VOL. 13, NO. 1, 1987

Functional and Anatomical Brain Imaging: Impact on Schizophrenia Research

by Monte S. Buchsbaum and Richard J. Haier

Abstract

A group of related new technologies has made it possible to study the brain's regional changes in metabolism, blood flow, electrical activity, and neurochemistry. Positron emission tomography (PET) produces slice images of radioisotope density—brain metabolism or receptor concentration can be quantitated. Studies in schizophrenia have indicated relative metabolic underactivity of the frontal lobes of schizophrenics. Decreased activity in the basal ganglia, which can be reversed with neuroleptic treatment, is also seen in schizophrenia. PET studies are in the early stages; standard methodology for isotope selection, task during tracer uptake, and quantitative analysis is still developing. Cerebral blood flow studies have shown similar patterns in the cortical surface. The electroencephalogram provides a short time resolution approach which can assess attention and arousal, but lacks some of the anatomic exactness and depth capabilities of PET. Magnetic resonance imaging furnishes anatomical images of gray and white matter previously unavailable with x-ray computed tomography. Advances in methodology and clinical studies with imaging are making neuroanatomic theories of schizophrenia more directly testable than ever before.

Imaging is the making visible of things hidden, absent, or not directly perceptible to the senses, or even abstract ideas. The new technologies of brain imaging not only bring the otherwise hidden organ into view, but they make visible the chemical, metabolic, and physiological processes that differ so widely across its complex structure. Most importantly, this is possible at repeated intervals during life. Schizophrenia, with its onset in adolescence, nonlocalizing deficits largely in higher mental functions, and a nonlethal and fluctuating course, has provided an illness puzzle not easily solved with the traditional tools of blood and urine chemistry and post-mortem anatomy. Imaging can provide regional neuroanatomical measurement and regional functional assessment as subtyping variables in the quest for homogeneous groups of patients with similar pathophysiology. And with positron emission tomography, pathophysiology can be explored within the brain.

The images reviewed here are created by computers. They are graphic representations of numbers measured at different positions in space. These numbers may be obtained from individual electrodes or probes positioned on the scalp or rings of crystals or antennas using mathematical techniques to infer the spatial source of the signal. The end result is a grid of numbers, like depth soundings in a bay, representing the topography of the signal. Computer graphics allow us to assign a different color to each range of numbers and build up a colored picture of the phenomenon under study.

The quality of these images depends both on the sensitivity and accuracy of each individual number and the spacing between the numbers. The slice (tomographic methods), including computed x-ray tomography, magnetic resonance imaging, and positron emission tomography, yields many numbers at closely spaced intervals and yields pictures that resemble, to varying

Reprint requests should be sent to Dr. M.S. Buchsbaum, Department of Psychiatry, University of California, Irvine, CA 92717.

degrees, actual visual images of a sliced brain. They are not actually brain pictures but representations of brain physiology or functional properties that parallel the visually perceptible differences between regions of closely packed neurons (gray matter) and bundles of axons (white matter) or cavities (ventricular space). The surface imaging methods, including electroencephalographic quantification and cerebral blood flow, typically obtain numbers from 16 to 32 individual sensors and have intervening positions filled by interpolation to form a picture. For both techniques, more accurate measurement and narrower spacing of measurement produces a picture with more detail; all methods are under active development.

This review focuses on the functional imaging methods. Computed tomography (CT scanning) was recently reviewed (Maser and Keith 1983; Weinberger, Wagner, and Wyatt 1983). Because these varied methods assess an extraordinarily complex structure in different behavioral states and are often pilot reports on small samples, we have focused on brain areas of traditional interest in schizophrenia, the frontal lobes and the basal ganglia. (Examples of the types of brain-imaging techniques reviewed appear in figures 1–18 at the end of this article.)

Positron Emission Tomography

Brain imaging with positron emission tomography (PET) has the capability to survey functional activity throughout the brain and thus to bring together the disparate lines of neurochemical and behavioral approaches to schizophrenia. It has adequate resolution to view both individual gyri of the cortex and discrete portions of the basal ganglia, so important in schizophrenia research. PET, using the mathematics of x-ray CT scanning to produce slice images of any chemical which is tagged with a radioisotope, opens an almost unlimited vista of metabolic studies. Positron-emitting atoms such as carbon-11 or fluorine-18 can be incorporated into sugar, amino acids, neurotransmitter precursors, or psychoactive medications. Using a combination of such radiopharmaceuticals, one could potentially reveal the anatomical area made hypermetabolic by a delusion, the distribution of synaptic receptors for a treatment medication, and the physiological effect of a drug with a repeat metabolic scan. This report reviews the initial studies of schizophrenia with PET and outlines some of the promise of the future.

Positron Emitters and Their Imaging.

Image acquisition. The PET scanner uses a ring arrangement of radiation detectors to produce slice images of the distribution of radioisotopes in the human brain (Brownell et al. 1982; Phelps et al. 1982; Phelps and Mazziotta 1985).

Positrons emitted with isotope decay interact with electrons in the brain in quite short distances (about 1 mm or less); an annihilation results and two 511,000 electron volt photons are emitted which travel in opposite directions at an angle of almost exactly 180 degrees. The detector crystals are located in a ring around the head. The nearly simultaneous arrival of the photons in crystals on opposite sides of the ring provides information that the positron annihilation event very likely occurred somewhere along a line joining the two crystals. This unique feature of positron decay allows great spatial precision in mathematically reconstructing the location of the density of isotopes. The single photon tomographic system, moving a single crystal around the head, lacks the degree of precision obtained with the more complex and costly PET device and more evanescent positron isotopes.

The resolution of current commercially available PET scanners is in the range of 5 to 12 mm or about the size of the caudate nucleus. Resolution is typically reported as full-width half-maximum (FWHM). A small diameter (< 1 mm) needle filled with radioactivity and oriented axially in the scanner (as an axel of the wheel of crystals) serves to measure resolution. A PET scan shows a cross-section—a circle 10 or more millimeters in diameter, intense in the center and falling off to one-half of the center value in a number of millimeters. The diameter of the circle where the count rate at the circumference is 50 percent of the central point is the FWHM value. In the brain, structures are not pinpoints of intensity but are globular and irregular. A structure as wide as the FWHM would have its measured value diluted by surrounding tissue by about 70 percent. Thus, very small but sufficiently intense structures can be visualized, but their quantitative interpretation would be confounded with surrounding brain structures. The caudate and thalamus, with volumes of the order of 5 cm^3, are well measured with PET resolution of 10 mm. The internal capsule and the globus pallidus in the 2 cm^3 range are fairly well quantitated, and structures such as the substantia nigra with less than 1 cm^3 may be seen in some individuals but are poorly quantitated (Mazziotta et al. 1981; Kessler, Ellis, and Eden, in press). This is dependent on PET resolution; with a

10 mm^3 volume resolution, for example, globus pallidus has good recovery (.70), but this falls to fair (.34) at 15 mm^3 (Mazziotta et al. 1981). Circular structures are more reliably measured than thin or wedge-shaped ones. The cortical mantle, 4–6 mm thick and folded as a ribbon, appears as an irregular band; this is sufficient to see the lobes, but individual gyri have blurred margins. This dilution may be important in quantitative PET work where, for example, gray matter/white matter differences in local concentration of isotopes may be between 10 percent and 100 percent. In contrast, the x-ray transmission differences seen in CT scans between cerebrospinal fluid and brain may be much larger, allowing quite a sharp ventricular cavity image to be produced. However, gray matter/white matter differences for CT are in the range of .5 percent, accounting for the capacity of the intrinsically lower resolution PET to reveal brain structures so dramatically in comparison to routine clinical CT.

Animal studies suffer especially from the limited resolution of PET. While the caudate in man is in the 10 mm range, in the rat it is in the 1 mm range; indeed the FWHM would include the entire brain of a rat. Large primates such as the baboon can be scanned, but the images allow only the largest structures to be visualized. PET is largely a human technique with current scanners.

Resolution is limited by, among other factors, uncertainty in how far positrons travel before encountering an electron, variation from exactly 180 degrees opposite travel, and the size of the gamma-sensitive crystal detector system. Basic positron physics limit the ultimate resolution of PET scanners to the 1.5 to 2.5 mm range, leaving a large improvement possible. Smaller detectors would allow more to be packed into the ring and result in more precise localization of the gamma coincidences. Shrinking the size of the assembly of crystals and the accompanying photomultiplier tubes which detect the photon is a soluble engineering problem.

Cyclotron production of positron emitters. The small atomic weight isotopes used in PET have quite short half-lives (^{15}O, 2 minutes; ^{13}N, 10 minutes; ^{11}C, 20 minutes; and ^{18}F, 110 minutes). Thus, to have a sufficient amount of isotope for patient study, a cyclotron to produce positron emitters from stable atoms and a radiochemistry laboratory for swift synthesis of radiopharmaceuticals are essential components of each PET operation (Wolf 1984).

The short half-life of positron emitters keeps radiation dose to the patient relatively low. For example, typical ^{18}F doses of 5 millicuries provide whole body doses in the 300 to 400 mR range; brain doses are less than half that of a typical CT scan. Roughly comparable x-ray procedures are an upper gastrointestinal series or 6–8 chest x-rays; a CT scan of the head typically has greater exposure than PET. Most PET centers limit scans to no more than three for an individual. Radiation dosimetry for ^{18}F deoxyglucose is reviewed by Jones et al. (1982).

Chemical tags for imaging. PET takes advantage of two properties of four positron-emitting radionuclides—carbon-11, nitrogen-13, oxygen-15, and fluorine-18. The first, already discussed above, is the geometry of positron decay. The second is their convenience for labeling neurochemical systems. Oxygen, nitrogen, and carbon are the biochemical building blocks of many cell constituents. Fluorine is a small, chemically reactive atom which can be attached to many biologically important molecules, often with little alteration in their function (Sokoloff 1982). Because of the relatively long half-life of ^{18}F, 110 minutes, it has been the isotope most widely used.

Metabolic rate imaging. Brain work requires energy. Metabolic energy is required for K^+ transport, and for the synthesis, transport, and reuptake of neurotransmitters. Glucose, burned to carbon dioxide and water, serves as the source of high energy phosphate bonds which fuel cell repolarization and other processes (see Sokoloff 1977, 1982). However, glucose itself, labeled with a positron emitter such as ^{11}C and injected into the patient's antecubital vein, would be metabolized rapidly and would begin to be breathed out as radioactive carbon dioxide before the scan could be completed. While very rapid scanning and mathematical techniques for separating metabolic products from source and blood flow have been developed (Raichle 1983), most PET centers have used an alternate method. An analog of glucose, 2-deoxyglucose, is labeled and injected instead. The missing oxygen at the 2-position allows its metabolism by hexokinase, the first step in the glycolytic path to CO_2—but limits further steps. The cells are thus labeled in proportion to their deoxyglucose uptake, which is largely complete within the 40 minutes after intravenous administration (see discussion in Nelson et al. 1985). At this point, the radioactivity is fixed in the brain, much as the latent image is fixed on a photographic film by opening and closing a camera shutter and exposing the silver in the emulsion to light. The patient can be moved to the scanner and the latent image reconstructed. Thus, the deoxyglucose scan shows mental activity in the 40 minutes of tracer uptake, not activity during the scan. For schizophrenia research, this separation of uptake and scanning is

convenient. The isotope may be injected in the comparatively controlled environment of a psychophysical test chamber with the patient participating in a task known to show deficits in schizophrenia. After completion of the task, the patient can then be moved to the scanner to acquire the image of brain metabolic rate during the task.

