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^{18}Fluorodeoxyglucose PET in Schizophrenia

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Abstract. Six chronic schizophrenic patients and six age-matched controls were studied with ^{18}fluorodeoxyglucose (^{18}FDG) positron emission tomography (PET). All patients were scanned when they had been free of medication for at least 2 weeks. Comparisons were made between the groups on regional ratios of cortical ^{18}FDG, with manual and automated measures. Only one of eight regions, the right temporal cortical region, showed a significant group difference, and this effect was not significant when adjustment was made for multiple comparisons. Secondary analyses suggest that ventricular enlargement and age may be associated with a relatively "hypofrontal" pattern of ^{18}FDG.

Key Words. Positron emission tomography, schizophrenia, ventricular enlargement.

As early as 1974, Ingvar and Franzen presented results suggesting that cerebral blood flow was regionally reduced in the frontal lobes of schizophrenic patients (Ingvar and Franzen, 1974; Franzen and Ingvar, 1975). A number of subsequent studies appear to confirm these findings. The method used in cerebral blood flow studies requires intracarotid injection or breathing of xenon-133, and external detection of emitted gamma rays with an array of collimated crystals. The resulting data provide mapping of a two-dimensional projection of the activity distribution with spatial resolution not better than 5 cm. The recent development of computerized tomographic reconstruction techniques has resulted in devices with the capability of accurate quantitative imaging of radiation from planar sections of the human body. In particular, positron emission tomography (PET) uses a circular array of crystal detectors to measure the coincident annihilation gamma rays from positron-emitting isotopes and to reconstruct quantitatively accurate images of planar sections through the body. The presently most widely used PET technique uses deoxyglucose labeled with fluorine^{18} (^{18}FDG), which has a half-life of 110 minutes. This labeled molecule is taken up and metabolized in tissue in a manner analogous to that for glucose, except that after phosphorylation the next step is metabolically blocked, and the fixed regional

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concentration of the isotope provides a relative measure of local glucose metabolism. A method by which the local cerebral metabolic rate for glucose (lCMRglc) may be calculated has been presented by Phelps et al. (1979) and Huang et al. (1980). It requires a measure of the arterial input function and a number of assumptions with regard to rate constants. The concentration of ^{18}FDG in specific brain regions may also be compared to the total brain or cortical uptake without such assumptions, and this provides a valid measure of relative glucose metabolic rate in any chosen brain region for that individual, which can then be compared to other individuals.

Since the development of this technique, two groups have published findings with fluoro-deoxyglucose (FDG) in schizophrenic patients. Farkas and his associates at New York University and the Brookhaven Laboratory (Farkas et al., 1984), and Buchsbaum and associates at the National Institute of Mental Health (Buchsbaum et al., 1982, 1984; De Lisi et al., 1985), have reported relatively lower frontal glucose utilization in schizophrenics compared to controls. In both cases, what is being measured is frontal glucose metabolic rate relative to that in the posterior part of the brain, or relative to the whole slice. Overall glucose metabolic rate does not appear to be different between schizophrenics and controls.

These findings raise a number of questions about the nature of this difference in schizophrenics. First, does the change represent a chronic alteration of brain activity, or does the hypofrontal pattern occur only when psychotic symptoms are present? In previous studies with schizophrenics (except for Buchsbaum et al., 1984), uptake occurred during a resting state. It is possible that the pattern observed is linked to differences in the cognition of the two groups during the rest period, rather than to a non-state-dependent pathophysiological difference. Another question that arises concerns the relationship of changes in cortical glucose utilization to structural brain changes, e.g., do changes in the volume of brain tissue affect the metabolic pattern?

The present study was conducted as an attempt to address some of these questions. The procedure was performed while the patients and controls responded to an auditory vigilance task. The inclusion of the vigilance task in the procedure represents an attempt to control and monitor the cognitive behavior of the subjects. We reasoned that if group differences were observed in cortical glucose utilization in spite of similar performance on the task, such differences might be interpreted as resulting from chronic brain alterations.

