Prefrontal and Temporal Blood Flow in Schizophrenia: Resting and Activation Technetium-99m-HMPAO SPECT Patterns in Young Neuroleptic-Naive Patients with Acute Disease

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This study assesses prefrontal and temporal regional cerebral blood flow (rCBF) changes in young, neuroleptic-naive schizophrenic patients with acute disease. **Methods:** A selected population of 10 young, never-treated schizophrenic women with acute disease was studied by two hexamethylpropyleneamine oxime (HMPAO) brain SPECT sessions, performed 48 hr apart, both at rest and during a prefrontal activation task using the Wisconsin Card Sort Test (WCST). All patients met *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edition-revised criteria for schizophrenia or schizophreniform disorder, were neuroleptic-naive and had acute symptoms. **Results:** Under resting conditions, the schizophrenic group had significantly higher rCBF in the prefrontal regions, mainly in the left side and including the anterior cingulate, than did the controls. In addition, schizophrenic patients showed significant interhemispheric differences in prefrontal and posterior temporal index values at rest (left hyperfrontality and left hypotemporality). During WCST activation, the control group showed significant increases in prefrontal blood flow, whereas the schizophrenic group did not. **Conclusion:** These results support a physiologic dysfunction of the prefrontal cortex in schizophrenia that is present at the onset of the illness prior to neuroleptic treatment. Furthermore, both left hyperfrontality and left hypotemporality may indicate a brain lateralization defect in schizophrenia.

Key Words: HMPAO; SPECT; Wisconsin Card Sort Test; schizophrenia; neuroleptic-naive

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Frontal lobe dysfunction in schizophrenia has been described by recent SPECT studies (*1–7*). Most studies are based on medicated patients with chronic disease, with an impairment of frontal regional cerebral blood flow (rCBF) being the most common pattern described. This so-called hypofrontality was found to become more evident during frontal activation tasks. Moreover, temporal rCBF abnormalities have also been reported in schizophrenia (*5,8,9*).

However, the results are inconsistent. Variations in the choice of method may explain some of these inconsistencies, but more important factors include the selection criteria for study populations. These criteria include age, gender, duration of illness (acute versus chronic), clinical status (positive versus negative symptoms), medication status (drug-naive, neuroleptic-withdrawal or chronic medicated) and cognitive behavior (resting versus activation tasks). Thus, studies with homogeneous samples are needed. Furthermore, rCBF studies of acute and never-treated ("neuroleptic-naive") schizophrenic patients are still rare in the literature.

The aim of this study was to measure prefrontal rCBF using hexamethylpropyleneamine oxime (HMPAO) SPECT at rest and during a specific cognitive activation task in a selected homogeneous population of young neuroleptic-naive schizophrenic patients with acute disease. The rCBF findings of temporal lobes are also discussed.

SUBJECTS AND METHODS

Subjects

Table 1 summarizes the characteristics of both schizophrenic and control groups. All 10 schizophrenic patients were right-handed women admitted to the psychiatric unit for the first time. The patients had never been treated with any neuroleptic drug (neuroleptic-naive) and presented acute and positive symptoms. Seven patients met DSM-III R criteria (*10*) for schizophrenia and three for schizophreniform disorder. The mean age was 22.7 yr, and the mean duration of illness was 15.1 mo. The psychopathology was quantified on the day of the SPECT study or on the previous day with the Brief Psychiatric Rating Scale, the Scale for

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TABLE 1
Characteristics of Patients and Controls

Characteristic	Value*
Patients (n = 10)	
Age (yr)	22.7 ± 4.8
Months of illness	15.1 ± 11.2
Years of education	12.7 ± 3.0
BPRS total score	33.8 ± 8.8
SAPS total score	61.4 ± 17.0
SANS total score	50.9 ± 25.1
Controls (n = 8)	
Age (yr)	24.6 ± 3.0
Years of education	16.7 ± 1.2

*All values are means ±s.d.

BPRS = Brief Psychiatric Rating Scale; SAPS = Scale for the Assessment of Positive Symptoms; SANS = Scale for the Assessment of Negative Symptoms. Values over 18 in BPRS and over 40 in both SAPS and SANS, are considered to be clearly pathologic.

the Assessment of Positive Symptoms and the Scale for the Assessment of Negative Symptoms (Table 1). Eight healthy age-matched, right-handed women were recruited as controls. There was no significant difference in education between both groups. All subjects underwent a CT scan before the actual SPECT procedure.