It is important to note that both excitatory and inhibitory cell processes require energy and both processes will be indexed by glucose uptake. Cells may also modify cell activity elsewhere with their projections. Thus, the mapping of functional deficits or neuropharmacological effects with glucose may be complex. Detailed analysis of autoradiographic changes with ^{14}C-deoxyglucose led Sokoloff (1984) to conclude that the metabolic rate changes shown with deoxyglucose represent mainly "alterations in the metabolic activity of synaptic terminals triggered by changes in Na+, K+, ATPase activity." Areas containing large masses of axons seem far less sensitive to change (Sokoloff 1984) and may be useful as reference areas for metabolic rate comparisons.

Typical Deoxyglucose Scan Procedure. In a typical scan procedure with deoxyglucose, the patient arrives an hour before the scan. An intravenous line with a plastic cannula is inserted into a vein in each arm so that when the isotope arrives no time or isotope is lost. A psychological task may be started just before isotope injection and must continue for 30–40 minutes. A challenge drug dose could also be given at this point. The tracer deoxyglucose is then injected in one arm and a series of 1 to 2 cc blood samples withdrawn from the other arm throughout the uptake and scanning period for the measurement of glucose and deoxyglucose. This arm is usually warmed with a hot pad to increase arteriovenous shunting so that glucose and 2-deoxyglucose concentration in samples approximates that achieved with arterial sampling (Phelps et al. 1979). After 30–40 minutes, 70–90 percent of the deoxyglucose has been taken up from the blood and the patient can be moved to the scanner. The patient lies on a special bed, and his head is placed into a holder to keep it still during the 3–15 minutes required to accumulate enough counts for an image. An individually fitted head holder may be made from thermosetting plastic casting material to hold the patient still during the scan and to allow the patient's head to be returned to the same position for a second scan on a later date. Now the coincidence gamma counts are collected by the computer, from one or more rings of crystals. The patient's bed may advance the patient further into the ring to count additional slice positions.

After acquisition of the count data, the computation of the final quantitative image begins. The image is typically smoothed to remove noise. A correction is made for the greater attenuation of radiation from central than peripheral tissue. Then, the data for deoxyglucose and glucose concentration in blood, together with their exact times, are united in a mathematical model of glucose metabolism (Sokoloff et al. 1977, 1982) and the metabolic rate of the brain (in micromoles of glucose per 100 grams of brain tissue per minute) is calculated for each of the squares that make up the final PET picture. These numerical values are then transformed by the computer into the color images of brain activity. This transformation is linear over the range of physiologically normal tissue; thus, raw count and metabolic rate pictures have the same appearance except that the scale is now expressed in units of rate.

Imaging Metabolic Rate in Schizophrenia.

Hypofrontality. A preliminary PET report by Farkas et al. (1980) in one never-medicated schizophrenic showed a relative metabolic hypofunction of the frontal lobe. This was consistent with the pioneering studies of regional cerebral blood flow by Ingvar and Franzen (1974). Using intracarotid injection of ^{133}Xe to assess regional flow, they observed that the ratio of frontal lobe to whole surface flow was reduced in patients with schizophrenia. Consistent cerebral blood flow changes in the frontal lobe have been found by a number of authors (see table 2). In the first published controlled series with PET, eight off-medication patients with schizophrenia and six normal controls (Buchsbaum et al. 1982*b*) were studied. Patients rested in a darkened room with their eyes closed, to replicate the conditions of Ingvar and Franzen (1974). The patients similarly had significantly lower frontal:whole slice glucose metabolic rate ratios (1.06) than normal controls (1.13). This was more strongly confirmed with linear trend analysis of variance (ANOVA) indicating the presence of a front to back gradient in metabolic rate in both groups, stronger in normals than in patients with schizophrenia.

A second study also found a reduced anteroposterior gradient in cerebral cortex in schizophrenia (Buchsbaum et al. 1984*a*) as well as in patients with bipolar affective disorder. These patients received brief electrical shocks to their right forearm during tracer uptake. This controlled task was chosen because of

its reported tendency to increase cerebral blood flow (Ingvar 1976) and because patients with schizophrenia had increased pain tolerance using exactly the same stimulation procedure (Davis et al. 1979; Davis, Buchsbaum, and Bunney 1979). Again, group differences were most strongly statistically confirmed by linear trend ANOVA; lower frontal lobe:whole slice ratios for patients with schizophrenia than normal controls were observed but did not reach statistical significance by t test ($p = .07$). Six additional studies have observed either lower or relatively lower frontal cortex metabolism in schizophrenia (see table 1). Each study was summarized for the right side, frontal area at the level of the centrum semiovale, as this was the strongest finding in the initial PET study, and uniform ratios calculated from tables in each article. The series of studies is heterogeneous with respect to sensory conditions, analytic methods, and patient medication. However, in table 1, note first that the phenomenon of hyperfrontality in resting normals appears in six of eight studies; this can be seen in the frontal:occipital ratios, taking values greater than 1.0. Only the Kling study showed a ratio lower than 1.0—one of two studies in which subjects' eyes were open. The Wiesel study did not give exactly comparable data, but a ratio of .99 was seen for the left side for Broca's areas (6 + 8)/(39 + 40) for normal volunteers.

The lower frontal:occipital ratios in schizophrenics were seen in all seven studies, although statistically

Table 1. Comparison of PET studies in schizophrenia

Study		Frontal/occipital ratio			Frontal/whole slice or whole hemisphere		
		Normals	Schizophrenics	p	Normals	Schizophrenics	p
(A)	Jernigan et al. (1985)[6]	1.10	1.03	NS	1.03	.98	NS
(B)	Buchsbaum et al. (1984*a*)	1.08	1.02	<.05[1]	1.14	1.09	<.05[1]
(C)	Buchsbaum et al. (1982*b*)	1.14	1.05	<.05[2]	1.12	1.06	<.05[1]
(D)	Farkas et al. (1984)[5]	1.14	1.07	<.05[3]	1.11	1.05	NT
(E)	Wolkin et al. (1985)	1.09	1.04	NS	1.08	1.04	<.05[4]
(F)	Kling et al. (1986)	.79	.74	NS	.97	.92	<.05[1]
(G)	Wiesel et al. (1985)[7]	—	—		1.16	1.12	NT
(H)	Sheppard et al. (1983)[8]	1.1	1.0	NS	—	—	—

	Level	Sample size of schizophrenics	Test condition	Comments
(A)	Midventricular	6	Auditory vigilance task, eyes closed	Off medication
(B)	Supraventricular	16	Somatosensory stimulation, eyes	Off medication
(C)	Supraventricular	8	Resting, eyes closed	Off medication
(D)	Supraventricular	11	Open room	6/13 medicated
(E)	Midventricular	10	Eyes open	Off medication
(F)	"High"	6	Eyes open, lying in scanner	6/6 medicated
(G)	Brodmann 9 + 10	13	Eyes closed	Off medication
(H)	Orbitomeatal + 6 cm	12	Eyes closed, open room	6/12 patients not >7 days off medication

Note.—Analysis for right hemisphere supraventricular slice when available. NT = not tested, NS = not significant.

[1]t test.

[2]Linear trend analysis of variance, significant.

[3]Analysis of covariance, significant.

[4]Difference for glucose metabolic rate but not tested for ratio of whole slice.

[5]Right and left combined, calculated from tables 1–3 from Farkas et al. (1984).

[6]Automated analysis

[7]Occipital data not given in report; frontal areas calculated from Brodmann area 9 + 10 data—canthomeatal level not given.

[8]Ratio calculated by authors to only 1 significant figure after the decimal.

significant in only three. Frontal lobe/whole slice values were similarly lower in seven studies, significantly so in four.

Two PET studies that have not statistically confirmed this pattern require detailed comment (Sheppard et al. 1983; Widen et al. 1983). Sheppard et al. (1983) examined 12 normal controls and 12 patients, 6 of whom were medicated within 7 days of scanning. Unlike the other PET studies, they scanned with oxygen-15 and oxygen-15 labeled carbon dioxide; oxygen uptake and cerebral blood flow were computed. Using an image analysis technique adapted from Buchsbaum et al. (1982*b*), those investigators calculated frontal:occipital ratios, but schizophrenic-normal comparisons did not reach significance. In addition to the use of different tracers, possible differences include (1) 50 percent of the patients were on or recently treated with neuroleptics and (2) scans were done in an open room without rigorous sensory or cognitive control. Widen et al. (1983) examined six schizophrenics but only two healthy volunteers with carbon-11 labeled glucose rather than deoxyglucose. Because they report such a small sample, their data were not included in table 1, but data from a continuation of the same series (Wiesel et al., in press) were included. They report on 13 patients and 8 volunteers. In this comparison, they found significantly reduced metabolic rates in prefrontal cortex in schizophrenics (Brodmann's areas 9 and 10) but higher rates in area 6 (premotor). Anteroposterior ratios were tested for areas (6 + 8)/(39 + 40), not corresponding exactly to the frontal:occipital ratios examined in several other PET reports.

A study of the four Genain quadruplets, 50-year-old monozygotics concordant for schizophrenia but differing widely in lifetime neuroleptic exposure and clinical severity, also showed low anteroposterior (A/P) ratios (Buchsbaum et al. 1984*c*). Hypofrontality was also shown in a portion of patients scanned with carbon-11 labeled glucose by Kishimoto et al. (in press). Devous et al. (1985) used single photon tomography with ^{133}Xe and observed 43 percent of schizophrenics with frontal hypoperfusion compared to 11 percent of controls.

Relative reductions in frontal lobe protein synthesis in schizophrenia were reported by Bustany et al. (1985). They used ^{11}C-L-methionine, an amino acid rapidly incorporated into neuronal and glial proteins, as a tracer and a three-compartment model to calculate the rate of local protein synthesis. Six patients with schizophrenia showed a frontal:occipital ratio of .80 in contrast to a ratio of .96 in normals (their ratio calculation, $t = 5.0$, $p < .001$). Patients with dementia had even lower ratios (.64). It is of interest that while protein synthesis in frontal lobes of patients with schizophrenia was actually higher than in normals (although not significantly so), it is the relative ratio that reveals the significant difference and thus parallels some of the glucose metabolic rate reports of table 1.

Basal ganglia and neuroleptic effects. Most studies have shown low metabolic rates in the basal ganglia of schizophrenics which are raised by neuroleptics. Five studies (Buchsbaum et al. 1982*b*; Sheppard et al. 1983; Sedvall et al. 1984; Wiesel et al., in press; Buchsbaum et al., in press) found significantly lower glucose metabolic rates in the basal ganglia of unmedicated schizophrenics than in normal volunteers. Wolkin et al. (1985) found similarly lower metabolic rates in the basal ganglia, but this difference was not statistically confirmed. The Sheppard study included some recently medicated patients, but as noted below, this might have diminished group differences rather than spuriously causing them. Two studies of medicated patients showed higher relative metabolic rates in the basal ganglia of schizophrenics than normals (Kling et al. 1986; Volkow et al. 1986). Relatively low metabolic rates in the basal ganglia have also been seen in patients with affective disorder (Baxter et al. 1985; Buchsbaum et al. 1986*b*).