Previous studies at the Palo Alto Veterans Administration Medical Center (PAVAMC) suggest that structural abnormalities occur only very rarely in the population of schizophrenics treated at this center (Jernigan et al., 1982). Another question we hoped to address was whether the previously reported metabolic abnormalities were linked to structural abnormalities, and thus might also be relatively rare in our patient population.

Methods

Subjects. Six male chronic schizophrenics, meeting Research Diagnostic Criteria (Spitzer et al., 1978), were recruited from the inpatient research unit of the PAVAMC. (For a clinical description of these patients, see Table 1). Controls were six male volunteers matched for age who were recruited from among hospital employees of two university-affiliated hospitals and from posted advertisements in the medical center. Patients who were being treated with

neuroleptics were withdrawn from medication at least 2 weeks before imaging. Three of the patients were also imaged while on neuroleptic medication: because of the small sample size, however, those data are not presented. During the last week before the imaging date, two warm-up sessions were conducted in which the subjects were reminded of the details of the imaging procedure, and then given several sets of the vigilance task. An attempt was made to simulate the imaging conditions: the subjects reclined with eyes blindfolded as in the subsequent imaging session. After the task, subjects were asked questions about their experience of the task: whether they found it easy or difficult; if their minds wandered; if they were feeling calm, anxious, or bored; and if they were having intrusive thoughts or hallucinations.

Table 1. Clinical data on schizophrenic subjects

Subject No.	Age (years)	Subtype	Age at 1st episode (years)	Age at current episode (years)	Duration of current episode (years)	BPRS score at testing
1	31	Chronic residual	23	23	8	44
2	34	Chronic paranoid	27	27	7	37
3	34	Chronic undifferentiated	24	24	10	45
4	36	Chronic undifferentiated	19	19	17	26
5	41	Chronic undifferentiated	32	32	9	26
6	54	Chronic residual	20	50	4	30

BPRS = Brief Psychiatric Rating Scale (Overall and Gorham, 1962).

Auditory Vigilance Task. The stimuli were tones of 800-ms duration with an interstimulus interval of approximately 2 seconds. The tones were either 400 Hz or 430 Hz, two easily discriminated frequencies. The higher-pitch tones occurred at random intervals and were 25% of the total number of tones. The subjects were asked to press a button whenever the higher-pitch tones occurred. The stimuli were presented via earphones that clipped onto the subjects' ears. They were generated by a microcomputer, and the subjects' responses were collected and the scores computed in real time. A printer produced a continuous log of the presentations and responses for the operator's information, so that the task could easily be monitored during imaging. When communication with the subject necessitated diversion of the subjects' attention from the task, this printed log was marked by the operator and the performance scores were later corrected to exclude the effects of errors made during such interruptions.

Imaging Procedure. On the day the images were taken, subjects were asked not to drink coffee and no medications were given. No meals were taken within 3 hours before the injection. Subjects were transported by car from Palo Alto to the Donner Laboratory in Berkeley. Two i.v. catheters were inserted for blood drawing and injection. A set of marks, originally made to guide positioning of the earlier CT scans, was reconstructed on the subject's face to guide selection of angle and level of the PET images. In this way, we attempted to match the PET images to selected CT sections. The CT sections were taken at angles ranging from approximately 0° to 20° relative to the cantho meatal line. Variability in the angle was due to attempts to avoid irradiation of the cornea. The CT angle was repeated on PET to ensure that structures visualized on CT were always obtained in the small number of planar PET sections available.

The subjects were blindfolded and positioned in the imaging ring. The angle was matched to that of the face marks by adjusting the tilt angle of the ring and superimposing the scanner's light line indicator onto the face marks. The earphones were then attached. The head position was secured by application of a warmed moldable plastic face mask that was attached to pins on the

underside of the head holder. When cool, this mask became rigid and thus form-fitted to the subject's face, reducing head mobility.

