

Regional Brain Glucose Metabolism in Chronic Schizophrenia

A Positron Emission Transaxial Tomographic Study

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• Thirteen diagnosed schizophrenics and 11 normal controls were studied with a method using the PETT III positron emission tomograph (PET) and fluorodeoxyglucose labeled with fluorine 18. Each subject also had a computed tomographic (CT) scan. For each subject, two brain levels, one through the basal ganglia and one through the semioval center, were analyzed for the mean regional metabolic glucose rate. Specifically, relationships between frontal and posterior regions were evaluated. The CT scans of matching levels were superimposed on the functional PET images to provide anatomic criteria for region of interest selection. While no whole-slice metabolic differences were apparent between groups, schizophrenics had significantly lower activity in the frontal lobes, relative to posterior regions. The medicated and drug-free groups did not differ from one another in these regards. Trait v state dependency of the phenomenon was analyzed, and several technological limitations were considered.

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The method of using fluorodeoxyglucose (FDG) labeled with fluorine 18^{1,3} and positron emission transaxial tomography (PETT)⁴⁻⁶ has been applied to the study of characterization of psychiatric disorders. We evaluated results for the first 13 experimental subjects undergoing these procedures and compared them with those of a normative data base of 11 subjects generated using the same experimental methods. Preliminary findings of decreased metabolic activity in the frontal lobes in a schizophrenic

patient⁷⁻⁹ are elaborated on in this more extensive study. A recent assessment of relative counts collected between geometrically defined regions following FDG ¹⁸F injection suggested a similar pattern in a sample of eight schizophrenic subjects.¹⁰ The frontal lobes have been shown previously to have decreased perfusion, using the xenon 133-intra-carotid method for regional cerebral blood flow (rCBF)¹¹ in a similar psychiatric population.^{12,13} While our patients all met behavioral inclusion criteria for "schizophrenic disorder" classification, we do not wish to imply that the disorder constitutes a single disease entity. The data reported here should be viewed as being associated with a particular symptom cluster.

There is a large body of experimental data that suggests a close link between regional oxygen use and glucose metabolism in the normal brain.¹⁴ Most of this information has been obtained by the Kety-Schmidt flow technique,^{15,16} which gives a global value for substrate uses. In contrast, PETT is sensitive to small, focal changes in metabolic rates, providing regional information. Several laboratories have used the FDG ¹⁸F method to examine the functional anatomy of the human brain.^{17,18} and sensorimotor systems,¹⁹⁻²⁵ and to evaluate specific neuropathologic states.²⁶⁻²⁹ These studies have been recently reviewed.³⁰

Our approach was predicated on the observation that in the normal brain, function is associated with anatomic organization,³¹⁻³⁵ and on the concept that abnormal behavior and mentation are associated with alterations in cerebral activity that may not be associated with gross anatomic changes.³⁶ This study extends our original findings of altered regional glucose metabolism in schizophrenic patients to a larger population. It also addresses the question of whether a metabolic pattern characteristic of schizophrenia can be detected in a sample of patients with chronic schizophrenia under conditions of minimal stimulation, when compared with "normal" subjects.

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SUBJECTS AND METHODS

Subjects

The experimental sample consisted of 16 volunteer male patients (median age, 26 years; range, 21 to 54 years), all ambulatory, who were capable of giving their informed consent for the study according to the guidelines for research involving human subjects set up by New York University Medical Center, New York, and Brookhaven National Laboratory, Upton, NY. Sixteen patients were part of a series meeting the criteria. Three of them were omitted because of experimental and technical problems in recording the metabolic data. All prospective patients were clinically examined by two psychiatrists, and a consensus diagnosis was obtained based on the Research Diagnostic Criteria³⁷ for schizophrenic disorders. All patients with significant nonpsychiatric medical illness and/or frank neurologic disease were excluded, as were those who showed any evidence of drug or alcohol abuse by history or clinical examination. Each subject was determined to be drug free, except for prescribed doses of psychotropic medication. Six of the final sample of 13 schizophrenics were being treated with neuroleptics. Results of routine clinical laboratory workups were all within normal limits.

The psychopathologic features of this patient population was documented by the Combined Instrument Schedule.³⁸ This is a combination of three already existing semistructured interviews: the Present State Examination,³⁹ Combined Mental State Schedule,⁴⁰ and Schedule for Affective Disorders and Schizophrenia.⁴¹ The Combined Instrument Schedule has been extensively used and validated.³⁸ In addition, a series of contiguous noncontrast computed tomographic (CT) section scans were taken on a scanner (General Electric Co, Model 8800) at 10-mm intervals and at an angle of 0° from the canthomeatal reference line to correspond with the angle of the PETT scans. All patients participating in the study showed normal CT scans by clinical criteria, although this was not a requirement for inclusion in the study.