Differences within portions of the basal ganglia may be important. The Sedvall study found the reduction in the lentiform nucleus but not the caudate, whereas Buchsbaum et al. (in press) found caudate to yield greater differences. Overlap in patients between the Sedvall and Wiesel samples is not specified, but the latter study has a larger sample size and also shows the lentiform decrease. One interesting consistency among Buchsbaum et al. (1982*b*), Sedvall et al. (1984), Wiesel et al. (1985), Wolkin et al. (1985), and Buchsbaum et al. (in press) is the concordance of strongest schizophrenia/normal differences on the left side (although not statistically confirmed in all studies independently).

Neuroleptics tend to increase metabolic rates in the basal ganglia. This appears to be a normalization of the low metabolic rates observed. In a preliminary analysis of scans in nine patients with schizophrenia on and off neuroleptic medication, we found that glucose metabolic rate in the entire brain, temporal cortex, and the region of the basal ganglia was increased (DeLisi et al. 1985). Similar metabolic rate elevations have been reported by Wolkin et al. (1985) and for the right but not left lentiform nucleus (Widen et al. 1983). More detailed analyses (Buchsbaum et al., in press) re-

vealed increases of 41 percent in the upper right putamen with less change in lower structures. Some associations between magnitude of improvement on the Brief Psychiatric Rating Scale and basal ganglia metabolic rate increase were noted both by Wolkin et al. and Buchsbaum et al., but a larger sample is clearly needed for replication. The larger right than left basal ganglia increases noted for putamen (Buchsbaum et al.), caudate (Wolkin et al.), and lentiform nucleus (Widen et al.) deserve further study.

The increase in metabolic activity in the right upper caudate and putamen with dopamine-blocking neuroleptics suggests that dopamine as a neurotransmitter is inhibitory in these regions. Moore and Bloom (1978) reported dopamine as an inhibitory neurotransmitter from data on 20 extracellularly recorded structures. The reported decrease of metabolic activity in the basal ganglia in Huntington's disease (Kuhl et al. 1985), also associated with a loss of dopaminergic activity, is similarly consistent.

Attention Deficit in Schizophrenia. Recent studies have indicated that certain deficits in attentional and information-processing tasks are among the most consistent abnormalities found to characterize populations at heightened risk for schizophrenic disorder (Asarnow et al. 1977; Erlenmeyer-Kimling and Cornblatt 1978; Nuechterlein 1983). One productive measure has been the continuous performance test (CPT). This visual vigilance task involves monitoring a series of briefly presented stimuli (usually numbers or letters) that appear one at a time at a rapid serial rate and signaling by a button press each time a predesignated target stimulus is presented. Adult chronic schizophrenic patients have been shown to obtain a significantly lower percentage of correct target detections on the CPT than chronic alcoholics or normal subjects, whereas chronic alcoholics score significantly more poorly than schizophrenics and normals on the digit-symbol substitution test, a self-paced number-symbol transposition task (Orzack and Kornetsky 1966). Hospitalized schizophrenic patients achieve fewer correct target detections on the CPT than hospitalized patients with either schizoaffective disorder or major affective disorder (Walker 1982). The abnormally low CPT target detection rate characterizes 40–50 percent rather than all of schizophrenic inpatients (Orzack and Kornetsky 1966; Walker and Shaye 1982). Furthermore, these poor CPT performers are more likely to have a family history of schizophrenia (Walker and Shaye 1982) or serious mental illness (Orzack and Kornetsky 1966) than schizophrenic patients who are good CPT performers.

The CPT is especially appropriate for PET studies with fluorodeoxyglucose (FDG) as it can be done for the 30 minutes of uptake and fills the interval with continuous vigilance activity by the subject. In a pilot investigation in normal controls, the metabolic rate of glucose was assessed in two groups of subjects. One group executed the standard CPT task for 30 minutes during FDG uptake. The second received no instructions except to use the flashes as a fixation point. Statistical analysis, based on exactly the same methods used previously to compare schizophrenics and normals, revealed that the CPT was associated with an increase in metabolic rate greatest in the right superior frontal gyrus—the same region in which patient/normal differences were greatest (Buchsbaum et al. 1984*a*; see table 1). Data on the basal ganglia in normals and schizophrenics are not yet available, but their role may be important in attentional defects (Schneider 1984; Goldberg 1985).

These findings of frontal and basal ganglia changes in functional activity in schizophrenia are consistent both with the dopamine theory of schizophrenia and with the psychological deficits observed in the syndrome. It should be noted at the outset that decreases in basal ganglia glucose metabolism need to be interpreted with the same caution as autopsy studies of dopamine receptor binding. While patients in most studies were off neuroleptic medication at the time of the scan, they had still been exposed previously to neuroleptics. Nevertheless, it is of interest that the low levels of metabolism observed in these dopamine-rich areas are normalized by neuroleptics. An influence of the frontal dopamine system on the basal ganglia is suggested by the frontal cortex lesion studies of Pycock, Kerwin, and Carter (1980); prefrontal lesions in the rat enhanced striatal spiperone binding. Thus, primary frontal lobe dopamine system lesions could be consistent with these findings. Recently, Benes, Davidson, and Bird (1986) have reported lowered neuronal density in the prefrontal cortex of schizophrenics. While the changes were not typical of neuronal degeneration, the possibility of abnormal maturation and/or perinatal insult is raised by this finding.

Both the frontal cortex and the basal ganglia are involved in the modulation and maintenance of attention (see Schneider 1984; Goldberg 1985), and frontal lobe damage may produce some symptoms of behavioral disorganization not entirely unlike schizophrenia.

Dopamine Receptor Binding. Comar and coworkers (1979) published the first clinical PET study in psychiatry, reporting on images obtained

with ^{11}C-chlorpromazine in patients with schizophrenia who had not been treated with neuroleptics for seveal months before the study. Since chlorpromazine has a high binding affinity for dopaminergic receptors in the brain, the PET scan values could reflect the number of the receptors/unit volume, receptor affinity for the labeled compound, and the concentrations of natural receptors present. Unfortunately, other factors would also affect labeling. Neuroleptic ligands bind to receptors other than the dopamine receptor. The presence of multiple dopamine receptors with different affinities complicates the direct interpretation of the quantitative image. Metabolic products of neuroleptics which retained the ^{11}C would appear. In addition, these drugs are lipid soluble, and enter fat and myelin. Distribution in proportion to blood flow thus could be important, especially shortly after injection. The resultant image reflects all of these influences on radiolabel distribution. The images of Comar et al. are actually not unlike the FDG images produced later. A fast penetration of the labeled molecules into the brain in the first 5 to 15 minutes after injection was observed, with the uptake in the frontal lobe only about half of the uptake in the occipital lobe. They noted the similarity of their results to the relative hypofrontality findings of Ingvar and Franzen (1974) for blood flow and discuss the problems of imaging neuroleptic binding.

Wagner et al. (1983) used ^{11}C-methylspiperone in PET studies. This tracer bound more selectively to the caudate than the cerebellum with a 4.4:1 ratio at 70–130 minutes. Preliminary reports of comparisons of patients with schizophrenia and normal controls have revealed greater D_2 dopamine receptor densities in the caudate nucleus of schizophrenics (Wong et al. 1986). Large decreases in concentration of ^{76}Bromine labeled bromspiperone relative to the cerebellum were found with PET in patients with progressive supranuclear palsy, an extrapyramidal disorder with loss of striatal dopamine receptors (Baron et al. 1985). This demonstrates the power of the methodology; whether diagnostic heterogeneity or biological differences obscure findings in schizophrenia remains to be determined.

Farde et al. (1985, 1986) introduced the use of ^{11}C-raclopride, a substituted benzamide, for PET studies on dopamine D_2 receptors. They observed specific uptake of this compound in the basal ganglia of normal volunteers and a marked reduction of uptake in the basal ganglia of patients with schizophrenia who were receiving neuroleptic treatment. Studies comparing groups of schizophrenics and normals are not yet available.

Garnett, Firman, and Nahmias (1983) used ^{18}F-L-dopa and showed caudate and frontal cortex concentration, demonstrating the versatility of PET approaches to dopamine neurochemistry in man.

Cerebral Blood Flow

The flow of blood to the brain and the distribution of this flow to individual brain regions is under precise physiological control. Changes in systemic blood pressure with posture shifts, exercise, or blood volume loss are met by adjustment of major artery resistance to flow (internal carotid, vertebrals, etc.). Changes in cerebral work in small brain regions, with concomitant blood flow need, appear met by changes in resistance of small arterioles (see review by Mchedlishvili 1980). Detailed studies with autoradiography in animals indicate a very close correspondence spatially between blood flow as assessed by iodoantipyrine diffusion, and glucose metabolic rate as assessed by deoxyglucose (Sokoloff 1977, 1981, 1982). Human studies with PET have also shown coupling of flow and glucose use in normal tissue (Baron et al. 1982).

Reductions in whole brain blood flow are seen in dementias where large cortical areas are inactive, but patients with schizophrenia do not seem to have reductions in whole brain cerebral blood flow or metabolic rate, as assessed by the Kety-Schmidt nitrous oxide method (Kety et al. 1948). Later imaging studies of metabolism with PET (Buchsbaum et al. 1984*a*) or blood flow with xenon inhalation (Ingvar and Franzen 1974; Gur et al. 1985) have not found differences when data from the whole brain or whole cortical surface were averaged together. This lack of whole brain findings is consistent with schizophrenia's more focal symptomatology as compared to the global deficits of dementia, and with the regionality of neurotransmitter systems which are candidates for the diathesis.

Most blood flow imaging studies in schizophrenia have used the radioactive nobel gas, xenon-133, as a tracer. A bolus of the isotope can be injected into the carotid artery in the neck, or the gas inhaled through a face mask, and the time course of the appearance and removal of the isotope recorded by crystal detectors placed at many locations on the scalp. Analysis of the rate of clearance yields an estimate of cerebral blood flow in a region directly underneath the crystal. Two main flow components in the gray matter and the underlying white matter are typ-

ically calculated; gray matter flows have shown the most consistent differences between schizophrenics and controls (Ingvar 1976).

The first study of regional blood flow in schizophrenia (Ingvar and Franzen 1974) tested older schizophrenics doing a visual picture identification task and younger, more cooperative patients doing a visual problem-solving test, Raven's progressive matrices. Patients with alcoholism served as controls. Flow was reduced about 7.6 percent in the frontal cortex in older subjects and 1 percent in younger subjects; in comparison to controls, this difference was not significant (our computation on their table 6). Postcentral regions showed increased flow (6.4 percent and 4.2 percent), in comparison to controls; this difference was also not significant. However, the ratio of frontal to postcentral flow—1.10 in normals, .95 in older schizophrenics, and 1.04 in younger schizophrenics—did significantly differentiate the groups. This was confirmed by ANOVA. Post hoc t tests we calculated on their table 6 reveal that both older (n = 9) and younger (n = 11) schizophrenics differed from controls (t = 5.42, and t = 2.18, respectively, $p < .05$, two-tailed). While this ratio was a post hoc choice initially, we chose it for replication in our PET studies and for comparison of cerebral blood flow (table 2).

Table 2 is constructed to match table 1, calculating frontal/posterior ratios where not given in the articles and using right side, resting data where possible. Blood flow anteroposterior ratios are similar to PET ratios and are lower in schizophrenics in six of seven studies, significantly so in five of seven studies.