The Donner 280-crystal dynamic positron tomograph uses a fixed array of bismuth germanate crystals with a 50 cm patient port (Derenzo et al., 1983). Data acquisition, reconstruction, image display, and kinetic analysis are performed with a PDP 11/44 computer. The resolution is 8 mm full width-half maximum and 1 cm axially. The level of the tomographic image plane is set by manual or computer-controlled bed movement to preestablished positions monitored by a digital positron counter.

The ^{18}FDG was produced at Crocker Nuclear Laboratory at the University of California at Davis. The target and synthesis cave were developed by Dr. Chester Mathis at Donner Laboratory.

Thirty to forty-five minutes before injection, several transmission images, lasting 10 minutes each, were made at the selected levels. These images are made with an external hoop source of 68-Gallium and provide information about the distribution of attenuating material (e.g., skull bone) within the section. They are used for attenuation correction of the emission data later obtained at the same levels. The transmission images also aided in locating the best sections for subsequent imaging because the shape of the skull could be compared to that in the CT sections. While the transmission images were being taken, a warming pad was applied to the hand and forearm from which "arterialized" blood samples were drawn.

Five minutes before injection, the vigilance task was begun. At injection, a dose ranging from 3 to 11 mCi of ^{18}FDG was administered. Blood samples were drawn from the warmed hand, initially at 5-second intervals and then at progressively longer intervals, until 40 minutes after injection. Emission data were collected at similar intervals during the uptake period. For the present study, three or four postuptake emission images were obtained, each representing 5 minutes of data and the first beginning at 40 minutes after injection. They were contiguous, but not overlapping, axial sections, approximately 1 cm thick. These images were corrected for attenuation using the earlier transmission image data. The data were later transferred to another image-processing system for automated regional analysis.

After the imaging session subjects were again asked questions about their cognitive and affective state during the session.

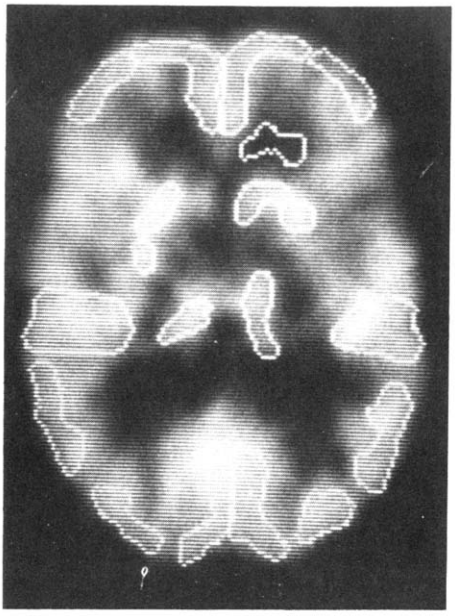
Image Selection and Analysis. Because of a within-study revision of the procedure for selection of image levels, only one level was available in all 12 subjects. This is the level at which thalamus and striatum are visualized.

The "raw" values were converted to regional ratios as described below. Analysis of the glucose metabolic rates will be reported elsewhere.

The measurement of relative regional ^{18}FDG distribution was attempted by three separate techniques: two manual techniques, and one semiautomated technique. The rationale for using these techniques is as follows: the automated technique was an attempt to maximize the objectivity and reproducibility of the measures, and to provide specifically defined regions for those cases in which the cortical rim might be hypoactive, and thus visually difficult to define reliably. These advantages were considered likely, however, to be gained at the expense of increased sensitivity possible with manual measures.