Eleven normal male volunteers (median age, 24 years; range, 23 to 50 years), who gave their informed consent to the study, served as the control group. They were part of 13 consecutive normal volunteers, two of whom had to be omitted for technical reasons. All met the criteria of absence of past psychiatric history and current psychiatric symptoms, such as mood and thought disturbances, perceptual and cognitive dysfunction, and excessive anxiety and hostility, as determined by the Structured Clinical Interview.⁴² The control subjects also were required to have normal EEGs using the 10-20 system and to have no abnormalities shown by general physical and neurologic examinations. Laboratory workup results, significant medical history, and history of drug and alcohol abuse were all normal. In addition, all controls performed within normal limits on each subtest of the Wechsler Adult Intelligence Scale,⁴³ as well as on Bender's Visual Motor Gestalt Test⁴⁴ and the Memory Test of Randt et al.⁴⁵ The age distribution of the schizophrenic and normal volunteer populations were similar.

Scanning

All subjects were admitted to the Medical Research Facility of the Brookhaven National Laboratory on the morning of the experimental procedure and allowed to rest in a private hospital room for at least one half hour before undergoing scanning. No caloric intake or ingestion of beverages containing caffeine was permitted for two hours before a PETT study. Patients who underwent scans later in the afternoon were given a light lunch up to two hours before the experiment.

Fluorodeoxyglucose tagged with ¹⁸F,⁴⁶⁻⁴⁸ ordinarily 25 mCi, was delivered to the scanning area from the cyclotron just prior to the PETT scan. This amount was adequate for two studies, allowing about two hours for each study. The specific activity of the compound was usually 3,600 mCi/mmol; typical subject doses were 5 to 10 mCi and were sterile and pyrogen free. Radiochemical purity was determined to be greater than 98% by thin-layer chromatography (TLC).

Prior to each study, the subject was familiarized with the environment of the scanning room and placed in a comfortable, supine position on a padded scanning bed. To elicit maximum

cooperation during the scan, all subjects were acquainted in some detail with the nature of the procedure, effects of head movement, and importance of compliance with respect to eye closure and the need to be awake during the tracer-uptake period. Allen's test was performed on each subject to ensure the presence of adequate collateral arterial circulation.

While the subject was lying on the scanning bed but before head positioning, a short intra-arterial cannula was inserted into the radial or ulnar artery at the wrist for the purpose of collecting blood samples during the study. The dose of tracer to be injected was drawn, and three baseline blood samples (2 mL each) were taken, one each for glucose, blood gases, and plasma. The subject was instructed to close his eyes and remain still. A bolus of tracer was then injected via a venous catheter into the arm contralateral to that used for drawing blood samples; the subject was aware of the time of injection. Subsequent to the uptake period, the patient was allowed to open his eyes. A small aliquot of the injected dose was taken from the syringe after injection and was counted in a calibrated sodium iodide well counter to determine accurately the activity of the injected compound.

During the 30-minute tracer-uptake period following injection, the subject was not spoken to unless necessary and was not touched. A constant, monotonous low-level noise from the computer and air conditioning fan to the right of the subject presented the major source of auditory stimulation. Blood samples for counting, 2 mL each, were taken, starting 15 s after injection and thereafter, every 15 s for the first minute, then at 1.5, 2, 3, 4, 6, 8, 10, 15, 20, 25, and 30 minutes and at 15-minute intervals until scanning was completed. An average of 20 samples were taken. They were kept on ice and centrifuged within ten minutes after being drawn, and 0.4-mL samples of plasma were counted in a calibrated sodium iodide well-scintillation counter at known times after injection. At 30 and 60 minutes and at the end of scanning, additional blood samples were taken for blood glucose determination. A heparinized catheter was used throughout the procedure to prevent coagulation of blood samples and clogging of catheters.

The subject's head was positioned in the aperture of the scanner, parallel to the canthomeatal reference line with careful alignment, using lateral and sagittal laser beams. The scanning procedure started 30 minutes after injection of the tracer.

The PETT III tomograph, a single-slice tomograph used in this study has been described in detail in the literature in terms of its capacity to provide analytic tissue measurements.⁴⁹ The spatial resolution of the tomograph operated in a medium-resolution mode is 1.8 cm in the plane of section and 2.2 cm in the axial direction. A minimum of 10⁶ total coincidence counts per scan were collected. Scan times were usually in the range of eight to 14 minutes, with ten minutes being the normal time. A complete study lasted approximately 1.5 hours. Calculations of metabolic rate were based on data collected no later than 60 minutes after injection. An effort was made to obtain a maximum number of contiguous scans at 10-mm intervals on the Z axis. Glucose metabolic rates were computed, as previously described.^{1,50} (Details of the computation methods used are available from A.P.W.)

