | | | | | | |
| Parietal right | | | | | | |
| Temporal left | −0.59† | | | | −0.65† | −0.70‡ |
| Temporal right | | | | | | −0.59† |
| Superior temporal left | −0.59† | | | | | |
| Superior temporal right | | | | | | |
| Inferior temporal left | | | | | −0.65† | −0.64† |
| Inferior temporal right | | | | −0.59† | −0.59† | −0.59† |
| Mesial temporal left | −0.63† | −0.67† | | −0.68‡ | | −0.80‡ |
| Mesial temporal right | | | | −0.66† | | −0.72‡ |
| Occipital left | | | | | | |
| Occipital right | | | | | | |
| Basal ganglia left | −0.60† | −0.59† | | | | −0.75‡ |
| Basal ganglia right | | | −0.63† | | | −0.59† |
| Thalamus left | −0.63† | | | | | −0.69‡ |
| Thalamus right | | | −0.74‡ | | | |

*Spearman correlation coefficients with r.
†p < 0.001; ‡p < 0.0005, two-tailed significance level.
Only correlation coefficients |x| > 0.58 are shown. Neg sum = sum score of all negative symptoms; neg 3 and neg 4 did not show correlation coefficients >0.58.

Differences between first and second examination of patients (rCBF) were tested with t-tests for paired samples. Differences between first and second examination in PANSS were tested with the Wilcoxon test. For correlation of rCBF ratios in different ROIs compared with each single positive (pos 1 through 7) and negative (neg 1 through 7) symptom, Spearman and Pearson correlation coefficients were used. Pearson's test is to be used on the condition that all variables are normally distributed. This test is easily confounded by outliers (26). Spearman's test is very exact even in small samples and not normally distributed values, and not very susceptible to outliers (26). In general, our data showed somewhat lower Spearman correlation coefficients than Pearson correlation coefficients. Therefore, Spearman correlation coefficients were taken to assure a maximum of safety and cautious conclusions. Since multiple correlations were performed, the statistical power of the coefficient obtained was determined (27) to exclude accidental significance which might increase through multiple testing. For 24 schizophrenic patients and a significance level of p < 0.05, the statistical power is greater than 91% if the correlation coefficient is r > 0.58. This statistical power is highly reliable for excluding capitalization on chance due to multiple correlation testing (27). Alternatively, if p values are adjusted according to Holm's sequentially rejecting multiple testing procedure for more frequent observations, a p value ≤ 0.001 can be discussed as significant at the 0.05 level (28). Therefore, only correlation coefficients with r > 0.58 (or p ≤ 0.001) were interpreted in the discussion. Either method yields the same result, i.e., these correlation coefficients are significant at the 0.05 level without capitalization on chance due to multiple testing.