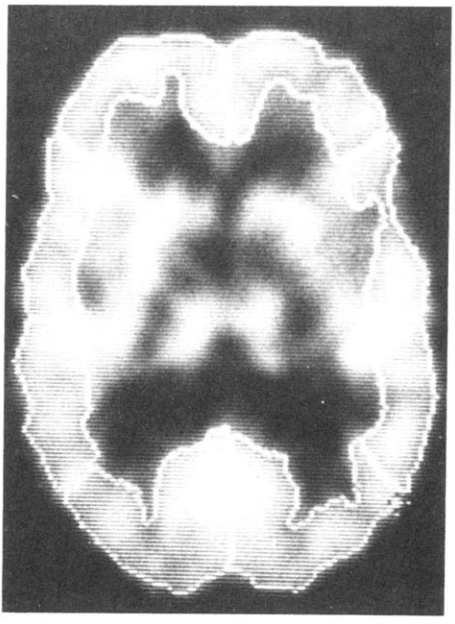
The two manual techniques both involved using a cursor to draw an irregularly-shaped region of interest around visually identified cortical areas at the display console. The first manual technique involved taking the values of small cortical regions in superior frontal, middle frontal, superior temporal, middle temporal, inferior temporal, and occipital lobes. This technique will be referred to as the "manual regions" technique. In the second manual technique, a line through the structural midline was drawn manually on a plastic overlay, followed by a line perpendicular to this line at its midpoint. Two additional lines drawn at 45° through the midpoint divided each hemisphere into quadrants. The cursor was then used to draw contiguous regions visually chosen to include the cortex within each quadrant. This technique is called "manual quadrants." The manual methods are illustrated in Figs. 1 and 2. All manual measurements were made without knowledge of subject identity.

Fig. 1. Illustration of representative section with "manual regions" drawn on the console



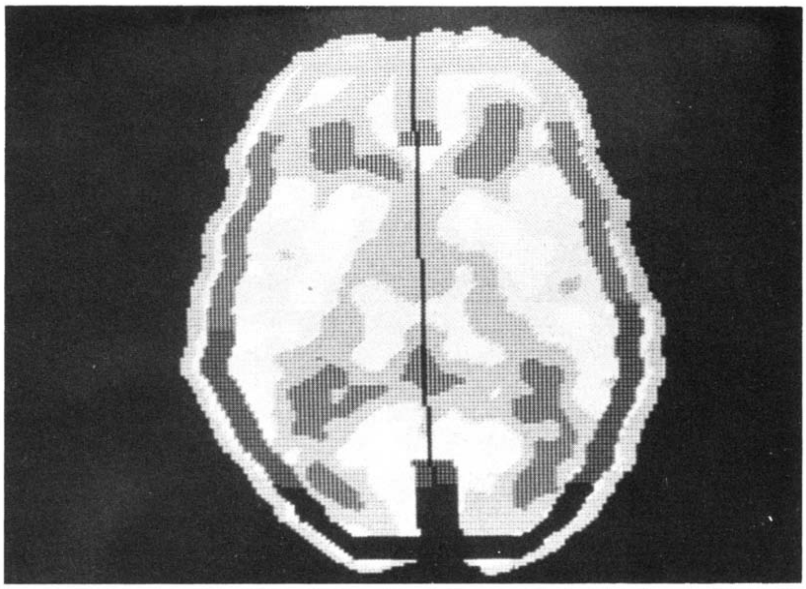
Although deep subcortical samples were also taken (as illustrated), partial voluming noise was so severe that the analysis of these samples was dropped.

Fig. 2. Illustration of representative section with "manual quadrants" drawn on the console



The semi-automated technique involved defining the cortical zones by computer. The edge of the brain was defined as the first pixel value exceeding 40% of the highest value in the image. Pixel values were events per volume element. Brighter areas reflect the detection of more events: darker areas, fewer events. Several points on the structural midline were manually identified and input to the program. The computer then stripped off the outer 1/6th of the total area of each hemisphere. This area was discarded because of partial voluming at the outer edge of the brain. The next 1/6th of the area of the hemisphere was defined as the cortical zone. The most anterior 1/4th of this strip is called the prefrontal zone; the next quarter, the presylvian zone; the third, the temporal zone; and the most posterior, the occipital zone. The zones are illustrated in Fig. 3.