For our study, two planes of section of the functional images were selected for analysis. The scan of the basal ganglia, in which the thalamus, head of the caudate nucleus, and frontal and occipital horns of the lateral ventricles are anatomically situated, was generally found at 40 or 50 mm above the canthomeatal zero line. The second scan was above the level of the bodies of the lateral ventricle, an area referred to as the semioval center. This level was characterized by two large areas of low activity separated partially or completely by a band of high activity, presumably the medial gray matter and a small portion of the cingulate gyrus.⁵⁰ This plane of section was generally found at 60 or 70 mm above the canthomeatal zero line.

The cortical mantle of the frontal lobes has a varied topological pattern that is probably related to functional heterogeneity.⁵¹ Although it would have been desirable to quantify the rate of glucose use in these respective areas, this could not be done reliably because of constraints in spatial resolution. This problem was compounded by uncertainties about the anatomic boundaries, position, and shape of these areas and about the partial-volume averaging effects^{52,53} of the gray matter structures in the selected plane of section.

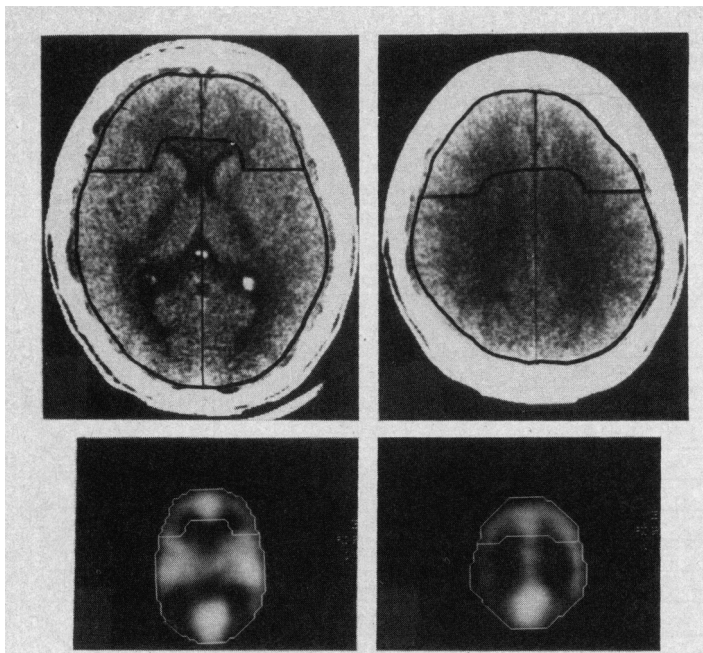


Fig 1.—Regions of interest outlined on computed tomographs, based on anatomic criteria previously described, at levels of basal ganglia (top left) and semioval center (top right) were transferred to corresponding functional positron emission transaxial tomographic (PETT) images (bottom). Mean metabolic rate was then computed from PETT images for frontal and posterior reference regions.

Table 1.—Comparison of Mean Metabolic Rates

Area Scanned	Subject	Rate, Mean \pm SD, mg Glucose/ 100 g Tissue/min	t(22)
Basal ganglia	Controls (n = 11)	3.57 \pm 0.50	1.02 (NS)
	Schizophrenics (n = 13)	3.27 \pm 0.86	
Semioval center	Controls (n = 11)	3.35 \pm 0.49	1.2 (NS)
	Schizophrenics (n = 13)	3.01 \pm 0.82	

Due to these difficulties, the region of interest (ROI) evaluated in this study consisted of the entire frontal region. Such a large ROI minimized the partial-volume effects in quantification. Separation of metabolic values for gray and white matter was not attempted with the PETT images; therefore, reported values represent a mixture of these anatomic regions weighted considerably toward the average metabolic values for white matter reported in the literature.⁶⁴ These quantified values are valid for a comparative study, such as ours, since patients and control subjects were compared using the same regional selection criteria. The CT scan that best corresponded to the selected PETT image was used to determine the ROI based on visual discernment of reliable landmarks, such as lateral ventricles and occipital lobe and medial gray matter structures.

Ellipse-corrected PETT scans were matched indirectly to CT scans of the same size, (inner table to inner table) anterior to posterior and left to right, within a three-pixel (approximately 1.2-cm) margin of error. Quantitative overlays of the PETT scan were then aligned with the CT image, prior to drawing ROIs. Regions of interest were defined as follows (Fig 1). On the scan of basal ganglia, the frontal lobe was defined posteriorly by a line bisecting the head of the caudate nucleus and perpendicular to the interhemispheric fissure. The ROI studied coursed anteriorly to avoid basal ganglia and the anterior horns of the lateral ventricles by approximately 1 to 2 cm on the CT scan. On the scan of the semioval center, the posterior border of the frontal lobe was defined by the central sulcus and bypassed the ventricle anteriorly.