## RESULTS

### Regional Cerebral Blood Flow Ratios

Nine neuroleptic-naive patients revealed hyperperfusion in frontal, anterior cingulate, parietal and/or temporal cortex ROIs. After neuroleptic treatment and clinical improvement, six normalized completely and three partially. In contrast, three drug-naive patients showed hypoperfusion in frontal, anterior cingulate, parietal and/or temporal cortex ROIs, of which two normalized completely after treatment and one partially. Comparing the ROI values of all neuroleptic-naive schizophrenic patients to control subjects, no statistical differences were found, neither to control subjects nor between the pre- and post-treatment examinations (Table 2). However, a subgroup of schizophrenic patients, the paranoid schizophrenic patients (n = 11), showed significantly increased rCBF ratios parietal left and in the basal ganglia compared to control subjects (parietal left: 0.86 ± 0.04 versus 0.81 ± 0.04, p < 0.05; basal ganglia left: 0.91 ± 0.04 versus 0.87 ± 0.04, p < 0.025; basal ganglia right: 0.92 ± 0.04 versus 0.88 ± 0.04, p < 0.025). Frontal inferior left rCBF ratio was also increased but did not reach the significance level (0.78 ± 0.03 versus 0.75 ± 0.03, 0.055 > p > 0.05). Comparing the paranoid schizophrenic patients to the paranoid-hallucinatory schizophrenic patients (n = 10), paranoids showed significantly increased inferior bifrontal rCBF ratios and the same tendency for the superior temporal right rCBF ratio (inferior frontal left: 0.78 ± 0.03 versus 0.70 ± 0.05, p < 0.025; inferior frontal right: 0.77 ± 0.03 versus 0.71 ± 0.05, p < 0.025; superior temporal right:
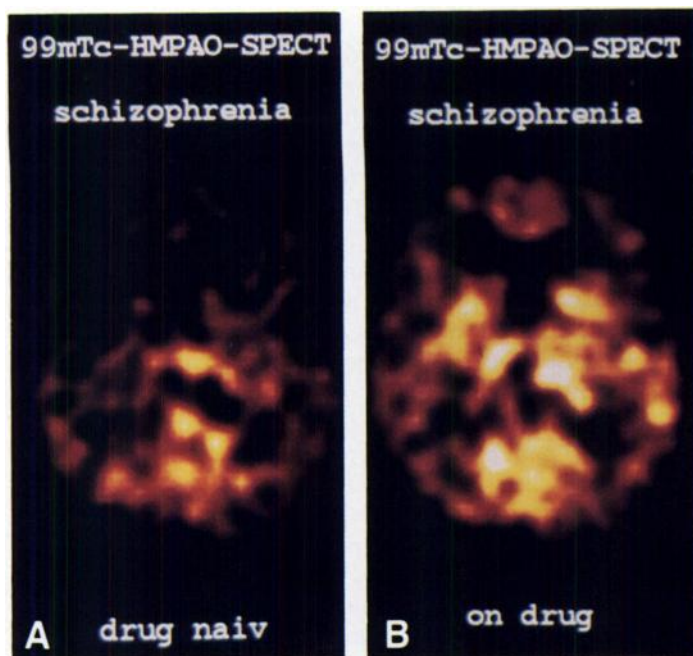
**FIGURE 1.** A 24-yr-old female schizophrenic patient presenting with high subscores for delusional ideas (pos 1), suspiciousness (pos 6), difficulties in abstract thinking (neg 5) and stereotyped ideas (neg 7). (A) SPECT in acute, neuroleptic-naive state with general hypoperfusion except of the thalami. (B) Hypoperfusion normalized after neuroleptic treatment and clinical improvement.
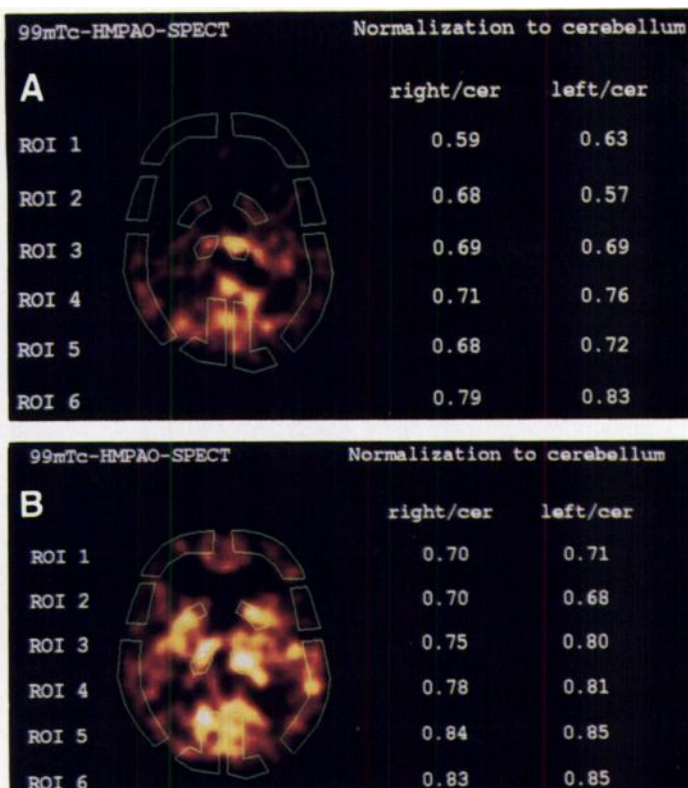


**FIGURE 2.** Semiquantitative evaluation of rCBF shows reduced rCBF-ratios except for thalami (A). After treatment, increase to normal rCBF-values (B).

0.79 ± 0.04 versus 0.76 ± 0.05, 0.082 > p > 0.05). After neuroleptic treatment and clinical improvement, paranoid schizophrenic patients showed a significant rCBF decrease inferior frontal left (from 0.78 ± 0.03 to 0.73 ± 0.04, p < 0.025). Then, no further differences in rCBF ratios between paranoid and paranoid-hallucinatory patients were found.