Fig. 3. Representative section displayed on the image-processing console, with automated cortical zones designated on the image



For each of the techniques described above, the raw values (in average events per pixel) were converted to ratios in the following way: all delineated regions within a hemisphere were averaged, and this value served as the denominator for a ratio with the sample value as numerator. Thus, for the automated technique, for example, the right prefrontal ratio is the average events per pixel for the right prefrontal zone expressed as a ratio with the average events per pixel for the total right cortical strip. Similarly, for the manual regions method, the right occipital ratio is the events per pixel in the occipital region divided by the average events per pixel for all right-hemisphere cortical regions.

Measures of ventricular size were made from the CT scans of all 12 subjects by subjective ranking of the scans. This ranking was done without knowledge of the subjects' group membership. In previous studies (Jernigan et al., 1982), we have shown that visual ranking is highly correlated with volumetric and planimetric ventricular measures.

Results

Descriptive statistics characterizing the two groups are provided in Table 2. The groups did not differ by age or ^{18}FDG dose received, nor did their baseline vigilance

performance differ. All subjects in both groups, with one exception, performed almost perfectly on the vigilance task. Scores ranged from 96% to 100% correct in these subjects. One schizophrenic patients who was fully cooperative nevertheless per-

Table 2. Sample characteristics

	Schizophrenics ($n = 6$)			Controls ($n = 6$)		
	Minimum	Mean	Maximum	Minimum	Mean	Maximum
Age (years)	31	38	54	33	42	56
Dose (mCi)	3.1	5.8	8.0	4.7	7.6	11.7
Vigilance (% correct)	77	96	100	99	99.9	100

formed below 80% on the task. The reason he gave for his difficulties was intrusive delusional thought content; and, in fact, he was tested on two occasions while on medication and his performance was much better.

The results of the major analyses are presented in Table 3. No group difference was

Table 3. Group means (standard deviations)

	Automated		Manual quadrants		Manual measures		
	S[1]	NC[1]	S[1]	NC[1]	Regions	S[1]	NC[1]
Right hemisphere							
Prefrontal	0.98	1.03	1.00	1.01	Prefrontal	0.99	1.03
	(0.056)	(0.065)	(0.027)	(0.045)		(0.066)	(0.071)
Presylvian	1.03	1.04	0.99	1.00	Perirolandic	1.05	1.02
	(0.047)	(0.045)	(0.039)	(0.036)		(0.023)	(0.054)
Temporal	1.04	1.00[2]	1.04	1.01[2]	Motor strip	1.05	1.02
	(0.032)	(0.040)	(0.022)	(0.007)		(0.059)	(0.028)
Occipital	0.95	0.94	0.97	0.98	Anterior temporal	1.00	0.97
	(0.049)	(0.059)	(0.045)	(0.051)		(0.043)	(0.024)
					Posterior temporal	0.93	0.93
						(0.041)	(0.040)
					Occipital	0.98	1.03
						(0.056)	(0.071)
Left hemisphere							
Prefrontal	1.00	1.01	1.00	1.00	Prefrontal	1.01	1.00
	(0.057)	(0.038)	(0.038)	(0.032)		(0.074)	(0.041)
Presylvian	1.03	1.05	1.00	1.02	Perirolandic	1.03	1.03
	(0.036)	(0.055)	(0.046)	(0.039)		(0.060)	(0.084)
Temporal	1.04	1.02	1.01	1.01	Motor strip	1.01	1.01
	(0.032)	(0.045)	(0.033)	(0.023)		(0.105)	(0.057)
Occipital	0.93	0.92	0.99	0.97	Anterior temporal	1.03	0.99
	(0.035)	(0.050)	(0.044)	(0.060)		(0.076)	(0.036)
					Posterior temporal	0.90	0.94
						(0.066)	(0.066)
					Occipital	1.02	1.03
						(0.074)	(0.041)

1. S = schizophrenic; NC = normal control.
2. $p < 0.05$, one-tailed, Mann-Whitney U test.

observed in the frontal ratio measures with any measurement technique. Nor did any other method of forming ratios of frontal with more posterior areas yield a significant group difference.