Table 2.—Regional Metabolic Rates in Normal Controls

Subject/ Age, yr*	Rate, mg Glucose/100 g Tissue/min			
	Basal Ganglia		Semioval Center	
	Frontal	Posterior	Frontal	Posterior
1/26	3.24	3.02	3.25	2.98
2/23	3.88	3.55	4.13	3.82
3/23	3.05	3.08	3.69	3.06
4/23	3.00	3.05	2.83	2.63
5/34	3.31	3.14	3.19	2.70
6/23	4.15	3.62	4.09	3.46
7/32	3.29	3.21	3.38	2.79
8/24	4.34	3.68	4.14	4.12
9/50	3.99	4.18	3.63	3.28
10/24	3.96	3.84	3.76	3.15
11/24	4.78	4.49	4.67	3.87
Mean \pm SD	3.73 \pm 0.58	3.53 \pm 0.49	3.71 \pm 0.53	3.26 \pm 0.50

*The median age was 24 years, and the range, 23 to 50 years.

The brain-bone interface was avoided by moving in one PETT pixel for all regions.

In view of the differences in thickness of the CT and PETT scans, the influence of the underlying ventricle in the axial direction was considered when viewing CT scans and defining ROIs. The posterior region, used for reference purposes in data analyses, was defined for both levels as the entire area in the skull not included in the frontal region. In our statistical analysis, the reference region was treated as the covariate, and the differences between frontal regions were evaluated by covariant analysis. This approach was required because the correlation between frontal and posterior regions was significant at both levels of the brain. It also avoided the necessity of assuming the existence of simple ratio relationships between regions.

The observed intersubject variability in the size of ROIs was due, in part, to differences in head size and the method of aligning PETT and CT scans. As to the sensitivity of the method, no relationship was found between the metabolic rate and size of the ROI.

RESULTS

Comparison of the mean metabolic rates of the whole plane of section between normal controls and schizophrenics showed no significant difference in glucose consumption on either level studied (basal ganglia scan, $t(22)=1.02$; semioval center scan, $t(22)=1.20$) (Table 1). While no differences were found between the two groups in whole-slice metabolic rates, regional differences were detected, suggesting an alteration in cerebral distribution of function in schizophrenics under our study conditions.

For computation of the local cerebral glucose metabolic rate (LCMRG) in the frontal lobes, the measured activity of the frontal region was compared with that of the posterior section (remainder of the brain slice) in a tomographic functional image of each brain (Tables 2 and 3). Comparison of average metabolic activity between the normal subjects and schizophrenics showed no significant mean difference for the posterior reference regions of the brain at the level of basal ganglia ($t(22)=1.74$) and the semioval center ($t(22)=1.20$). However, significant correlations were found between the metabolic activity of the frontal and posterior reference regions at both levels studied for controls and schizophrenics ($r \geq 0.9$ in each case with nine and eleven subjects, respectively; $P < .01$). These metabolic relationships, calculated by the method of least squares, are shown in Figs 2 through 5.

Examination of the figures indicates that the linear metabolic relationship between frontal and posterior regions for controls was similar to that for schizophrenics. The difference in frontal region activity between the two groups is more easily seen on the composite graphs shown in Figs 6 and 7. These composites make it clear that the line representing the metabolic activity relationship

Table 3.—Regional Metabolic Rates in Schizophrenics

Patient/ Age, yr*	Medication	Rate, mg Glucose/100 g Tissue/min			
		Basal Ganglia		Semi-oval Center	
		Frontal	Posterior	Frontal	Posterior
1/35†	Yes	2.62	3.05	2.55	2.49
2/25	Yes	3.77	4.06	3.34	2.96
3/21‡	No	2.87	3.13	2.67	2.63
4/54	Yes	2.75	3.47	2.60	2.72
5/25	No	4.68	4.42	4.58	4.02
6/23	No	3.39	3.50	3.40	3.13
7/40	Yes	2.04	2.41	2.24	2.11
8/32	No	2.21	2.21	2.19	2.02
9/26	Yes	3.20	2.95	3.43	2.97
10/25	No	1.88	2.00	2.22	1.77
11/31	Yes	2.58	3.02	3.15	3.16
12/23‡	No	4.52	4.97	4.69	4.56
13/25	No	3.64	3.93	4.12	3.86
Mean ± SD	...	3.09 ± 0.89	3.32 ± 0.87	3.16 ± 0.86	2.95 ± 0.82

*The median age was 26 years, and the range, 21 to 54 years.

†This patient committed suicide two weeks subsequent to the experiment.

‡Neuroleptics were never prescribed for these patients.