### PANSS Score

After neuroleptic treatment and clinical improvement, the sum score of positive symptoms was reduced significantly (p < 0.0005), while there were no significant changes in negative symptoms (Table 1). During the active phase, paranoid schizophrenic patients revealed values for each single positive and negative symptom similar to paranoid hallucinatory patients, except for hallucinatory behavior (pos 3; paranoids 2.5 points versus paranoid hallucinatories 4.5 points, p < 0.05, U-test), and the same tendency for stereotyped ideas (neg 7; 1.4 points versus 2.5 points, 0.1 > p > 0.05). After treatment, no differences between these two subgroups were found.

### Correlation of rCBF in Thirteen ROIs to Cumlulative Positive and Negative Scores

In neuroleptic-naive schizophrenic patients, sum score of all positive symptoms (pos sum) in PANSS showed only weak positive correlations to frontal, cingulate and left temporal rCBF ratios (r = +0.3), whereas the sum score of all negative symptoms (neg sum) showed weak negative correlations to frontal, cingulate and temporal rCBF ratios (r = −0.3). Following neuroleptic treatment and clinical improvement, no correlations between residual positive sum scores and rCBF ratios were found. In contrast, remaining negative sum scores showed a strong negative correlation to frontal, cingulate, temporal, basal ganglia and thalamic rCBF ratios (r = −0.59 to −0.80, p < 0.001 to p < 0.0005; Tables 3 and 4).

### Correlation of rCBF in Thirteen ROIs to Each Single Positive and Negative Symptom

*Neuroleptic-Naive Patients.* In neuroleptic-naive schizophrenic patients, delusional ideas (pos 1), hallucinatory behavior (pos 3) and suspiciousness (pos 6) correlated significantly and strongly negatively to bifrontal, cingulate, left temporal and left thalamic rCBF ratios: r = −0.59 to −0.66, p < 0.001 to p < 0.0005 (Table 3, Figs. 1 and 2). Formal thought disorders (pos 2) and grandiosity (pos 5) showed significant and strong positive correlations to bifrontal and bitemporal rCBF ratios: r = +0.59 to +0.70, p < 0.001 to p < 0.0005 (Table 3 and Figs. 3 and 4). Excitement (pos 4), hostility (pos 7) and negative symptoms 1–6 (neg 1–6) showed no correlations to rCBF ratios with r > 0.58. Only negative symptom 7 (neg 7, stereotyped ideas), correlated significantly and strongly negatively to left frontal, cingulate, left parietal and left temporal rCBF ratios: r = −0.59 to −0.65, p < 0.001 to p < 0.0005 (Table 3). The linear regressions of pos 2 and pos 6 versus bifrontal rCBF ratio (mean ratio for superior, inferior and posterior frontal ROIs left and right) are shown in Figure 5.

*Treated Patients.* Following neuroleptic treatment and clinical improvement, no significant correlations between residual positive symptoms and rCBF ratios were found. Negative symptom 1 (neg 1), which is affective flattening, and emotional withdrawal (neg 2), correlated significantly and strongly negatively to frontal, temporal, basal ganglia and thalamic rCBF ratios on the left side: r = −0.59 to −0.67, p < 0.001. Difficulties in abstract thinking (neg 5) correlated negatively to frontal, cingulate, basal ganglia and thalamic rCBF ratios on the right side: r = −0.63 to −0.74, p < 0.001 to p < 0.0005. Reduced spontaneity (neg 6) and stereotyped ideas (neg 7) correlated negatively to bitemporal rCBF ratios: r = −0.59 to −0.71, p < 0.001 to p < 0.0005 (Table 4). The linear regression of neg 2 versus left frontal rCBF ratio (mean ratio for superior, inferior and posterior frontal ROIs left) is shown in Figure 6.
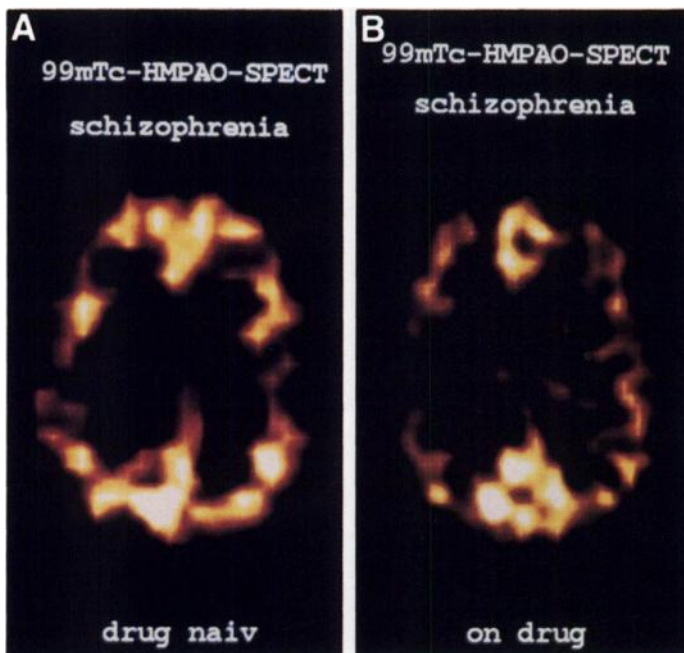
**FIGURE 3.** A 17-yr-old male schizophrenic patient presenting with high subscores for positive symptoms such as formal thought disorders (pos 2) and grandiosity (pos 5) and low for all negative symptoms. Technetium-99m-HMPAO SPECT in acute, neuroleptic-naive state with bifrontal hyperperfusion (A). Bifrontal hyperperfusion normalized after neuroleptic treatment and clinical improvement (B).