Methods

Study Procedure. Two HMPAO brain SPECTS were performed in each subject; the first at rest and the second during frontal activation using the Wisconsin Card Sorting Test (WCST). In a baseline resting condition, the subjects were seated in a quiet room with their eyes open 5 min before and after the tracer injection. Two days after the resting study, the subjects were activated by the WCST, a problem-solving abstract thinking test that is thought to assess prefrontal lobe function in a fairly selective manner (*2,11*). Two of 64 response cards must be matched to four stimulus cards. The subjects were instructed to indicate their choices by placing the response cards below the chosen stimulus card. The WCST was started 10 min before tracer injection, and continued until the end of the test. The tracer injection was given while the subjects were well engaged with the WCST.

SPECT Acquisition. The SPECT study was performed using a rotating gamma camera (Elscint SP4-HR, Haifa, Israel) equipped with a low-energy all-purpose parallel-hole collimator. Data acquisition started 20 min after intravenous injection of 740 MBq of ^{99m}Tc-HMPAO (Ceretec, Amersham, Madrid, Spain). Sixty 30-sec frames were collected during a 360° rotation in a 64 × 64 matrix with a zoom of 1.5, obtaining a 4.5-mm pixel size.

SPECT Data Analysis. Image data were processed on an Elscint SP1 computer (Apex SP-x Functions, software version 3.12). Reconstruction was performed by filtered backprojection using a Butterworth filter (cutoff frequency 0.35, power factor 5.8) without attenuation correction. The spatial resolution was 16 mm (FWHM) in the transaxial plane.

For each subject, images from both SPECT studies were reconstructed with a thickness of 1 pixel. Both three-dimensional images were aligned by using software written in C language and based on full three-dimensional correlation (displacement and rotation). The alignment was carried out in a Hewlett Packard APOLLO 720 Work Station. After alignment, the two images were transfered to the APEX system where 2-pixel thick oblique slices taken from the frontocerebellar direction were obtained, using the same angular orientation and position in both studies. The SPECT images were finally presented