With both the automated and the manual quadrants methods, there was a small group difference in the right temporal area, with schizophrenics showing somewhat higher ratios than controls.

On these major analyses, the three measurement techniques are in essential agreement. Since the manual quadrants method and the automated method sample roughly comparable anatomical areas, the correlations of corresponding measures from these two techniques are given in Table 4. Except for the left temporal area, all

Table 4. Correlations of manual quadrants and automated measures

	Pearson *r*'s	
	Right hemisphere	**Left hemisphere**
Prefrontal	0.76[1]	0.84[2]
Presylvian	0.84[2]	0.77[1]
Temporal	0.56[3]	0.04
Occipital	0.79[2]	0.81[2]

1. $p < 0.01$, 1-tailed.
2. $p < 0.001$, 1-tailed.
3. $p < 0.05$, 1-tailed.

measures show high correlations. In Table 5, the automated cortical ratios are presented for each subject in the study to facilitate comparison with results from other studies. For simplicity, secondary analyses are presented using the automated measures only.

Secondary Analyses. For the secondary analyses, all subjects are combined to examine the effects of other variables on the cortical ratios. These analyses are primarily exploratory and are designed to lead to hypotheses about sources of variation in the pattern of glucose utilization over the cortex. Correlation coefficients are used to assess relationships between potential mediating variables and the ratios. It should be noted that the meaning of statistical significance is greatly altered in this context, and no inferences may legitimately be drawn from such post hoc statistical analyses. They are included because suggestive results from these analyses may alert other investigators to potentially confounding factors that could affect future studies. Due to the great expense involved in clinical PET studies, it is very important that information relevant to methodology be described, even if it is tentative.

The correlations of age with the various cortical ratios are presented in Fig. 4. The pattern is produced because the older subjects had relatively higher occipital ratios. To illustrate the scatter of these points, they are plotted for the combined occipital ratios (right and left averaged) in Fig. 5.

The correlations of CT ventricular rank with the PET ratios are presented in Fig. 6. Again, there is evidence for a shift in ^{18}FDG cortical pattern with increasing ventricular size, with relatively lower frontal ratios occurring in association with larger ventricles. The values for the combined frontal ratios are plotted against ventricular rank in Fig. 7.

Table 5. Automated cortical ratios[1]

	Schizophrenics			Controls		
Region	Subject No.	Right	Left	Subject No.	Right	Left
Prefrontal	1	1.070	1.080	7	1.025	1.017
	2	0.974	1.023	8	0.994	1.009
	3	1.012	1.019	9	1.099	1.066
	4	0.912	0.912	10	1.110	1.016
	5	0.938	0.963	11	0.964	0.949
	6	0.977	0.992	12	0.963	0.996
Presylvian	1	1.024	1.051	7	1.012	1.014
	2	1.114	1.059	8	1.096	1.083
	3	0.991	0.996	9	1.097	1.081
	4	1.028	1.060	10	1.024	1.112
	5	0.979	1.025	11	0.997	0.968
	6	1.024	1.024	12	1.008	1.044
Temporal	1	0.995	0.988	7	1.013	1.030
	2	1.026	1.023	8	0.982	1.034
	3	1.048	1.065	9	0.970	0.986
	4	1.079	1.060	10	0.947	0.950
	5	1.068	1.073	11	1.052	1.079
	6	1.014	1.036	12	1.031	1.027
Occipital	1	0.911	0.881	7	0.951	0.931
	2	0.886	0.895	8	0.928	0.873
	3	0.949	0.950	9	0.834	0.867
	4	0.982	0.969	10	0.918	0.912
	5	1.015	0.939	11	0.987	1.004
	6	0.985	0.948	12	0.998	0.934