## DISCUSSION

### Neuroleptic-Naive Schizophrenic Patients during the Acute Phase

A comparison of rCBF from all neuroleptic-naive patients to control subjects revealed no significant differences. Dividing the neuroleptic-naive patients into different subgroups, however, revealed rCBF changes: paranoid schizophrenic patients had significantly increased rCBF ratios in left parietal and basal ganglia areas, and a tendency towards increased inferior frontal



**FIGURE 4.** Semiquantitative evaluation of rCBF shows increased bifrontal rCBF ratios (0.88, 0.89, 0.90, 0.86) in the acute, neuroleptic-naive state (A). After neuroleptic treatment and clinical improvement, reduction to normal bifrontal rCBF ratios (0.77, 0.77, 0.75, 0.76) (B).

left rCBF ratio. Compared to paranoid-hallucinatory patients they showed significantly increased inferior bifrontal rCBF ratios. According to PANSS, paranoid-hallucinatory schizophrenic patients had significantly higher scores for hallucinatory behavior (pos 3) than paranoid patients and the same tendency for stereotyped ideas (neg 7). Since pos 3 and neg 7 correlate negatively to rCBF (Table 3), this could account for the decreased rCBF values of paranoid-hallucinatory patients compared to paranoid schizophrenic patients. Perhaps the perfusion changes of paranoids are not only due to positive/negative symptoms. Paulman et al. (15) have reported multiple regional deficits in bilateral hemispheric increased rCBF in chronic paranoid schizophrenic patients.

The most frequent PET/SPECT pattern reported in schizophrenia is hypofrontality. According to several authors, hypofrontality may be associated by the chronicity of illness, with a predominance of negative symptoms and the aging process (29–31). Some authors have pointed out that any observed rCBF pattern in schizophrenic patients may depend on the medication status of the patients examined (32), but even in unmedicated schizophrenic patients different rCBF patterns have been described. Some groups found hyperfrontality in unmedicated patients with acute disease (8–10,13,32). Catafau et al. (8) found prefrontally increased blood flow in neuroleptic-naive schizophrenic patients, which they ascribed to positive symptoms. These authors concluded that there is no evidence of hypofrontality in young schizophrenic patients with acute disease who had never been exposed to neuroleptics. Other researchers measured hypofrontality in neuroleptic-naive patients (33). Most frequently, it has been supposed that the small number of patients examined and the variety of techniques employed are the reasons for these findings.

Therefore, in the present investigation, a comparatively large number of neuroleptic-naive, actively psychotic schizophrenic patients (n = 24) was scrutinized. The results clearly demonstrate that both hyperfrontality as well as hypofrontality can be measured in neuroleptic-naive schizophrenic patients. This does not depend on different techniques but only on the magnitude and proportion of the seven positive symptoms (Figs. 1A–4A, 5; Table 3).

According to the DSM-III-R criteria, only one of the seven positive symptoms with more than four points in PANSS is needed to diagnose the acuteness of schizophrenia (17). Thus, without differentiating acute schizophrenic patients according to the seven positive symptoms in PANSS, one may assign them to one group, as most recent authors did, not taking into account the following: formal thought disorders (pos 2) and grandiosity (pos 5) correlate positively to frontal rCBF ratios (thus leading to hyperfrontality, Table 3), but delusional ideas (pos 1) and suspiciousness (pos 6) correlate negatively to frontal-to-cingulate rCBF ratios (thus contributing to hypofrontality, Table 3). This is why: (a) comparing all neuroleptic-naive patients in one group did not reveal significant rCBF changes and (b) for the weak correlation of the sum score of all positive symtoms to rCBF since the different positive symptoms show opposite rCBF changes, thereby cancelling out deviations. In acute schizophrenic patients, only stereotyped ideas (neg 7) as a single negative symptom correlate negatively to left frontal rCBF ratio (thus contributing to hypofrontality, Table 3).