Computer Electroencephalographic Topography (CET)

Electrical Signals From the Scalp. The carrying of information from one neuron to the next involves both the chemical transmission at the synapse and the electrical transmission down the axon. We have already described the possibilities for

Table 2. Comparison of cerebral blood flow studies in schizophrenia

Study		Frontal/posterior ratio: Normals	Frontal/posterior ratio: Schizophrenics	Hemisphere	p
(1)	Ingvar & Franzen (1974)	1.10	1.04	L	<.05
(2)	Ingvar & Franzen (1974)	1.10	.95	L	<.05
(3)	Ariel et al. (1983)	1.10	1.05	R	<.05
(4)	Mathew et al. (1982)	1.05	1.00	R	NS[1]
(5)	Chabrol et al. (1986)	1.15	1.01	B	<.05
(6)	Weinberger, Berman & Zec (1986)	1.12	1.07	B	<.05[2]
(7)	Gur et al. (1985)	1.08	1.08	R	NS

	Level	Sample size of schizophrenics	Test condition	Comments
(1)	Pre-rolandic & frontal/postcentral	11	Raven's progressive matrices	Schizophrenics, medicated
(2)	Same	9	Visual identification	Older sample
(3)	Precentral/postcentral	29	Resting	Mostly medicated
(4)	Superior frontal/occipital	23	Resting	Mostly medicated
(5)	Eight frontal detectors/24 posterior detectors	10	Not specified	Adolescents, off medication
(6)	Prefrontal/whole brain	20	Resting	Off medication
(7)	Anterior/posterior	19	Resting	Off medication

[1]Personal communication.
[2]Significantly different by ANOVA, our estimation of ratio from authors' figure 4.

imaging chemical processes in the three dimensions with PET. The electrical processes are more spatially complex, involving long and short neurons sending signals in all directions. Electrical signals can be recorded from the scalp, reflecting the total of these processes, but their anatomical location is consequently somewhat less well defined than with the precise physics of PET. The location of electrical signals is also made uncertain by the amplifiers which yield a signal reflecting the difference in voltage between two electrodes; this method avoids problems of noise and baseline shifts inherent in high gain amplification of biological signals. Thus, the activity at each point on the scalp is displayed as a difference to a reference point chosen to be as neutral and noncontributory as possible. The ear is the most common reference. However, despite the ear's distance from the temporal lobe, some brain activity can still be recorded from it.

Nevertheless, scalp EEG and evoked activity do have a relationship, often close, to underlying brain activity. The alpha rhythm, a smooth, 10-cycle/second pattern of greatest amplitude in the occipital area over visual cortex, is sharply diminished by visual stimuli. A slower alpha over temporal auditory areas is blocked by auditory stimuli (Grillon and Buchsbaum 1985). Correlations between alpha amplitude recorded on scalp over visual cortex and simultaneous PET assessment of glucose metabolic rate (Buchsbaum et al. 1984*b*) demonstrate a close spatial relationship. The relationship between evoked potential recordings from scalp and underlying sensory cortex further supports some scalp/cortex relationship. Recordings on a 1 cm square scalp and separately located cortical areas responding to finger and thumb stimulation (Duff 1980) suggest that considerable detail can be resolved under some controlled conditions. Under other conditions, combinations of long and short neurons, neuronal orientation in the brain's core, and activity closer to the reference site may possibly confound spatial interpretation. Correlations between CT, magnetic resonance imaging, and PET with electrical maps will be an important strategy in determining the accuracy of scalp electrical topography.

Computerized topographic maps are formed by first recording the EEG or evoked potential at 16 or more scalp locations. The amount of activity at each EEG frequency (delta, theta, etc.) is then quantitated by spectral analysis or the evoked potential amplitude measured at a specific latency after the stimulus.

This array of 16 or more data points is now used to construct the topographic map. The outline of the brain is represented as a series of vertical and horizontal coordinates. Typically, a brain outline contains several hundred to several thousand discrete vertical and horizontal locations, like small tiles in a mosaic. Inside the outline, the coordinates of each electrode and the value of the electrophysiological measure are known. These tiles are termed "pixels," or picture elements. Thus, for 16 or so pixels, the value and its corresponding color is known. The remainder must be colored by interpolation. Each pixel's distance to the nearest three or four known values can be calculated, and its approximate value can be predicted based on its relative proximity to these locations. In this way, the entire grid of pixels has values estimated. Next, a color value scale is assigned to the electrophysiological variable and the map is then generated. A description of mapping technique is found in Buchsbaum et al. (1982*d*), and Duffy (1986) presents a wide range of clinical applications and methodological comment.

The advantages of CET over PET need also to be considered. CET is much less costly, does not involve radioisotope administration, can be repeated without additional risk any number of times, and, most importantly, resolves time periods as short as 1–2 seconds for EEG and 1–4 milliseconds for evoked potentials. This is a better than 100-fold improvement above PET with oxygen uptake or blood flow measurement. Resolution may be of the order of 2–4 cm, not greatly different from xenon inhalation blood flow (Buchsbaum et al. 1982).

EEG and evoked potential research in schizophrenia has been reviewed in the *Schizophrenia Bulletin* (Buchsbaum 1977; Itil 1977; Roth 1977; Shagass 1977; Spohn and Patterson 1979). Most studies have not exploited the regional resolution available with EEG but have used a single EEG channel. This review will focus on the new topographic studies and their relationship to the findings with PET and regional cerebral blood flow.

EEG Alpha Activity. Alpha activity is a continuous 10-cycle/second activity which appears over the occipital region when subjects rest with their eyes closed. It is diminished when subjects open their eyes or are alerted by a cognitive task. Alpha is generally decreased in schizophrenia and may be decreased in the offspring of schizophrenics (Abenson 1970; Itil 1977). In the first EEG topography maps in schizophrenia, alpha activity was most decreased at the occiput in unmedicated schizophrenics, in comparison to controls (Buchsbaum et al. 1982*a*). Alpha was also decreased in the four Genain quadruplets (Rosenthal 1963), identical siblings concordant

for schizophrenia (Buchsbaum et al. 1984*c*). Similar topographic reductions in resting alpha were found by Guenther and Breitling (1985). Morihisa, Duffy, and Wyatt (1983) also found decreased alpha in unmedicated schizophrenics. Greatest group discrimination was found with bilateral midtemporal leads, but topographic maps of resting alpha were not presented.

In the initial PET studies, EEG was collected with eyes closed and subjects resting during FDG uptake for PET scanning. Normals showed high glucose use in frontal areas and little glucose use in primary visual areas. Patients with schizophrenia showed relatively high glucose use in occipital cortex. Thus, local regional metabolic changes paralleled the EEG collected simultaneously, as cerebral blood flow has. Jacquy et al. (1980) found high alpha associated with low flow in 21 normal volunteers assessed by rheoencephalography.

Delta Activity. Delta activity is an irregular, 1–5 cycle/second rhythm, typically increased in normals with drowsiness. It has a distribution generally greatest in parietal and temporal cortex, but extending into the occiput as well. Delta increases have been shown in patients with schizophrenia and offspring of schizophrenics (see Spohn and Patterson's 1979 review). Neuroleptics reduce delta in patients with schizophrenia (Lifshitz and Gradijan 1974), consistent with a normalization of the EEG in schizophrenia. In normals, however, delta increases at the occiput are often seen with neuroleptics (e.g., Fink 1974).

Blood flow studies had provided an early link to EEG delta. Using the xenon technique, Ingvar (1976) and Tolonen and Sulg (1981) reported correlations between resting EEG slow activity and blood flow. In our first PET study (Buchsbaum et al. 1982*b*), we chose the eyes closed/resting condition for FDG uptake to match the earlier Ingvar studies and to allow comparable resting EEG to be recorded. These studies (Buchsbaum et al. 1982*a*) revealed an increase in delta activity in the frontal lobes of patients with schizophrenia, an electrophysiological correlate of the hypofrontal metabolic pattern observed and consistent with the earlier hypofrontal cerebral blood flow studies (Ingvar and Franzen 1974). Three subsequent topographic studies confirmed the pattern of elevated frontal delta activity (Morihisa, Duffy, and Wyatt 1983; Morstyn, Duffy, and McCarley 1983; Guenther and Breitling 1985; Morihisa and McAnulty 1985).

The correlation between high delta and low glucose metabolic rate seen with PET was consistent with the association of delta and drowsiness. However, delta increases were seen in normals given sensory motor tasks (Guenther and Breitling 1985); increases were observed to be smaller in the schizophrenic subjects. The study of Morstyn, Duffy, and McCarley (1983) adds tasks, but the direction of delta effects is not given.

Other authors (e.g., Lifshitz and Gradijan 1972) have interpreted delta as indicating lower levels of cortical arousal in schizophrenics. Data showing that neuroleptics decrease delta in schizophrenics have been taken to support the arousal concept, based on "sedating" properties of neuroleptics. This putative sedation is especially unclear in the schizophrenic whose psychomotor task performance is typically enhanced by neuroleptics. Spohn and Patterson (1979) reject this view as based on an oversimplified concept of "arousal." Added to this controversy must now be the apparent oversimplication of delta as a unitary effect across the cortical surface. Further, the data of Lifshitz and Gradijan (1974) suggest that acute medication withdrawal may increase delta. Region of recording, task condition, and medication treatment of the patient must all be controlled for clear interpretation of the direction of effects. Nevertheless, all three topographic studies find a schizophrenic-normal difference in frontal leads.

Evoked Potentials. The recording of the brain's specific response to a sensory signal is a useful correlate of underlying information-processing disturbances seen in schizophrenia (see Buchsbaum 1977; Spohn and Patterson 1979; Zubin et al., in press). Diminished evoked potential amplitude has generally been observed in schizophrenia with early multilead studies showing more posterior amplitude maxima (Shagass et al. 1980). Initial topographic maps of selective attention enhancement of evoked potential amplitude showed a temporoparietal, rather than frontal, difference between normals and schizophrenics, however (Buchsbaum et al. 1982*c*). A somatosensory stimulus produced topographic differences in somatosensory cortex (Buchsbaum et al. 1986*a*), suggesting the importance of stimulus modality and task for locale of EP differences.

Anatomical Imaging With X-Ray Computed Tomography (CT) and Magnetic Resonance Imaging (MRI)

CT Imaging. Like PET scanning, CT images are formed by tomographic reconstruction of a radiation beam. Here, however, the x-ray beam source is external, rather than internal, isotopes and the image is of

x-ray density. Structures dense to x-rays (skull) appear as low values (while on film) and structures which pass x-rays (cerebrospinal fluid) appear black. Tissue values are close to fluid values, but the outlines of the ventricular cavity can be seen. The similarity in x-ray density between gray and white matter produces a salt and pepper texture over the tissue areas. Normally, the space between cortical gyri is small and not visible, but if gyri atrophy, a fluid-filled sulcal space becomes visible. A number of studies have indicated enlargement of the ventricles and sulcal atrophy (see Meltzer, in this *Special Report;* Maser and Keith 1983; Weinberger, Wagner, and Wyatt 1983). While ventricular enlargement provides no direct evidence about shrinkage of a particular part of the brain, the regional distribution of sulcal atrophy can be examined.