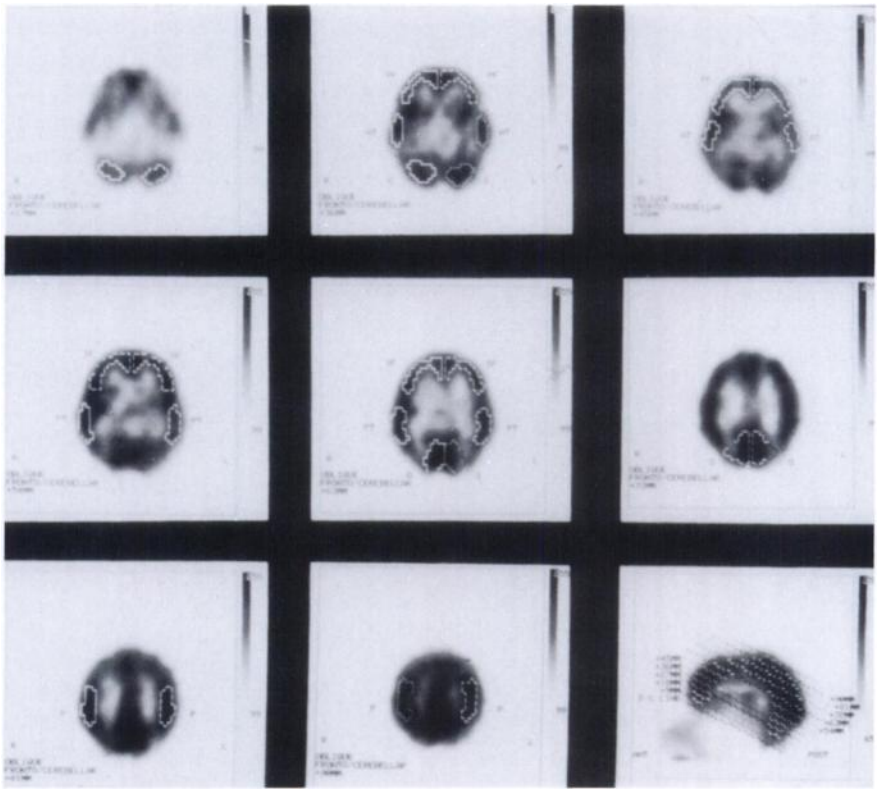

FIGURE 1. Template used to draw regions of interest. PF = prefrontal; SF = superior frontal; AT = anterior temporal; PT = posterior temporal; P = parietal; O = occipital; C = cerebellum. Note that prefrontal ROIs include the anterior cingulate cortex.

on a polychromatic scale (20 colors) and standardized as previously reported (*12*).

Semiquantitative rCBF analysis was performed by drawing irregular regions of interest (ROIs) in eight standardized 9-mm thick oblique slices taken from the frontocerebellar direction (Fig. 1). This was done in the resting study, and the ROIs drawn were copied for the activation study. ROIs were always drawn blindly by the same nuclear medicine physician, first on the left hemisphere (14 ROIs), and then mirrored ROIs were placed on the right hemisphere (total = 28 ROIs). Each ROI was drawn on two consecutive slices, and mean count values per pixel were obtained. For each hemisphere, prefrontal-to-whole-brain ratios were obtained as: prefrontal index (PI) = 100 × mean counts per pixel of prefrontal ROIs/mean counts per pixel of all ROIs drawn. Using the same formulas, anterior and posterior temporal indices were also obtained for each hemisphere.

The mean percentage of the PI change was also calculated between both studies in controls and schizophrenics as 100 × (PIa − PIr)/PIr (where a = activation and r = rest).

Statistical Analysis. For the comparison of the rCBF values and WCST performance between normal controls and schizophrenic patients, the Mann-Whitney U test was applied. The differences between resting and activation rCBF values and interhemispheric rCBF differences for each group were tested with the Wilcoxon test.

RESULTS

All CT scans were reported to be within normal limits, except for those from three patients. One patient showed mild atrophy of the cerebellar vermis, another had mild cerebral atrophy. The third showed mild to moderate lateral ventricular enlargement.

Table 2 presents the mean prefrontal and temporal relative perfusion indices at rest and during frontal activation in controls and schizophrenic patients. The statistically significant differences found are summarized in Table 3.

TABLE 2
Mean Prefrontal and Temporal Relative Perfusion Indices at Rest and During Frontal Activation in Controls and Schizophrenics*

	At rest		Activation	
ROI	Left	Right	Left	Right
Controls (n = 8)				
PF	98.9 ± 1.1	98.2 ± 1.6	101.9 ± 1.9	101.1 ± 2.2
AT	98.3 ± 3.4	99.8 ± 3.2	98.8 ± 3.6	99.2 ± 2.6
PT	99.8 ± 1.7	101.8 ± 3.4	99.7 ± 2.5	99.6 ± 3.0
Schizophrenics (n = 10)				
PF	102.4 ± 2.0	100.5 ± 2.8	101.6 ± 2.5	99.9 ± 3.1
AT	98.9 ± 2.2	99.3 ± 3.8	100.2 ± 2.5	99.0 ± 3.9
PT	96.7 ± 1.9	99.7 ± 2.9	98.0 ± 2.1	100.2 ± 1.9

*All values are means ±s.d.

PF = prefrontal; AT = anterior temporal; PT = posterior temporal; ROI = region of interest.

TABLE 3
Statistically Significant Differences

Between groups (resting conditions)		Mean difference
LPF	$p < 0.001$*	↑ Schz
RPF	$p < 0.05$*	↑ Schz
LPT	$0.10 > p > 0.05$*	↓ Schz
Within groups		
Interhemispheric (resting conditions)		
PF (Schz)	$p < 0.05$†	↑ LPF
PT (Schz)	$p < 0.05$†	↓ LPT
Resting versus activation (WCST)		
LPF (Ctrl)	$p < 0.02$†	↑ during WCST
RPF (Ctrl)	$p < 0.02$†	↑ during WCST

*Mann-Whitney U-test.

†Wilcoxon test.