1. Subjects in both groups arranged in ascending order by age.

Fig. 4. Illustration of pattern of correlation of age with automated cortical ratios (*$p < 0.05$)

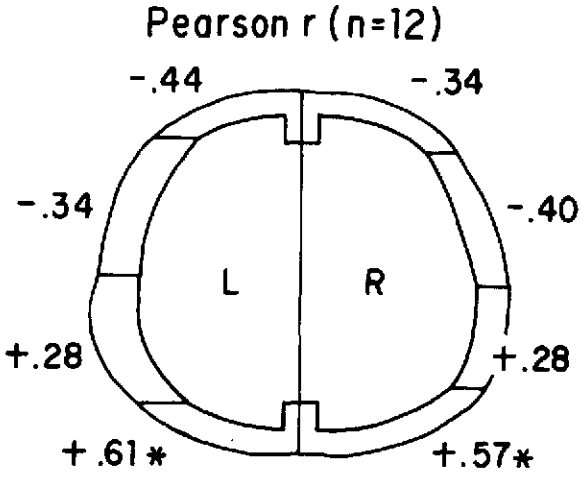


Fig. 5. Scattergram of bilateral occipital cortical ratio with age

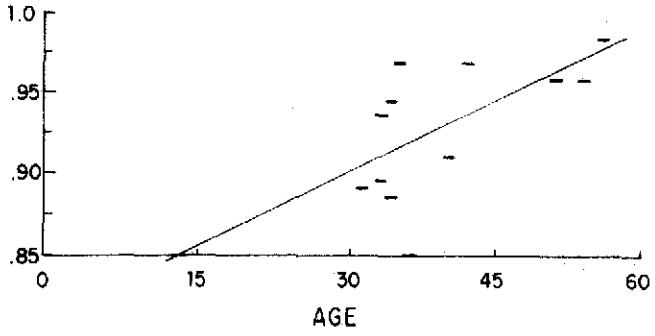


Fig. 6. Illustration of pattern of correlation of ventricular size with automated cortical ratios (*$p < 0.05$)

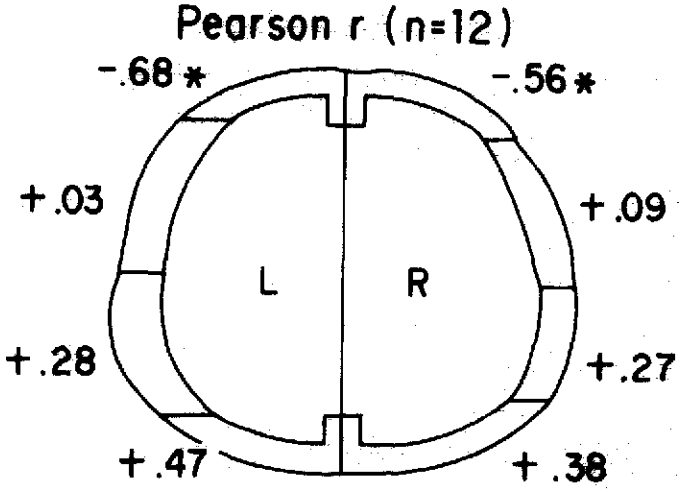
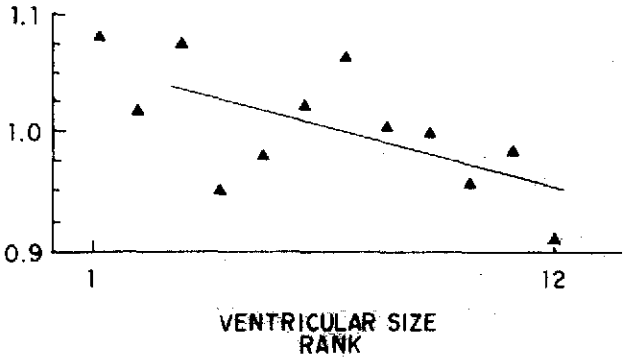