Frontal, rather than general, atrophy was found to characterize patients with schizophrenia in the first examination of specific lobes (Doran et al. 1985). The actual x-ray attenuation values can also be examined as an index of brain density. Anterior, rather than posterior, density decreases were seen by Golden et al. (1981), averaging over large brain regions. However, increased density in right anterior white matter was found by Largen and coworkers (Largen, Calderon, and Smith 1983; Largen et al. 1984), a finding interpreted as consistent with fibrillary gliosis, which might follow a history of chronic inflammation, possibly from viral infection. Both of these findings follow the anatomical pattern seen in the PET and blood flow studies described above.

CT scanning can produce measures of blood flow by producing a series of rapid scans following the injection of a bolus of x-ray dense solution intravenously (e.g., Hypaque). Rate of contrast washout can be measured and interpreted as flow. Recently, Dysken et al. (1987) noted abnormally delayed washout in a group of patients with schizophrenia and suggested that areas of increased blood-brain barrier could be involved. No particular brain region was identified as most likely to show this deficit.

Three studies have examined the relationship of VBR and metabolic rate assessed by PET. Buchsbaum et al. (1982*b*) found a correlation of ($-.42$ between anterior/posterior ratio and VBR, which was of marginal statistical significance. Jernigan et al. (1985) found similar and significant negative correlations ($-.56$ on the right) between frontal slice ratios and ventricular size. Lastly, Kling et al. (1986) reported negative but nonsignificant regression coefficients for VBR and posterior inferior frontal and posterior superior temporal cortex.

Magnetic Resonance Imaging. The morphological limitations of CT are broken with the sensitivity of MRI to gray and white matter distinctions. A high-strength magnetic field orients the hydrogen atoms in the brain. Oriented, their resonant echo to radio frequency pulses can be detected and constructed into an image using techniques similar to those for PET and CT. MRI opens the possibility of assessing the physical dimensions of the brain's nuclei as well as the regional distribution of the hydrogen atom signals under a variety of pulse conditions. The physiological significance of these quantitative signal-intensity measures is not fully understood, but regional differences between normals and schizophrenics may still identify target structures for further neuropsychological, neuroendocrine, or functional imaging studies.

The first MRI study in schizophrenia was by Smith et al. (1984). In this small sample (nine patients and five normals), neither area measurements nor signal intensity regional assessments showed significant differences. In a followup with a larger sample (Smith et al. 1987), decreased values in anterior frontal white matter and temporal white matter were found. Patients showed a right greater than left temporal asymmetry.

In a study aimed specifically at the frontal lobe, Andreasen et al. (1986) found schizophrenics to have significantly smaller frontal lobes as well as smaller cerebrums and craniums, a finding associated with cognitive impairment.

The combination of anatomical MRI with PET, cerebral blood flow, and EEG imaging will provide opportunities for cross-validation of regional changes, evaluation of the significance of anatomical size and density, and unprecedented precision in studies heretofore never available in life.

The future of MRI includes the possibility of creating images of other atoms. The much lower concentrations of suitable atomic nuclei such as phosphorous make imaging difficult. Tracers such as fluorine-19 for fluorodeoxyglucose (Kanazawa et al. 1986) or a nitroxide stable free radical (Coffman et al. 1985) may be adaptable to imaging as magnetic field strengths, field uniformity, and pulse precision are enhanced.

Future Strategies

For metabolic and cerebral blood flow imaging, the key scientific problem may be the selection of the task for the schizophrenic during imaging. The task must exercise the

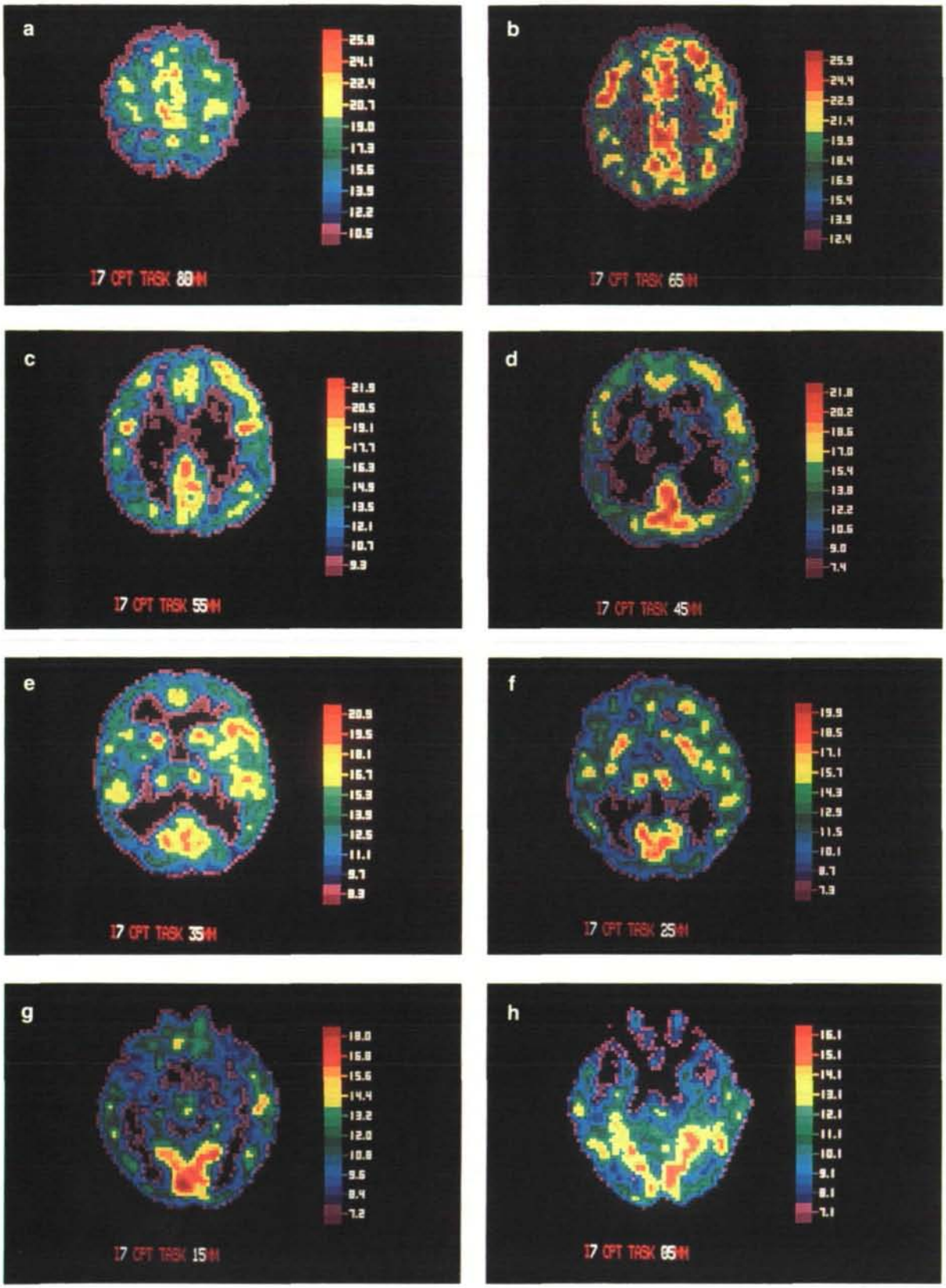

Figure 1*a–h.* Positron emission tomography in a normal subject

This figure shows 8 successive levels of the brain. The subject is doing the continuous performance task (Nuechterlein 1983) during the 35-minute isotope uptake period. Red areas show the highest rate of glucose metabolism. *(a)* Topmost slice, largely gray matter. *(b)* Cortical gray matter ring is active with lower metabolic rate in the white matter of the centrum semiovale. *(c)* & *(d)* Slices above the ventricles and basal ganglia; large inactive areas are largely white matter. *(e)* & *(f)* Show the basal ganglia & thalamus activity in the center. *(g)* Infraventricular level; primary visual cortex is active. *(h)* Bottom of visual cortex & top of cerebellum appear.

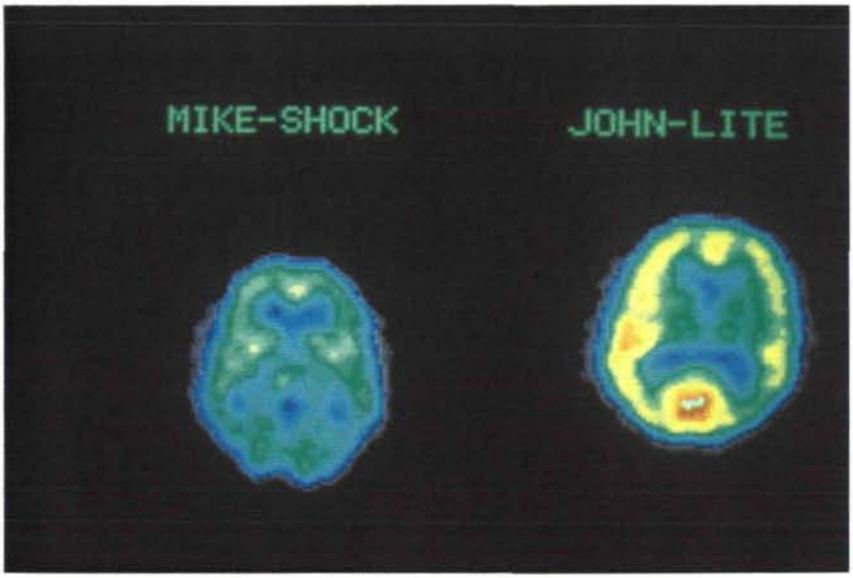

Figure 2. Task effects in normal identical adult twins

During deoxyglucose uptake, John is counting a series of light flashes, while Mike is resting with eyes closed receiving a series of brief electrical shocks to his left forearm—the same stimulation used in earlier schizophrenia studies (Davis et al. 1979). Note visual cortex activation in John (bottom of slice) which is absent in Mike, who shows activity in left thalamus, final relay to cortex.

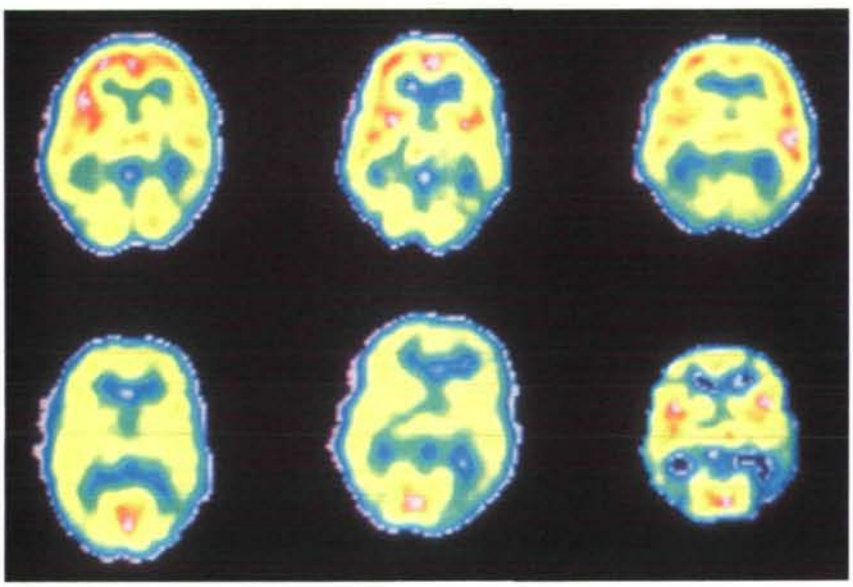

Figure 3. Visual & somatosensory stimulation

Three normal subjects doing shock task (top row) compared to 3 normal subjects doing visual vigilance task (bottom row). Note thalamus activation (top) and visual cortex activation (bottom).