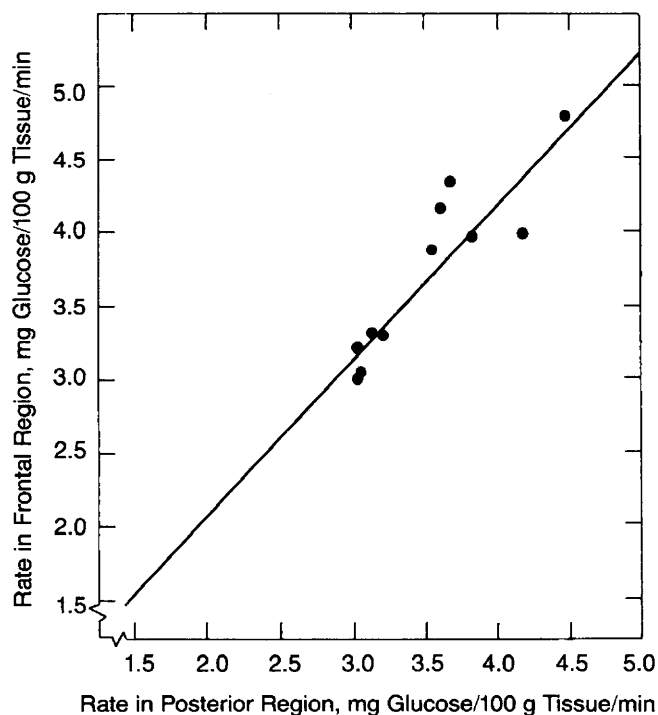


Fig 2.—Local cerebral metabolic rate for glucose in posterior v frontal regions in normal controls at basal ganglia level. Relationship as calculated by least squares is $y - 3.73 = 1.07(x - 3.53)$.

between frontal and posterior regions for controls lies above that for schizophrenics in each plane of section. Covariant analysis confirmed the visual impression, and the difference in height translated into a mean difference in metabolic rate of 0.47 mg of glucose per 100 g of tissue per minute, for an average control-schizophrenic posterior reading of 3.42 mg/g/min at the basal ganglia level. There was also a mean difference of 0.26 mg/g/min for the average control-schizophrenic posterior reading of 3.11 mg/g/min at the semi-oval center level ($P = .01$ and $P = .05$, respectively). The distance between the parallel lines represents for each level the difference in frontal region readings taken at the

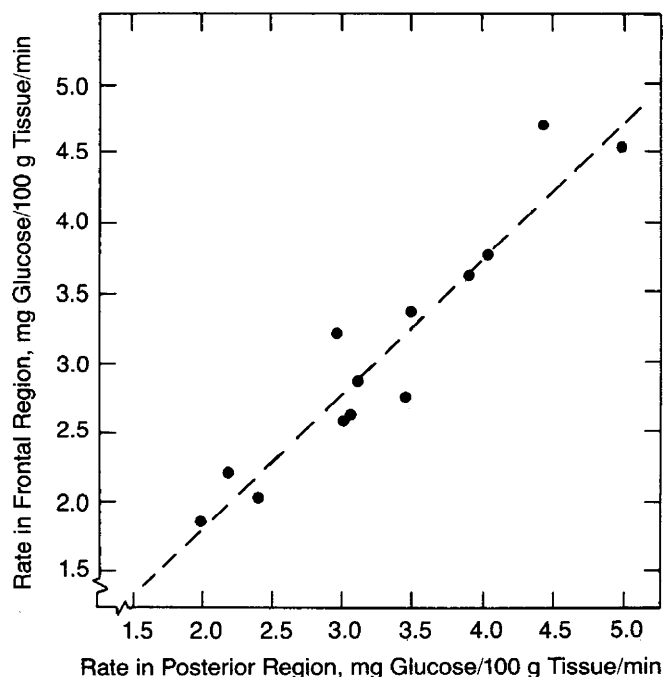


Fig 3.—Local cerebral metabolic rate for glucose in posterior v frontal regions in schizophrenic subjects at basal ganglia level. Relationship as calculated by least squares is $y - 3.09 = 0.97(x - 3.31)$.

average posterior region reading. The average frontal region readings shown on each figure were referred to as adjusted averages, ie, averages adjusted for controls and schizophrenics to the same group-representative posterior region reading of 3.42 mg/g/min (basal ganglia level) and 3.11 mg/g/min (semi-oval center level).

Further analyses of the data on schizophrenics were conducted to determine whether the six patients receiving neuroleptic treatment differed from the seven patients who were never prescribed neuroleptics or who had been drug free for at least six months prior to the study (Table 3). No mean differences were found for either