Some studies reported so-called schizophrenic hypotemporality (7,15,34). Since morphological abnormalities in the temporal lobe, mainly on the left side, of schizophrenic patients are well-known, a link between such abnormalities and left tempo-
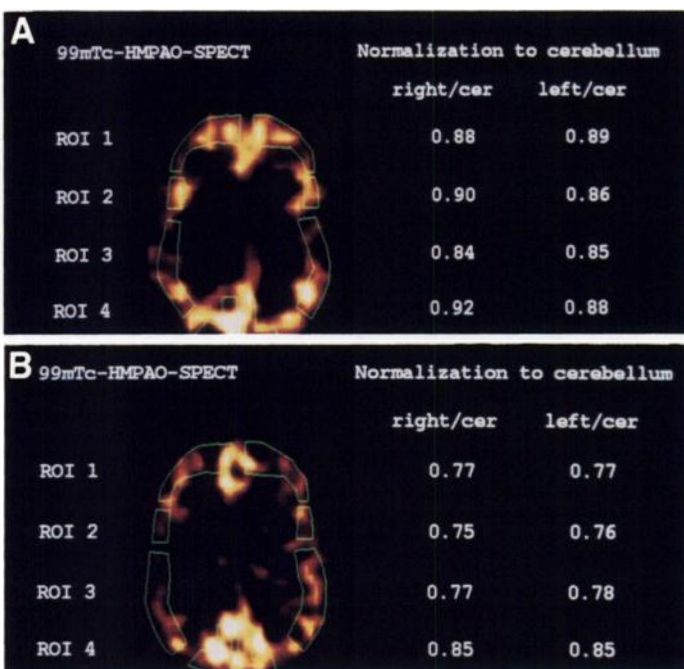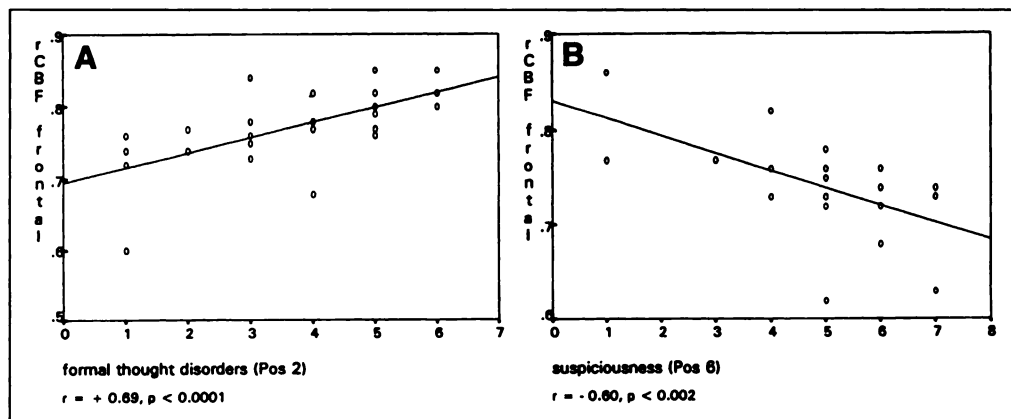
FIGURE 5. Regression analysis of pos 2 and pos 6, quantified on a point scale according to PANSS (increasing scores reflecting severity of symptoms) compared with frontal rCBF in neuroleptic naive, acute schizophrenic patients (n = 24). Pos 2 shows a strong positive correlation to frontal rCBF (A). In contrast, pos 6 reveals a strong negative correlation to frontal rCBF (B).

ral hypoperfusion is assumed (8,36). Recently, our group demonstrated that, with a SPECT/PETmethod resolution in the range of 7 to 15 mm FWHM, only medium-to-severe atrophy significantly reduces the rCBF values measured, in comparison to patients without or with only slight atrophy (25). Therefore, in the present study, all patients underwent recent CT to exclude medium or severe atrophy. Nevertheless, we found hypo- as well as hyperperfusion of the temporal lobes in neuroleptic-naive patients, mainly on the left side, depending on the magnitude and proportion of each positive symptom. As for frontal perfusion, some of the positive symptoms correlate positively and some negatively to temporal rCBF. We feel that these rCBF changes are not due to morphological alterations but represent correlates to psychopathological alterations.