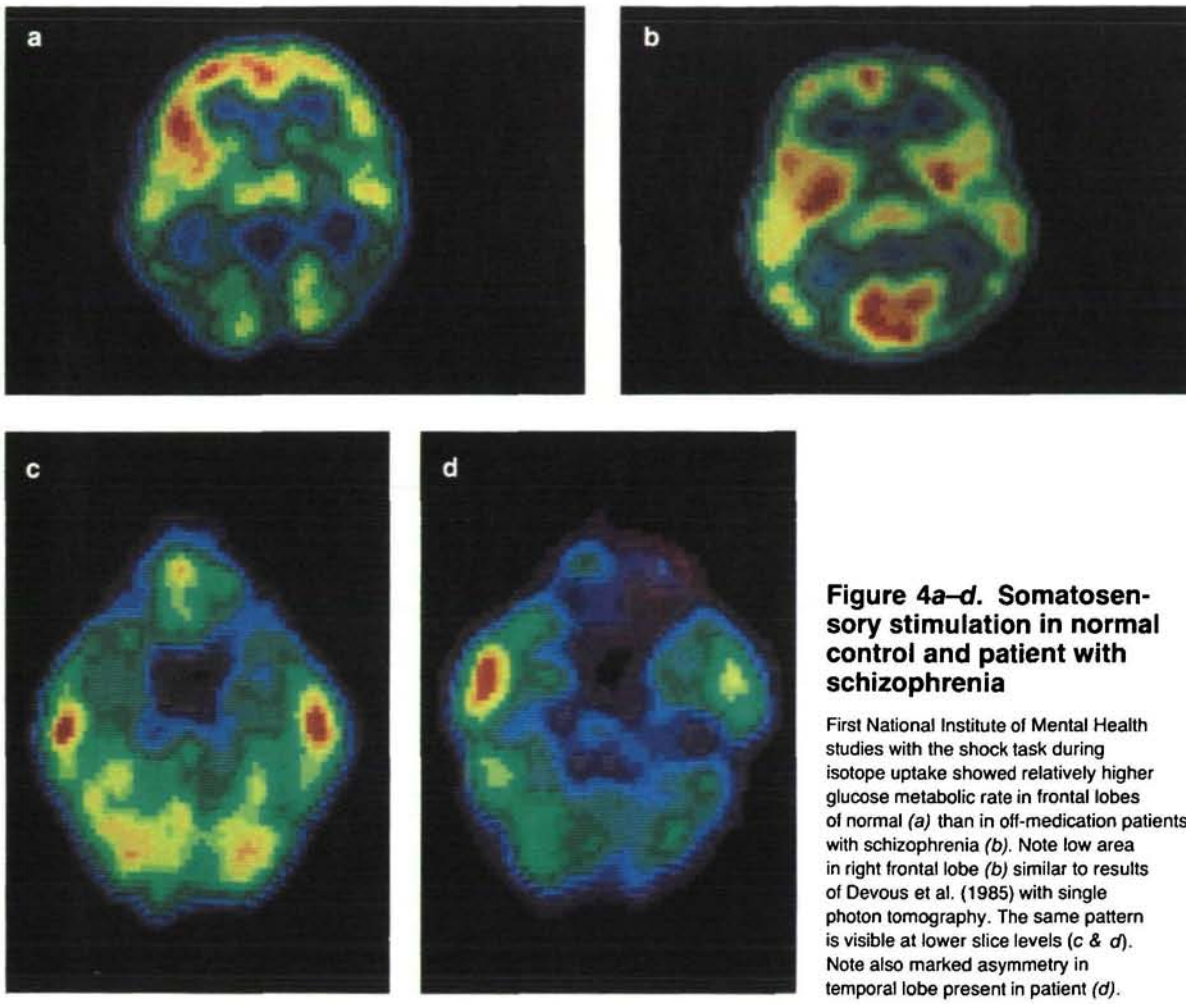

Figure 4*a–d*. Somatosensory stimulation in normal control and patient with schizophrenia

First National Institute of Mental Health studies with the shock task during isotope uptake showed relatively higher glucose metabolic rate in frontal lobes of normal *(a)* than in off-medication patients with schizophrenia *(b)*. Note low area in right frontal lobe *(b)* similar to results of Devous et al. (1985) with single photon tomography. The same pattern is visible at lower slice levels (*c* & *d*). Note also marked asymmetry in temporal lobe present in patient *(d)*.

Figure 5. Genain quadruplets

These sisters are genetically identical and concordant for schizophrenia (Rosenthal 1963). They have been studied at the National Institute of Mental Health over the last 20 years.

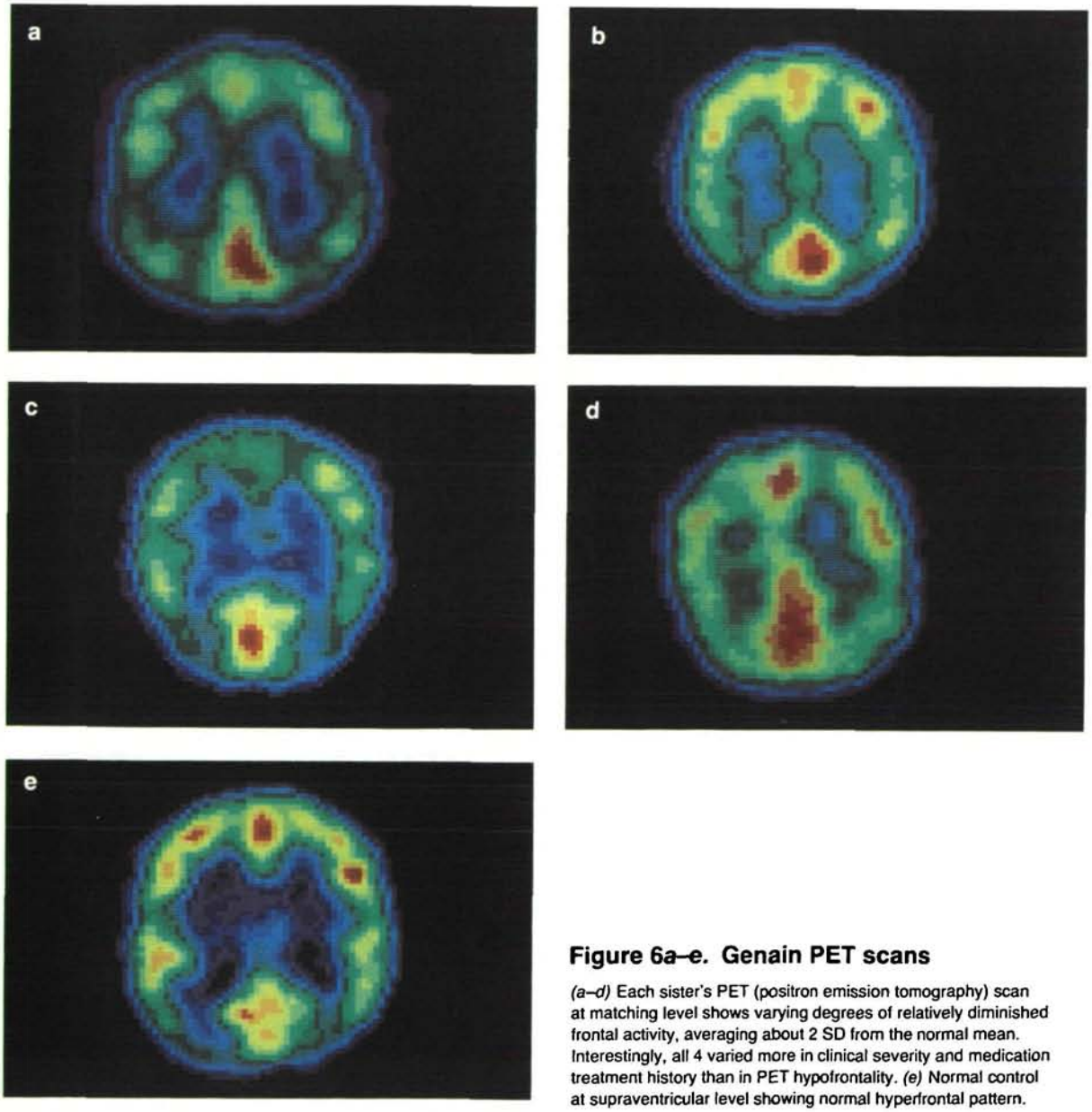

Figure 6a–e. Genain PET scans

(a–d) Each sister's PET (positron emission tomography) scan at matching level shows varying degrees of relatively diminished frontal activity, averaging about 2 SD from the normal mean. Interestingly, all 4 varied more in clinical severity and medication treatment history than in PET hypofrontality. *(e)* Normal control at supraventricular level showing normal hyperfrontal pattern.

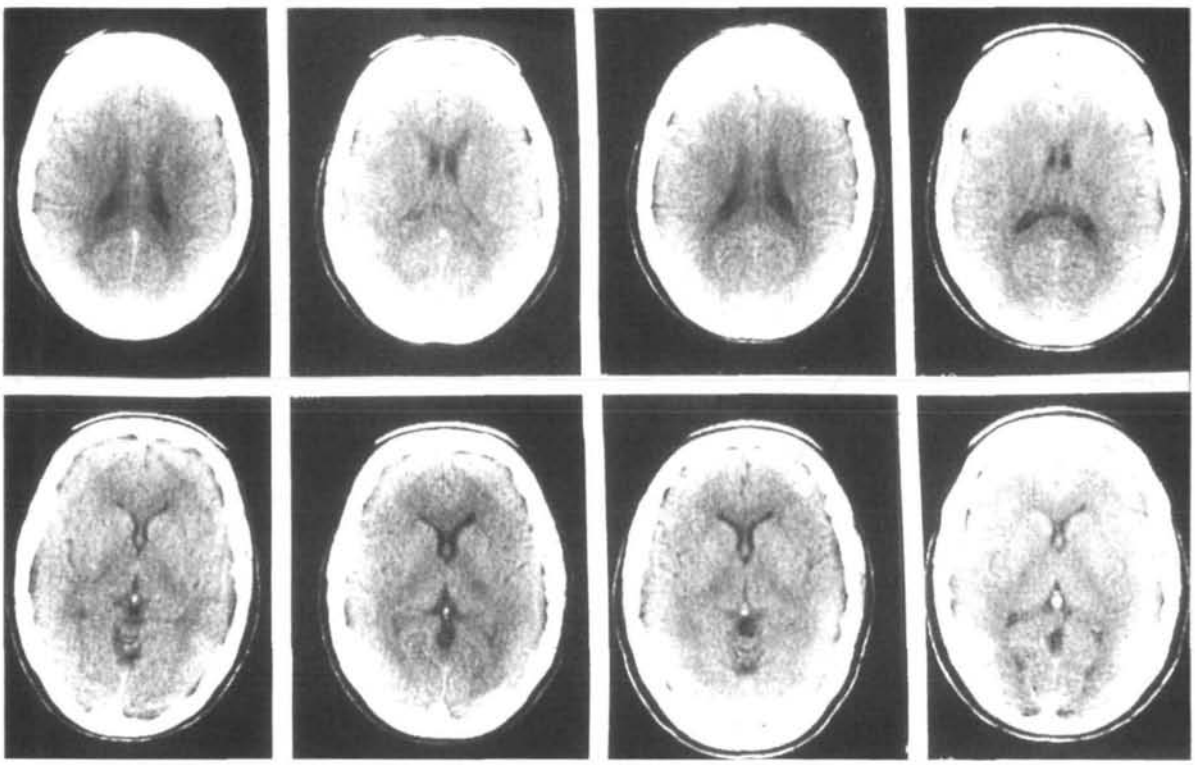

Figure 7. Computed tomography on Genain quadruplets

Scans on 2 levels reveal remarkable anatomical similarity. Ventricular size is not enlarged (Buchsbaum et al. 1984*b*).