Fig. 7. Scattergram of bilateral frontal cortical ratio with ventricular size



Discussion

The major analyses of the cortical ratios yield only very weak evidence for a group difference. The effect observed in the temporal area is not significant when alpha is adjusted for the number of tests performed. As a test of the "hypofrontality" hypothesis, however, this study does not have high power, since only six subjects were examined from each group. For example, for a 1.7 Z effect size as reported by Buchsbaum et al. (1982), a two-tailed *t* test in a study with *n* of 10 would have power of only approximately 0.68 (Rothpearl et al., 1981). It should also be noted that only one axial brain level was examined. It is possible that the effect is present at some other level. Thus, the results may not be interpreted as disconfirmatory.

The secondary analyses, as explained above, must be interpreted with great caution. We present them because they raise the possibility that the findings of others may have been influenced by factors not systematically reported in those studies. The present study is not the first in which "hypofrontality" on PET has been associated with age. Kuhl et al. (1982) reported that cerebral glucose utilization declined with age in a group of 40 normal volunteer subjects from 18 to 78 years old. They also noted that the ratio of superior frontal to superior parietal cortex declined with age in these subjects. Duara et al. (1983) also examined the relationship of glucose metabolic rate to age using PET. They did not find age effects, but a smaller group ($n = 21$) was examined and no ratios of frontal values to posterior values were included. De Leon et al. (1984) examined the relationship of age to regional measures of glucose utilization and found none, but the regions were smaller and included more white matter than the ones in the present study. This group also examined the relationship of structural changes on CT with the PET measures and found no relationship. DeLisi et al. (1985) found no significant association of cerebral atrophy with hypofrontality on PET, but the correlation of ventricular size with frontal ratios was not reported.

The possible effects of age on cortical glucose utilization are unlikely to have mediated the effects in earlier studies of schizophrenia, since age was controlled. However, if older subjects are more "hypofrontal" than younger subjects, this effect must be carefully considered in subsequent investigations.

The possibility that ventricular enlargement may be associated with a hypofrontal, or hyperoccipital, pattern raises the possibility that only those patients with structural changes show the abnormality. If so, the prevalence of this hypofrontal "marker" may, like the prevalence of the structural "markers," be much lower than early studies suggest. If this association exists, it may be because fluid is actually present in the sampled region (partially volumed) and thus the measured activity is lowered. To produce a regional finding, it is necessary that more fluid be inadvertently included in the frontal than the posterior measures. Alternatively, it may be that the brain changes that result in ventricular enlargement also result in a diminution in frontal cortical activity relative to that in other cortical regions.

Our initial attempts to accomplish automated regional delineation of local brain activity are encouraging. These measures showed quite good agreement with the manual measures. The high correlations between the manual and the automated quadrant measures set conservative limits for the reliability of both methods, and in most cases these are suprisingly high. It should be noted, however, that the automated

method described here is likely to be more vulnerable to partial voluming effects, and may in some cases be less sensitive than manual measures. On the other hand, in some cases, especially when brain regions show reduced activity, the manual selection of a region is very difficult. Furthermore, even when manual measures are made without knowledge of group or clinical variables, they are not done without knowledge of other aspects of the images. Therefore, if frontal areas are visibly hypoactive, for example, it is impossible to select posterior samples without knowledge of this fact. In some multivariate designs, this problem can vitiate the scientific validity of the results.

Our conclusions are that the presence of "hypofrontality," like that of other potential markers, is variable within the schizophrenic population, and that possibly a variety of other conditions lead to similar alterations in regional ^{18}FDG distribution, as was suggested by Buchsbaum et al. (1984). The acquisition and interpretation of these dynamic brain images is obviously an exceedingly complex process. Careful measurement or manipulation of many factors is required if the results are to yield theoretically interesting information.

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