## Neuroleptic-naive Patients after Neuroleptic Treatment and Clinical Improvement

Most authors describe hypofrontality in medicated schizophrenic patients (1-7). In the present study, subsequent to neuroleptic medication and clinical improvement (and reduction of positive symptoms), the sum score of all negative symptoms showed a strong negative correlation to frontal, cingulate, temporal, basal ganglia and thalamic rCBF ratios, which agrees with literature findings reporting decreased regional and/or global cerebral perfusion (1-7). It is of interest, however, that affective flattening (neg 1) and emotional withdrawal (neg 2) reveal an exclusively negative correlation to left hemispheric rCBF ratios (including the basal ganglia and thalami), while difficulties in abstract thinking (neg 5) corre-

lates negatively to right hemispheric rCBF ratios (including basal ganglia and thalami), reduced spontaneity (neg 6) and stereotyped ideas (neg 7) show a negative correlation to bitemporal rCBF ratios. Liddle et al. (35) reported increased blood flow in the basal ganglia and decreased prefrontal and left parietal blood flow in medicated patients as a correlation to psychomotor poverty (including poverty of speech, affective flattening, and decreased spontaneous movement). Our results do not agree with these findings for the basal ganglia, since we found a negative correlation. We performed correlations for each single negative symptom (not for a mixture of negative and general psychopathological symptoms) according to PANSS and found strong correlations even for single symptoms. There is no report of a lateralization effect to the right hemisphere for difficulties in abstract thinking (neg 5) in the literature.

No further differences in rCBF were found between paranoid and paranoid-hallucinatory schizophrenic patients after treatment and clinical improvement in this study. Therefore, the difference between paranoid and paranoid-hallucinatory patients seems to be related to the active state of psychosis. Since the patient subgroups were rather small (11 versus 10), more studies are needed for each group.

The possibility that SPECT scan-related anxiety could explain the changed perfusion pattern in schizophrenic patients must be considered. Since all patients had enough time to get accustomed to the environment before the injection procedure started and since injections were performed in a separate room (not lying under the gamma camera, which may lead to more anxiety) we tried to minimize this risk. The lack of patient motion during tracer injection and scanning (with the help of diazepam if required) minimized artifactually changed perfusion ratios: no differences of posterior frontal ("precentral") rCBF ratios between schizophrenic patients (even in the subgroups) and control subjects were found in the present study (Table 2).
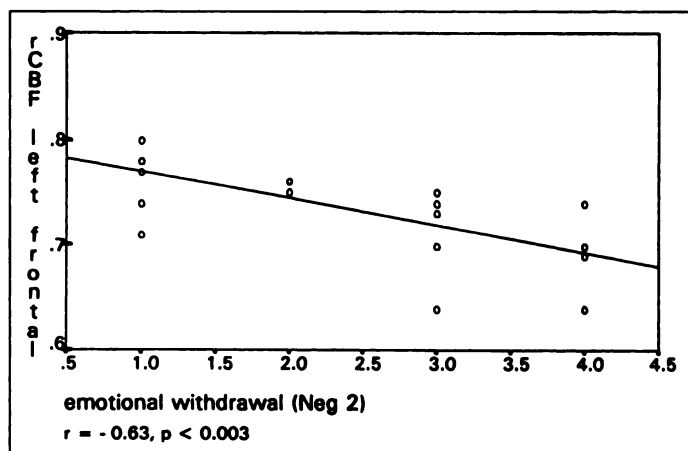


FIGURE 6. Regression analysis of neg 2 quantified on a point scale according to PANSS (increasing scores reflecting severity of symptoms) compared with left frontal rCBF in neuroleptic-naive patients after neuroleptical treatment and clinical improvement. Neg 2 shows a strong negative correlation to left frontal rCBF.