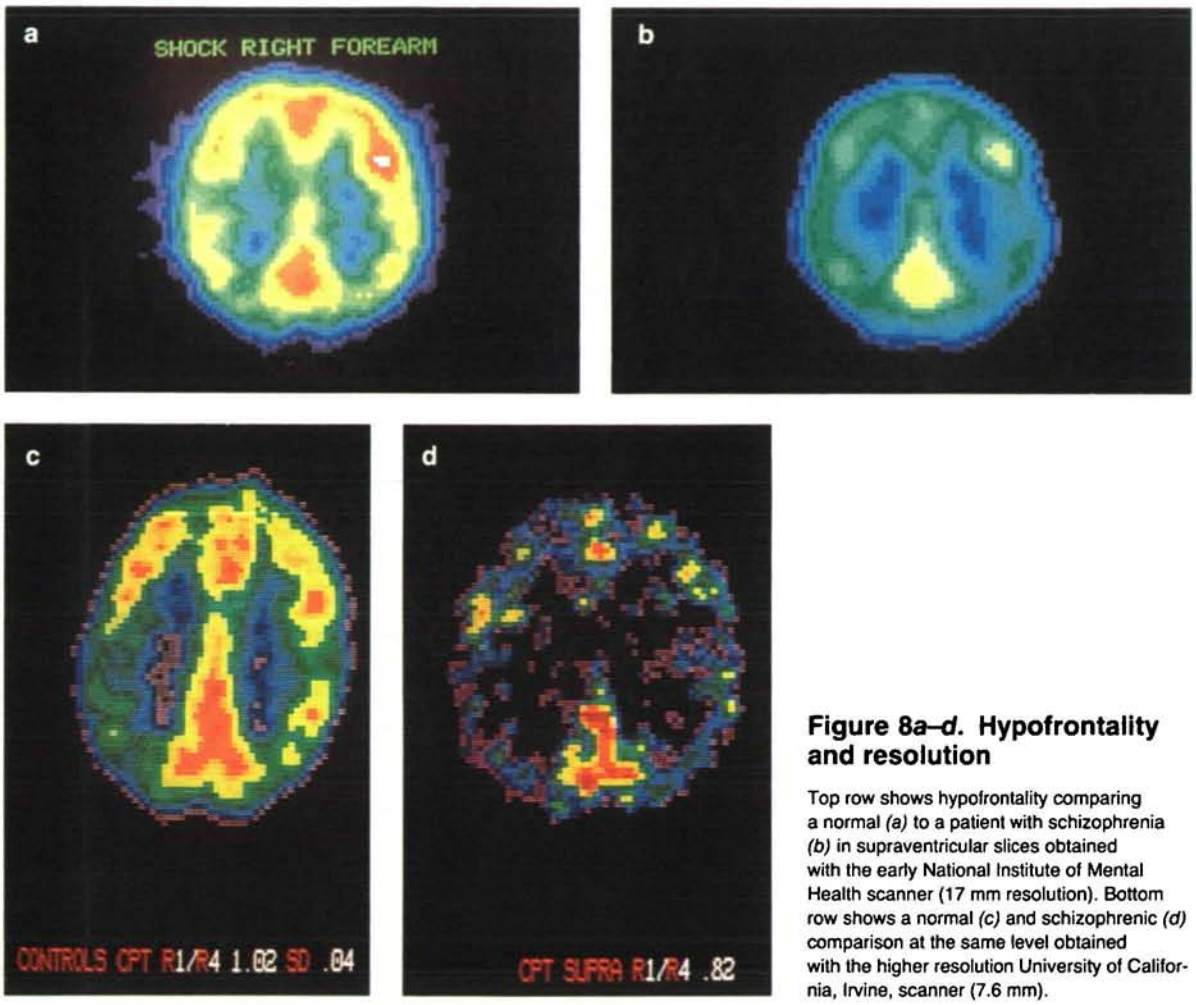

Figure 8a–*d*. Hypofrontality and resolution

Top row shows hypofrontality comparing a normal *(a)* to a patient with schizophrenia *(b)* in supraventricular slices obtained with the early National Institute of Mental Health scanner (17 mm resolution). Bottom row shows a normal *(c)* and schizophrenic *(d)* comparison at the same level obtained with the higher resolution University of California, Irvine, scanner (7.6 mm).

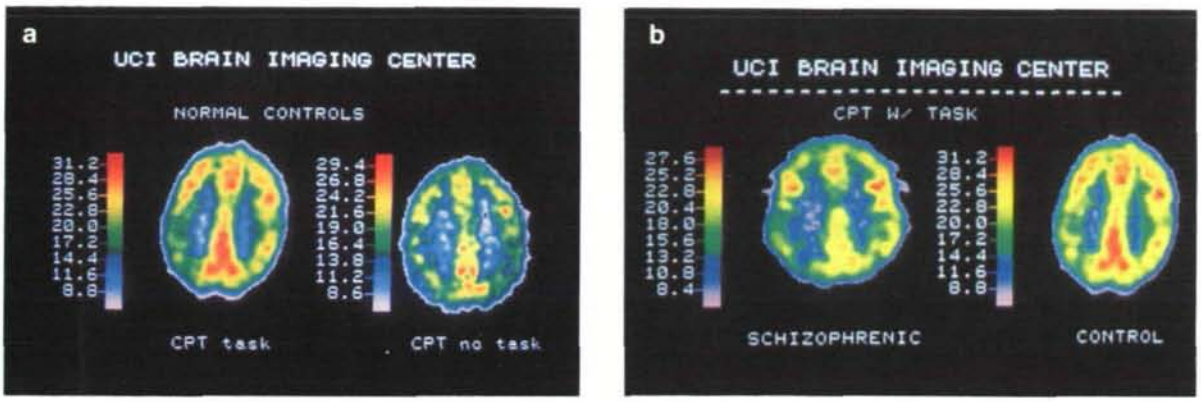

Figure 9a–b. Continuous performance test

Poor performance on this visual vigilance task has been found in many schizophrenics. *(a)* Normal subject performing task (left) compared to normal subject viewing stimuli passively without task instructions (right). *(b)* Schizophrenics doing the task are more similar to normals doing the control task. Schizophrenic performance is poor but significantly above chance levels.

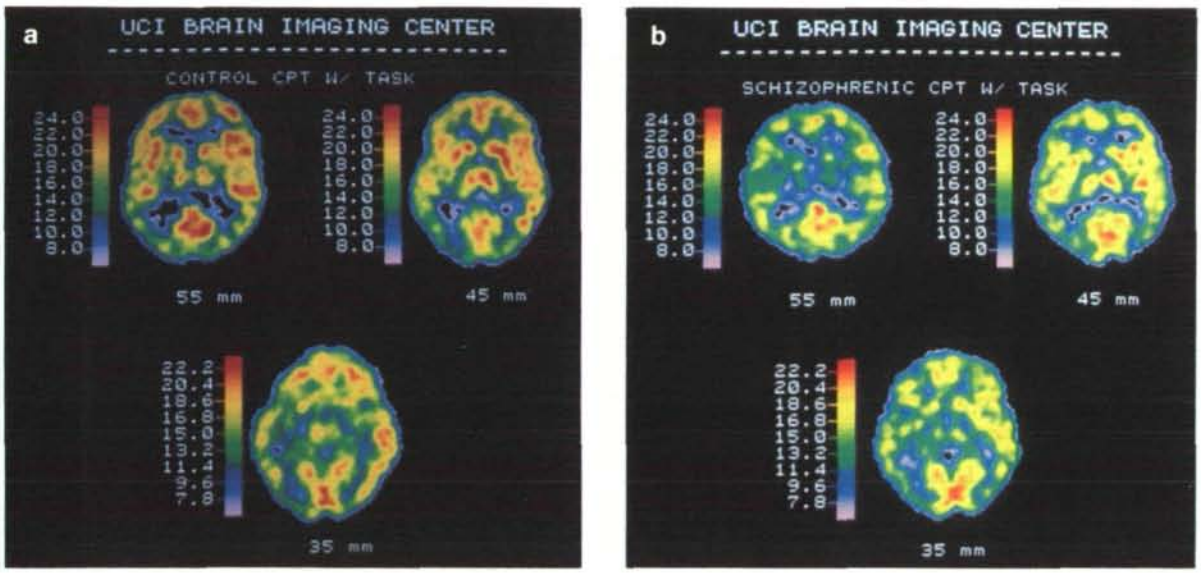

Figure 10a–b. Extent of hypofrontality

(a) In most normals, frontal regions are relatively metabolically active from superior to inferior level. *(b)* Hypofrontality in schizophrenics varies, in some individuals appearing widely at several levels as in this example.

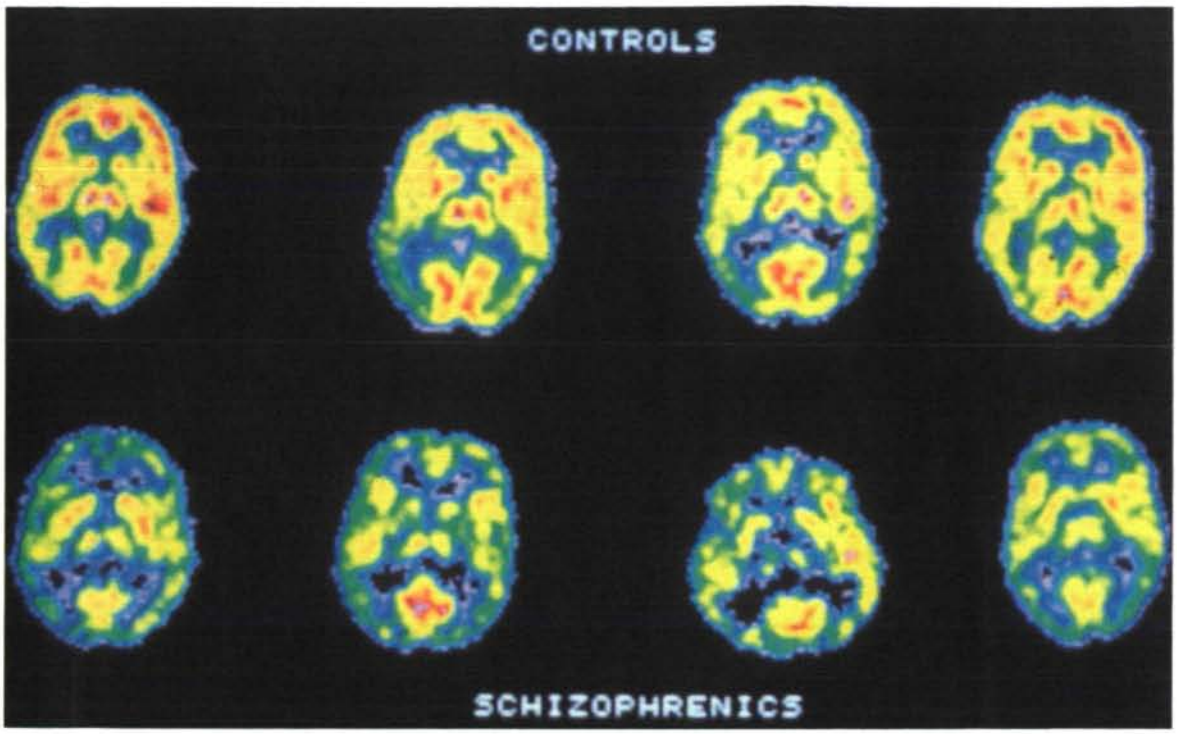

Figure 11. Individual variation in positron emission tomography (PET) scans

Four normal individuals (top row) and 4 schizophrenics (bottom row) show range of hypofrontality and diminished basal ganglia metabolism.