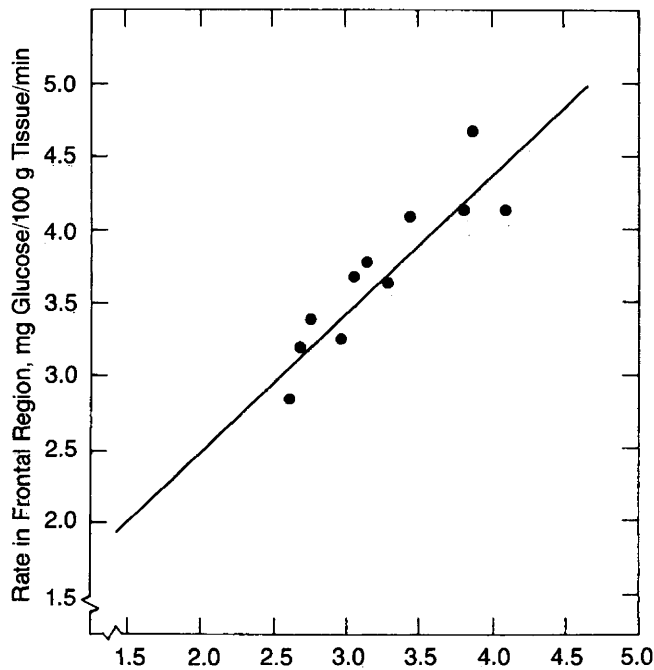


Fig 4.—Local cerebral metabolic rate for glucose in posterior v frontal regions in normal controls at semioval center level. Relationship as calculated by least squares is $y - 3.71 = 0.95(x - 3.26)$.

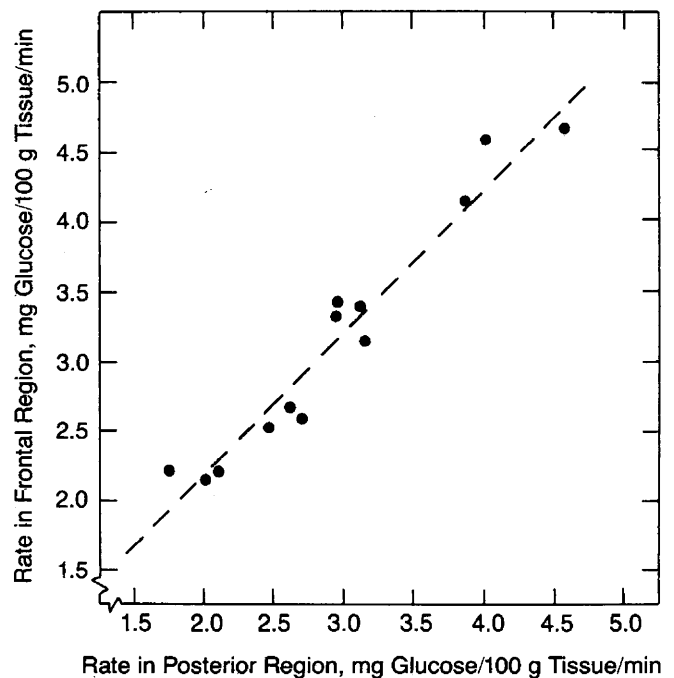


Fig 5.—Local cerebral metabolic rate for glucose in posterior v frontal regions in schizophrenic subjects at semioval center level. Relationship as calculated by least squares is $y - 3.16 = 1.03(x - 2.95)$.

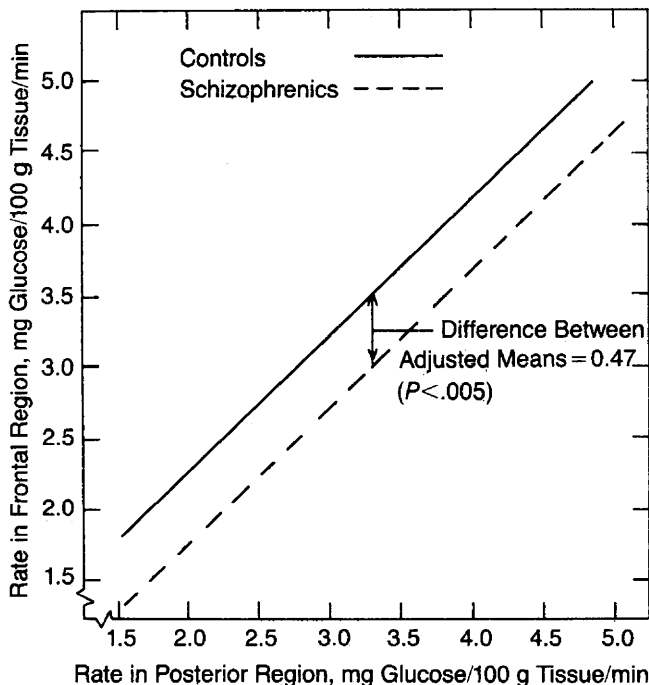


Fig 6.—Composite figure comparing frontal-posterior region relationship of schizophrenics and normal controls at basal ganglia level. Difference between adjusted frontal region means (adjusted using covariant analysis to common posterior mean) is 0.47 mg of glucose per 100 g of tissue per minute ($P < .005$) (arrow). Parallel relationships have slope of 0.99, which represents weighted average of two nonsignificantly different slopes of normal and schizophrenic subjects (see Figs 2 and 3).