LPF = left prefrontal; RPF = right prefrontal; LPT = left posterior temporal; PF = prefrontal; PT = posterior temporal; Schz = schizophrenic patients; Ctrl = controls; ↑ = increased regional cerebral blood flow (rCBF); ↓ = decreased rCBF; WCST = Wisconsin Card Sort Test.

Resting Conditions

The schizophrenic group had significantly higher prefrontal blood flow than the controls. This difference was more pronounced in the left prefrontal region (Mann-Whitney U-test, $p < 0.001$). Schizophrenic patients, however, showed lower posterior temporal, rCBF ratios than did normal controls, although this difference was not found to be statistically significant (Mann-Whitney U test, $p = 0.10–0.05$) (Fig. 2). No significant differences between controls and schizophrenic patients were found in right posterior temporal region or anterior temporal regions.

Furthermore, schizophrenic patients showed significant interhemispheric differences in PI and posterior temporal index values at rest. Higher rCBF ratios in left prefrontal region and lower rCBF ratios in left posterior temporal region were found (Wilcoxon test, $p < 0.05$).

Activation with the WCST

The control group showed significant increases in prefrontal blood flow (Wilcoxon test, $p < 0.02$) (Fig. 3); the

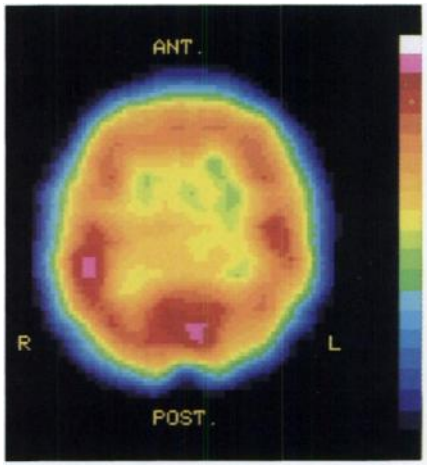

FIGURE 2. Resting rCBF distribution at the level of posterior temporal region (frontocerebellar line +63mm) in a schizophrenic patient. An asymmetry between both posterior temporal regions can be seen, with a relative perfusion impairment on the left side.

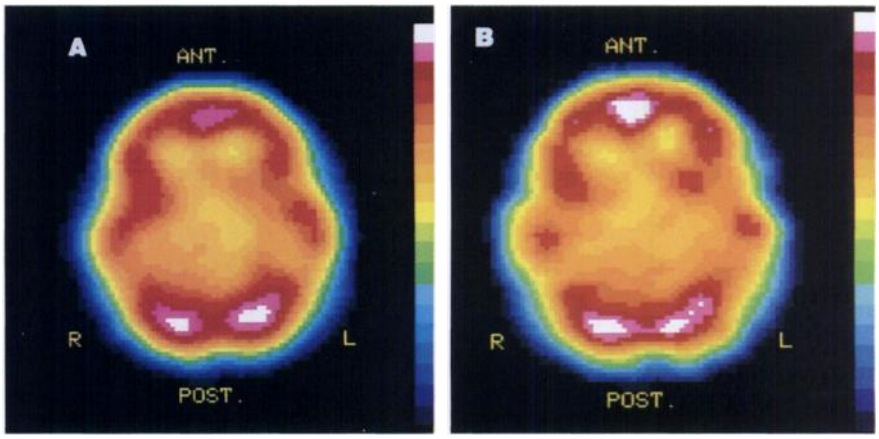

FIGURE 3. HMPAO-SPECT slices at 36 mm above the frontocerebellar line in a representative control subject. (A) Resting scan. (B) WCST activation scan. A substantial increase in prefrontal rCBF (including the anterior cingulate) during the WCST is shown.

prefrontal rCBF in schizophrenic patients did not increase. Thus, schizophrenic patients were unable to activate the prefrontal cortex. In fact, in six schizophrenic patients, the prefrontal rCBF decreased when performing the WCST (Fig. 4). The temporal rCBF was not modified during activation in either controls or schizophrenic patients.