## CONCLUSION

Perfusion changes in several cerebral regions in neuroleptic-naive schizophrenic patients showed highly significant positive or negative correlations to single psychopathological symptoms, which underlines the necessity to divide patients by symptoms into different subgroups before comparing different factors and results from other studies. Before treatment, there is a lateralization effect of changes to the left hemisphere, which is in good agreement with the literature (8,36-38). Acute paranoid schizophrenic patients may be differentiated from paranoid-hallucinatory patients during the active state of psychosis. After neuroleptic treatment and clinical improvement,

positive symptoms decreased; remaining negative symptoms correlate negatively to rCBF in different locations. Especially for difficulties in abstract thinking, an exclusive lateralization to the right side is found, which shows that both hemispheres are involved whenever negative symptoms predominate. These findings may explain inconsistent recent results in rCBF patterns in drug-naive or neuroleptic-treated schizophrenic patients.

## ACKNOWLEDGMENT
We thank Dr. A. Rodón for editorial assistance.

## REFERENCES
1. Brodie JD, Christman DR, Corona JF, et al. Patterns of metabolic activity in the treatment of schizophrenia. Ann Neurol 1984;15:166–169.
2. Buchsbaum MS, Ingvar DH, Kessler R, et al. Cerebral glucography with positron tomography. Use in normal subjects and in patients with schizophrenia. Arch Gen Psychiatry 1982;39:251–259.
3. DeLisi LE, Buchsbaum MS, Holcomb HH, et al. Clinical correlates of decreased anteroposterior metabolic gradients in positron emission tomography of schizophrenic patients. Am J Psychiatry 1985;142:78–81.
4. Farkas T, Wolf AP, Jaeger J, Brodie JD, et al. Regional brain glucose metabolism in chronic schizophrenia. A positron emission transaxial tomographic study. Arch Gen Psychiatry 1984;41:293–300.
5. Ingvar DH, Franzén G. Abnormalities of cerebral blood flow distribution in patients with chronic schizophrenia. Acta Psychiatr Scand 1974;50:425–462.
6. Lewis SW, Ford RA, Syed GM, Reveley AM, Toone BU. A controlled study of 99mTc-HMPAO single-photon emission imaging in chronic schizophrenia. Psychol Med 1992;22:27–35.
7. Wolkin A, Jaeger J, Brodie JD, et al. Persistence of cerebral metabolic abnormalities in chronic schizophrenia as determined by positron emission tomography. Am J Psychiatry 1985;142:564–571.
8. Catafau AM, Parellada E, Lomeña FJ, et al. Prefrontal and temporal blood flow in schizophrenia. J Nucl Med 1994;35:935–941.
9. Cleghorn JM, Garnett ES, Nahmias C, et al. Increased frontal and reduced parietal glucose metabolism in acute untreated schizophrenia. Psychiatry Res 1989;28:119–133.
10. Szechtman H, Nahmias C, Garnett ES, et al. Effect of neuroleptics on altered cerebral glucose metabolism in schizophrenia. Arch Gen Psychiatry 1988;45:523–532.
11. Volkow ND, Brodie JD, Wolf AP, Angrist B, Russel J, Cancro R. Brain metabolism in patients with schizophrenia before and after acute neuroleptic administration. J Neurol Neurosurg Psychiatry 1986;49:1199–1202.
12. Wiesel FA, Wik G, Sjögren I, Blomqvist G, Greitz T, Stone-Elander S. Regional brain glucose metabolism in drug free schizophrenic patients and clinical correlates. Acta Psychiatr Scand 1987;76:628–641.
13. Sheppard G, Manchanda R, Gruzelier J, et al. Oxygen-15 positron emission tomographic scanning in predominantly never treated acute schizophrenic patients. Lancet 1983;2:1448–1452.
14. Devous MD Sr, Paulman RG, Herman J, et al. Single-photon tomography studies with schizophrenic patients. J Clin Exp Neuropsychol 1988;10:321–322.
15. Paulman RG, Devous MD Sr, Gregory RR, et al. Hypofrontality and cognitive
16. Syed GMS, Barret JJ, Toone BK. What does rCBF SPECT offer in schizophrenia? Nucl Med Commun 1992;13:879–884.
17. American Psychiatric Association DSM-III-R. Diagnostic and statistical manual of mental disorders, 3rd revised ed. Washington DC: American Psychiatric Press; 1987.
18. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 1987;13:261–276.
19. Overall JE, Gorham DR, et al. The brief psychiatric rating scale. Psychol Rep 1962;10:799–812.