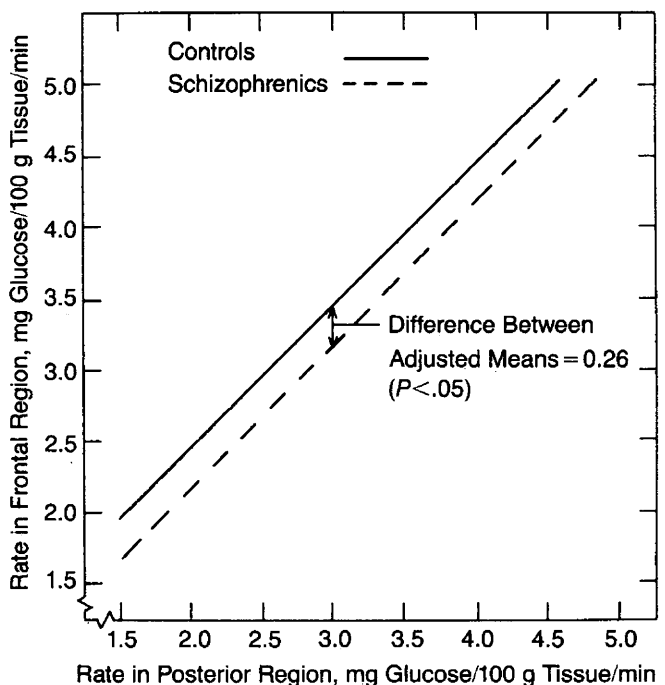


Fig 7.—Composite figure comparing frontal-posterior region relationship of schizophrenics and normal controls at semioval center level. Difference between adjusted frontal region means (adjusted using covariate analysis to common posterior mean) is 0.26 mg of glucose per 100 g of tissue per minute ($P < .05$) (arrow). Parallel relationships have slope of 1.01, which represents weighted average of two nonsignificantly different slopes of normal and schizophrenic subjects (see Figs 4 and 5).

frontal or posterior regions at either level studied. Covariant analysis to determine whether relative frontoposterior differences exist between the two groups yielded uniformly nonsignificant differences for both levels.

COMMENT

Our data provide direct quantitative confirmation of altered cerebral metabolic activity in patients with schizophrenia. The differences observed between schizophrenics and normal controls lend support to the finding of decreased frontal lobe metabolism in this pathologic condition and confirm our initial report of a single case.⁷ The two patients in this study (5 and 12) who exhibited more florid symptoms during clinical examination than the remainder of the sample were found to have metabolic rates at the upper end of the distribution of rates for schizophrenics (Table 3). While these two cases could not be separated from the rest on statistical grounds, analyses of symptomatology as well as cognitive stimulation studies are currently underway on an expanded patient sample, using a higher-resolution scanner, to explore further the relationship between symptomatology, cognitive function, and cerebral activity.

The assumption that the glucose metabolic rate is a measure of neural function requires that glucose be the main exogenous substrate for energy use in the brain. Kety⁶⁶ reported an oxygen-glucose ration of 5.6 (92% aerobic glycolysis), suggesting that this assumption is a valid one under normal circumstances. Since the brain can use a variety of alternative substrates, including ketone bodies,⁶⁶ under unusual conditions such as starvation and diabetes, these factors were controlled in our study.

A characteristic of the FDG ¹⁸F method is the necessity of integrating a dynamic mental process during a time base of approximately 30 minutes as an index of gross metabolic activity. This strategy precludes a detailed assessment of altered *in vivo* metabolic patterns, as has been suggested for carbon dioxide evolution from glucose tagged with carbon 14⁶⁷ and methyl methionine tagged with carbon 14⁶⁸ in schizophrenics. However, it should be noted that because of the absence of a model, the temporal sequence of the labeled compound *in vivo*, and the absence of knowledge of the detailed biochemical pathways and reactions of the materials used by these authors, further study is required to clarify the import of their results regarding schizophrenia.

A major technical constraint in our study involved the relatively poor resolution of the tomograph, which prevented use of small ROIs for analysis. While partial-volume averaging effects can contribute considerably to the error in any system, the large ROI examined here, combining gray and white matter, reduced the problem^{52,53} of missing areas of significant metabolic activity. However, one must remain aware of the reduced sensitivity of single-slice instruments of low resolution to detect local changes.