Figure 5 represents, on a bar graph, the mean percent change of the PI for each hemisphere between rest and activation studies in controls and schizophrenic patients. The control group showed a mean percent increase of 2.63% (left) and 2.75% (right), whereas the schizophrenic group had negative values −0.45% (left) and −0.62% (right), thus indicating a decrease in prefrontal rCBF. However, this decrease was not statistically significant.

The WCST performance data from controls and patients are presented in Table 4. All patients completed the test, matching both sets of 64 response cards. Schizophrenic patients performed the WCST poorly compared to controls. Significant differences were found in all variables, except in correct responses and categories achieved.

DISCUSSION

Resting hypofrontality has been the most frequent PET and SPECT pattern reported in schizophrenia. As suggested by several authors, the resting hypofrontality may be caused by the chronicity of illness, with a predominance of negative symptoms and long-term neuroleptic treatment effect and the aging process (*13–15*). In this study, a homogeneous population of neuroleptic-naive young schizophrenic patients with active psychosis was selected in which an increase in prefrontal rCBF (mainly left) was the most frequent pattern observed in resting (baseline) conditions. These results agree with findings from resting-state PET studies that did not find hypofrontality or found resting hyperfrontality in young neuroleptic-naive schizophrenic patients with acute disease (*16–18*). This prefrontally increased blood flow may be explained by the positive symptoms since these patients presented with mainly positive symptoms.

The possibility that SPECT scan-related anxiety could explain the resting hyperfrontality pattern in these patients must be considered. However, this seems unlikely since several studies found that more anxious patients had relatively lower frontal perfusion ratios (*19,20*). In addition, the most striking change was found in the anterior cingulate cortex included in the "prefrontal" ROI (Fig. 1). The anterior cingulate cortex is a limbic brain structure that has been involved in schizophrenia psychosis. It receives a prominent dopamine projection (*21*) that has been implicated in both attentional mechanisms and the emotional

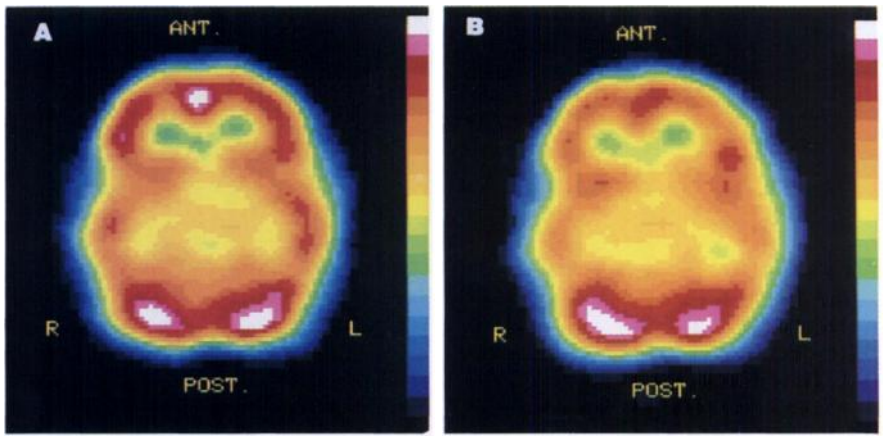

FIGURE 4. HMPAO-SPECT slices at 36 mm above the frontocerebellar line in a representative schizophrenic patient. (A) Resting scan. (B) WCST activation scan. Prefrontal hyperperfusion at rest (including the anterior cingulate) and a decrease in prefrontal flow during the WCST is shown.

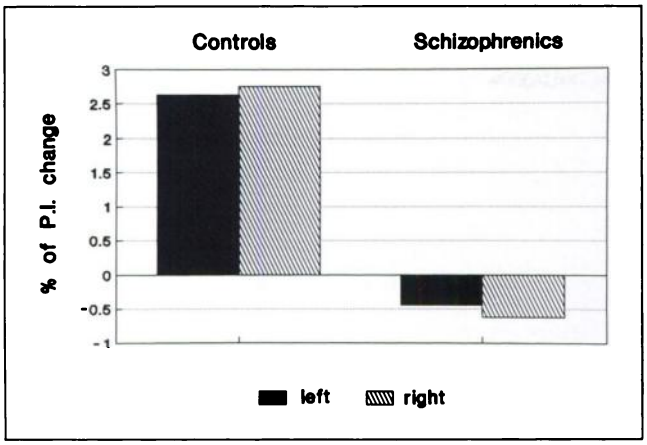

FIGURE 5. Mean percentage of PI change between resting and WCST activation scans in controls and schizophrenic patients.

component of higher cognitive activity (*22*), which seem to be essential features of schizophrenia. Finally, it has extensive connections with many other cortical regions, including the prefrontal cortex (*23*). Some reports found abnormalities in the cingulate cortex cytoarchitecture of schizophrenic patients (*24,25*).