20. Kaiser HJ, Sabri O, Wagenknecht G, Lege B, Hellwig D, Büll U. A method of correlating and merging cerebral morphology and function by a special headholder. Nucl Med 1994;33:123–126.
21. Chang LT. A method for attenuation correction in radionuclide computed tomography. IEEE Trans Nucl Sci 1978;25:638–643.
22. Talairach J, Touroux P. Referentially oriented cerebral MRI anatomy. Atlas of stereotoxic anatomical correlations for gray and white matter. New York: Thieme; 1993.
23. Kretschmann HJ, Weinrich W. Clinical neuroanatomy and cranial diagnostic imaging, 2nd ed. New York: Thieme; 1991.
24. Kojima A, Matsumoto M, Takahashi M, et al. Effect of spatial resolution on SPECT quantification values. J Nucl Med 1989;30:508–514.
25. Sabri O, Hellwig D, Kaiser HJ, et al. Effects of morphological changes on perfusion and metabolism in cerebral microangiopathy. Nucl Med 1995;34:50–56.
26. Sachs L. Applied statistics, 6th ed. Berlin: Springer; 1984.
27. Bavry JLSTAT-Power. Statistical design analysis system. Scientific Software, Inc: 1991.
28. Holm S. A simple sequentially rejective multiple test procedure. Scand J Stat 1979;6:65–70.
29. Volkow ND, Wolf AP, Brodie JD, Cancro R. Clinical interpretation of metabolic and neurochemical abnormalities in schizophrenic patients studied with positron-emission tomography. In: Volkow ND, Wolf AP, eds. Positron emission tomography in schizophrenia research. Washington DC: American Psychiatric Press; 1991:59–73.
30. Volkow ND, Wolf AP, Van Gelder P, et al. Phenomenological correlates of metabolic activity in 18 patients with chronic schizophrenia. Am J Psychiatry 1987;144:151–158.
31. Wolkin A, Sanfilipo M, Wolf AP, et al. Negative symptoms and hypofrontality in chronic schizophrenia. Arch Gen Psychiatry 1992;49:959–965.
32. Ebmeier KP, Blackwood DHR, Murray C, et al. Single-photon emission computed tomography with 99mTc-exametazime in unmedicated schizophrenic patients. Biol Psychiatry 1993;33:487–495.
33. Andreasen NC, Rezai K, Alliger R, et al. Hypofrontality in neuroleptic-naive patients and in patients with chronic schizophrenia. Arch Gen Psychiatry 1992;49:943–958.
34. Gur RC, Resnick SM, Gur RC, et al. Regional brain function in schizophrenia. II. Repeated evaluation with positron emission tomography. Arch Gen Psychiatry 1987;44:126–129.
35. Liddle PF, Friston KJ, Frith CD, et al. Patterns of cerebral blood flow in schizophrenia. Br J Psychiatry 1992;160:179–186.
36. Crow TJ. Temporal lobe asymmetries as the key to the etiology of schizophrenia. Schizophr Bull 1990;16:433–443.
37. Berman KF, Weinberger DR. Functional localization in the brain in schizophrenia. In: Tasman A, Goldfinger SM, eds. American Psychiatric Association review of psychiatry. Washington DC: American Psychiatric Press; 1991;10:25–29.
38. Buchsbaum MS. Positron emission tomography and regional brain metabolism in schizophrenia research. In: Volkow ND, Wolf AP, eds. Positron emission tomography in schizophrenia research. Washington DC: American Psychiatric Press; 1991:27–45.

# Asymmetry of Basal Ganglia Perfusion in Tourette's Syndrome Shown by Technetium-99m-HMPAO SPECT

Peter S. Klieger, Kristi A. Fett, Theresa Dimitsopulos and Roger Kurlan
*Division of Nuclear Medicine and Department of Neurology, University of Rochester Medical Center*

Our study involved performing brain perfusion SPECT scans on Tourette's subjects to observe any common perfusion abnormalities involving the cerebral cortex or subcortical structures. **Method:** Six patients with Tourette's syndrome and nine normal control subjects underwent a brain SPECT study with 99mTc-HMPAO. Regions of interest were generated over the cerebral cortex, basal ganglia, thalamus and cerebellum to evaluate any relative perfusion abnormalities or asymmetry in the Tourette's subjects. **Results:** Five of the six Tourette's subjects demonstrated a significant decrease in right basal ganglia activity which was not present in any of the normal control subjects. **Conclusion:** Our study suggests an etiology for Tourette's syndrome involving the right basal ganglia. Furthermore, brain SPECT may be useful in the evaluation of these patients if it proves to be sufficiently sensitive and specific in larger study populations.

**Key Words:** Tourette's syndrome; SPECT; basal ganglia

**J Nucl Med 1997; 38:188–191**