None of our schizophrenic patients had evidence of cortical atrophy or ventricular dilatation shown by clinical evaluation of CT scans. (More precise analysis of the CT data for our sample may have shown more subtle morphologic alterations than may have been detected by visual inspection. It is unlikely that these alterations in ventricular-brain ratio would have had a measurable effect on the LCMRG reported here.) Normal gross anatomy has been suggested as characteristic of a schizophrenic subgroup distinct from cases exhibiting cortical atrophy and ventricular dilatation by CT.⁵⁹⁻⁶⁵ In view of the lack of gross morphologic differences shown by CT scans from the two populations, it can reasonably be assumed that partial-

volume effects were similar for the two groups examined in this study. Thus, the alteration in regional metabolism reported for schizophrenia was detected in spite of considerable anatomic averaging. The true regional metabolic differences in schizophrenia may, in fact, be considerably larger than those reported here. The quantitative calculations in this paper required that the sensitivity of the Sokoloff model to flow and transport constants be minimized,⁶⁶ a requirement met by the experimental condition. The conclusion that the physiologic state in schizophrenic groups approximates that of a normal population is supported by the similarity in mean overall rates of glucose use, suggesting that the errors are minimal and the calculations valid.

Finally, as in all studies involving schizophrenics, the obvious heterogeneity of clinical appearances suggested caution in generalizing. Indeed, it is remarkable that, despite the variability inherent in diagnoses using Research Diagnostic Criteria³⁷ and structured interviews, the finding of hypofrontality is so consistent, given the heterogeneity present in studies of attempts to find biologic markers, eg, platelet monoamine oxidase levels⁶⁷ and amphetamine response.⁶⁸ Probit analysis of our PETT data suggests that our population of schizophrenics should have been grouped as a unimodal entity, despite the range of absolute glucose metabolic rates, clinical variation within the group, and the inclusion of patients who had never received medication, were currently medication free, or were taking medication.

The LCMRGs found in patients with and without medication were consistent with a hypothesis that hypofrontality (ie, hypoactivity of glucose metabolism in regions of the frontal lobes) may reflect an underlying biologic alteration that can persist, despite medication therapy. Although our subjects were all awake, these results may have reflected a difference in psychophysiologic state, such as arousal, between the two populations under resting conditions,⁶⁹ or they may have represented frontal lobe dysfunction.^{70,71} In animals, deficits similar to those found in patients with this frontal region syndrome were observed, along with lesions of the thalamofrontal pathways, an observation that forms the basis for one interpretation of diminished frontal blood flow in schizophrenia.¹³

Proposals of a defect involving the cerebellum,⁷²⁻⁷⁴ subcortical dopamine systems,⁷⁵ and their respective frontal pathways provide further possible explanations for the observed hypofrontality in schizophrenics without gross structural abnormalities in frontal regions. On the basis of these data, we do not suggest that effective treatment must necessarily improve, ie, "normalize," this altered distribution of LCMRG. Since the LCMRG reflects neuronal function, it is possible that improvement in the clinical state might be reflected in an increased metabolic rate. However, it may also be true that the relationship between the frontal regions and the rest of the brain remains substantially the same as when reflected by neuronal functioning, despite symptom diminution. Analysis of other brain regions will undoubtedly shed further light on the nature of the brain function distribution and the alteration of this distribution in patients with psychopathologic conditions.

Based on the findings reported here and elsewhere, functional imaging of the brain by PETT using FDG ¹⁸F has been established as an effective tool for studying a possible correlation between regional brain glucose metabolism and psychiatric illness. In future studies, issues of cause in the context of genetic, familial, and socioeconomic factors will be addressed. In addition, cognitive, psychopharmacologic, and sensory perturbations will be introduced and corre-

lated to a subject's steady-state condition. Different labeled compounds and tracer strategies can be used to probe more specific biochemical pathways. Thus, the biochemical representation of altered behavioral responses to environmental stimuli can be examined.

Changes in neuronal functioning immediately following administration of psychotropic medication can also be correlated with associated behavioral changes. This link is made possible by use of 2-deoxy-D-glucose labeled with carbon 11, which allows sequential studies to be done on the same day.^{76,77} With the advent of more sophisticated PETT instruments (eg, with a seven simultaneous slice capability, higher sensitivity, and resolution down to 0.8 cm full width half maximum), it is possible to focus on smaller-volume elements of the brain and to elucidate distributed expressions of metabolic activity in controls and those with demonstrable disease.

Studies such as these should help to increase our understanding of the nature of various syndromes included under the rubric of schizophrenia, thus permitting more accurate prognosis and treatment. Whether the finding of hypofrontality in the LCMRG in schizophrenics is a direct presentation of a pathophysiologic process, as we have argued here,

or a biologic marker of vulnerability in a variety of illnesses involving the frontal region should be clarified by future studies. Our approach to the study of schizophrenia can be directly extended to the measure of functional neuro-anatomic effects of treatment in many psychiatric disorders. Clinical response may be associated with the "normalization" of the metabolic pattern in patients with affective disorders or acute schizophreniform appearances, but it may remain altered in those with irreversible psychopathologic conditions. The resolution of controversies, such as the origin and treatment of tardive dyskinesia and state *v* trait in psychiatric populations, are effected extensions of our current efforts.

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