Although no definitive results have yet been found on temporal rCBF abnormalities, schizophrenic hypotemporality was reported in some studies (*8,26,27*). In the current study, a relative impairment in left posterior temporal rCBF was also observed. This finding was consistent with the large body of evidence involving the temporal lobe in the pathogenesis of schizophrenia. Moreover, morphologic abnormalities in the temporal lobe detected by CT scan, MRI and postmortem studies were observed, particularly in the left hemisphere (*28*).

Resting hyperfrontality (mainly left) and the relative left decrease in posterior temporal rCBF described in this study, may be related to the "lateralization defect" hypothesis of schizophrenia reported in several studies and reviewed by Berman and Weinberger (*2*) and Buchsbaum (*29*). This hypothesis states that schizophrenic patients have abnormal left hemispheric function.

Concerning rCBF during cognitive activation with the WCST, schizophrenic patients were unable to activate the prefrontal cortex in response to a frontal stimulus. Moreover, in six of them, a clear reduction in prefrontal blood flow was observed. Thus, these schizophrenic patients showed relative hypofrontality, defined by Andreasen et al. (*4*) as "the inability to increase frontal blood flow in response to a frontal stimulus."

Because schizophrenic patients had significantly impaired results in the WCST performance compared to controls, a possible explanation for their failure to activate prefrontal cortex could be a lack of motivation in the WCST. This seems unlikely since all patients were well engaged in the task, attempting to perform and complete the test with the same number of responses as the controls. However, the possibility that in fact what was being evaluated was a second resting scan, cannot be ruled out. In all cases evaluated in this study, the resting state was evaluated first, followed by the cognitive activation study. As reported by several authors (*4,30*), this approach may confound habituation effects on the scan procedure with task performance. Thus, there is a possibility that the observed rCBF results reflect an order effect rather than a WCST performance effect. In rest-rest studies with ^{133}Xe SPECT in normal subjects, approximately a 2% rCBF reduction in the second measurement was found (Mena I, *personal communication*). On the other hand, Barlett et al. (*31*) determined the test-retest stability of regional cerebral glucose metabolism with PET deoxyglucose in eight schizophrenic patients and 11 normal controls in resting conditions, finding a comparable stability in both groups and concluding that the baseline resting state is an appropriate reference state for schizophrenic subjects in deoxyglucose PET experiments. However, it is important to state that ^{133}Xe and PET rCBF measurements, although more complex than HMPAO-SPECT semiquantifications, are substantially more exact and sensitive. A rCBF decrease of only 2% measured by ^{133}Xe might not be reflected in ^{99m}Tc-HMPAO scans, especially when a single head system is used. Recently, Smith et al. (*32*) reported test-retest variability using HMPAO-SPECT and a high-resolution three-headed camera in five healthy volunteers. Their results suggest that the regional variance is in general agreement with the PET data (*31*) and support the feasibility of this technique for repeated activation studies. One way to get around the order effect is to randomize the order of resting and activation scans.

It should be noted that the majority of rCBF and PET studies of schizophrenic patients examined during a task that activates the frontal cortex have found hypofrontality (*2–4,33–36*). The results reported here also supplement these findings by illustrating that the relative activation deficit in the prefrontal region is present at the onset of the

TABLE 4
Performance Scores on the Wisconsin Card Sort Test*

WCST variables	Controls (n = 8)	Schizophrenic patients (n = 10)	M-W p value
Correct	104.4 ± 16.0	78.7 ± 25.6	NS
Errors	23.6 ± 16.0	48.3 ± 25.7	<0.01
Perseverative responses	16.4 ± 10.5	32.5 ± 29.0	<0.01
Nonperseverative errors	09.5 ± 10.3	19.1 ± 9.1	<0.01
Perseverative errors	14.1 ± 06.3	29.2 ± 27.0	<0.02
Categories	09.1 ± 02.5	04.9 ± 02.8	NS

*All values are means ±s.d.
WCST = Wisconsin Card Sorting Test; M-W = Mann-Whitney U-test; NS = not significant.

illness and occurs before any treatment effects have ensued because these patients had never received neuroleptic medication.

Finally, it appears that the small number of subjects included in this study might limit the generalizability of the results. Furthermore, considering the large number of statistical comparisons made, the possibility of type I errors cannot be excluded. Thus, studies with larger homogeneous samples are needed to obtain definitive conclusions.

CONCLUSION

There is no evidence of resting hypofrontality in young schizophrenic patients with acute disease who have never been exposed to neuroleptics; a pattern of hyperfrontality at rest and hypofrontality only during a prefrontal linked task may coexist. These results contribute to the growing literature supporting a physiologic dysfunction of the prefrontal cortex in schizophrenia by demonstrating that this pattern is present at the onset of the illness and prior to neuroleptic treatment. A significant impairment of left posterior temporal perfusion in schizophrenic patients was observed relative to the right hemisphere. Both left hyperfrontality and left hypotemporality may indicate a brain lateralization defect in schizophrenia. In summary, this study reported evidence for both prefrontal and temporal lobe dysfunction in schizophrenia.

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FIRST IMPRESSIONS

Biliary-Enteric Fistulae

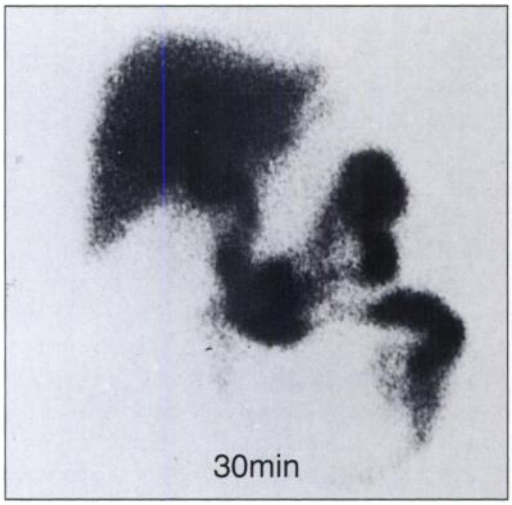

FIGURE 1.

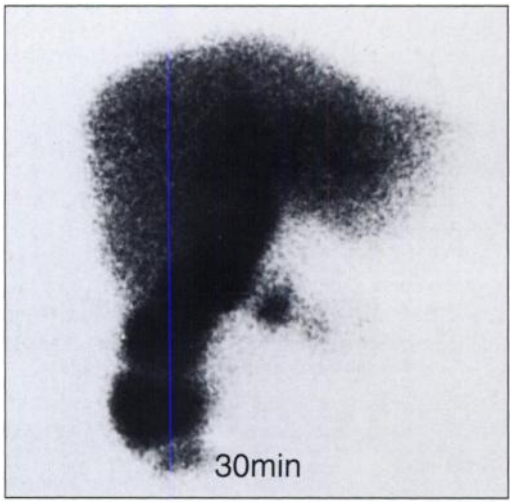

FIGURE 2.

PURPOSE
A 55-yr-old man with acute cholecystitis and cholelithiasis had a cholestectomy and anastomosis of the bile duct to the jejunum. Postsurgical cholescintigraphy showed normal drainage to the small bowel (Fig. 1). Four years later, the patient had abdominal pain, fever and elevated bilirubin; the clinical diagnosis was cholecystitis. Cholescintigraphy showed abnormal drainage of ^{99m}Tc-mebrofenin in the colon without passage through the small bowel (Fig. 2) suggestive of biliary-enteric fistulae.

TRACER
Technetium-99m-mebrofenin, 5 mCi (185 MBq) (Choletec, Mallinckrodt)

ROUTE OF ADMINISTRATION
Intravenous

IMAGING TIME AFTER INJECTION
Thirty minutes

INSTRUMENTATION
General Electric LFOV gamma camera with LEAP collimator

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