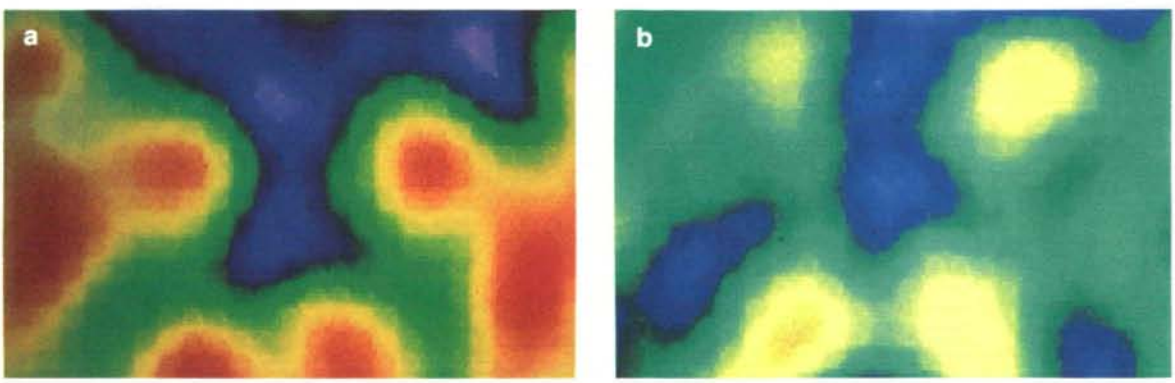

Figure 12*a–b*. Basal ganglia in normal and schizophrenic subjects

Normal *(a)* shows active caudate; contrast with less active patient *(b)*.

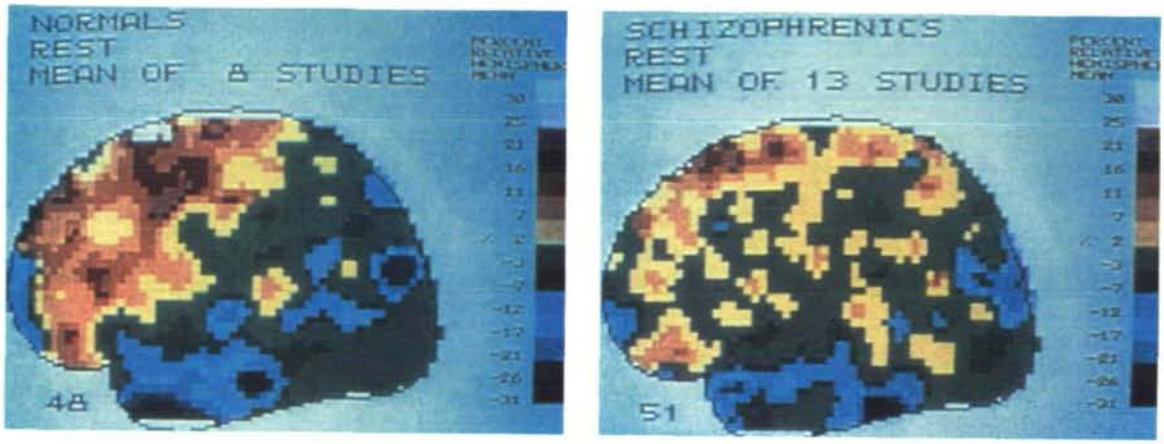

Figure 13. Cerebral blood flow

Normals have increased flow in frontal lobes relative to posterior region. Patients with schizophrenia show diminished gradient from front to back, paralleling the positron emission tomography findings. (Photo courtesy D. Ingvar.)

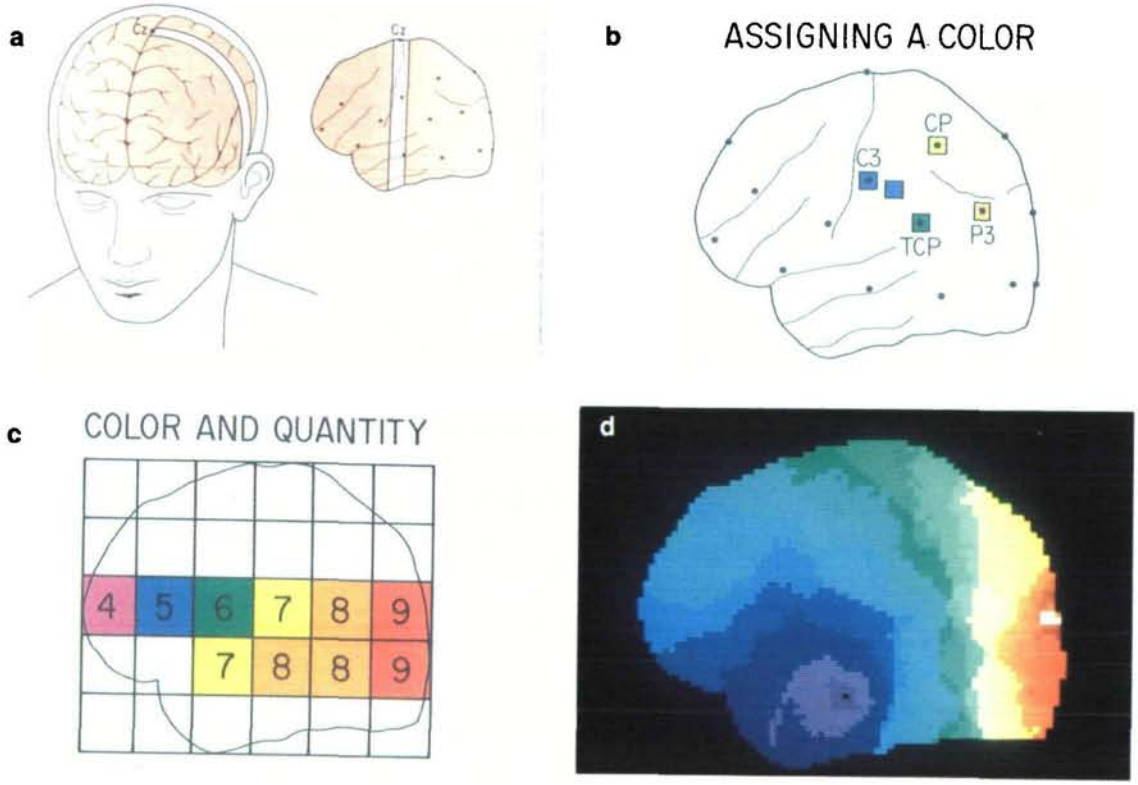

Figure 14*a–d*. Computer electroencephalographic topography (CET)

(a) Brain map outline is developed from coronal slice-by-slice approximate equal area projection. *(b)* Brain activity is measured at ≥ 16 electrode locations and approximated at intervening locations by interpolation. *(c)* Measured activity is expressed in a color scale with each quantitative level corresponding to a color. *(d)* Finished map of the alpha rhythm showing high activity over the occipital cortex in this average of 16 subjects resting with eyes closed.

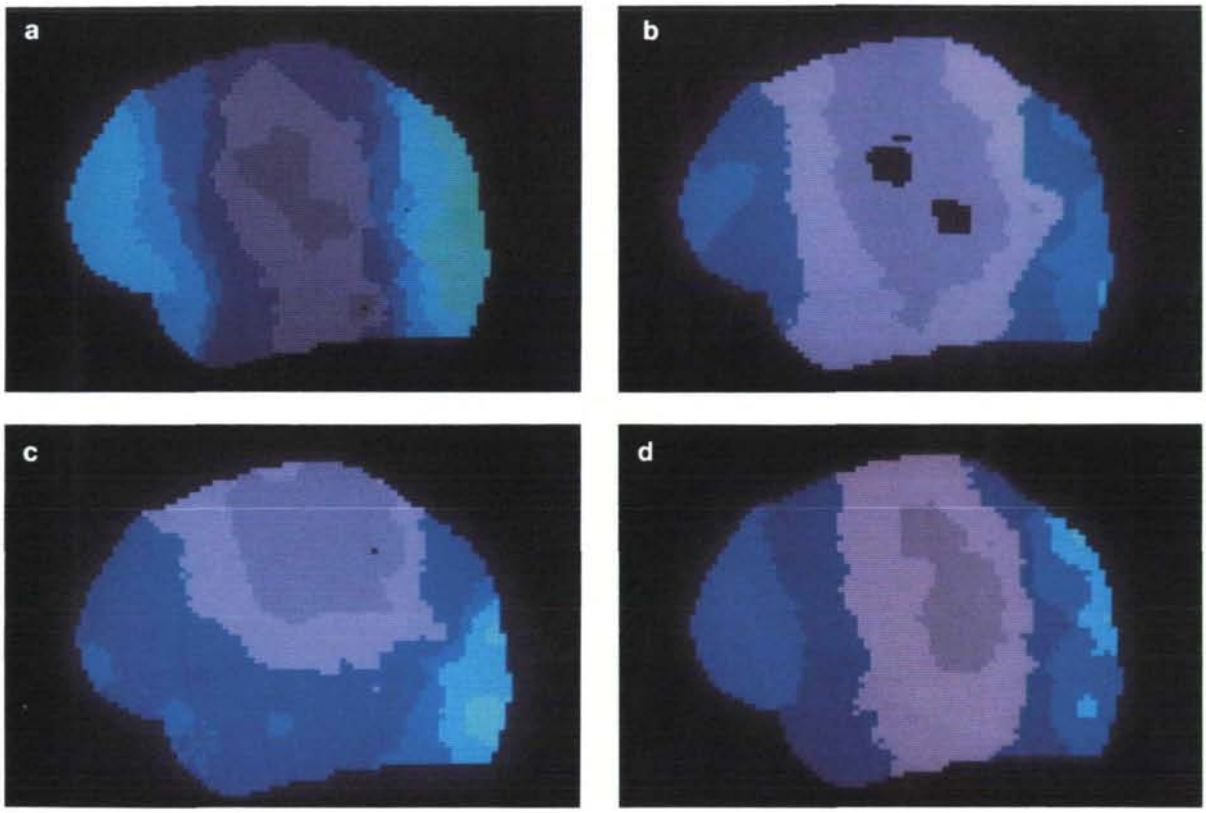

Figure 15*a–d*. Alpha CET maps in the Genain quadruplets

CET = computer electroencephalographic activity. Low levels of alpha activity are seen in all 4 sisters in comparison to the normal of illustration figure 14*d*.

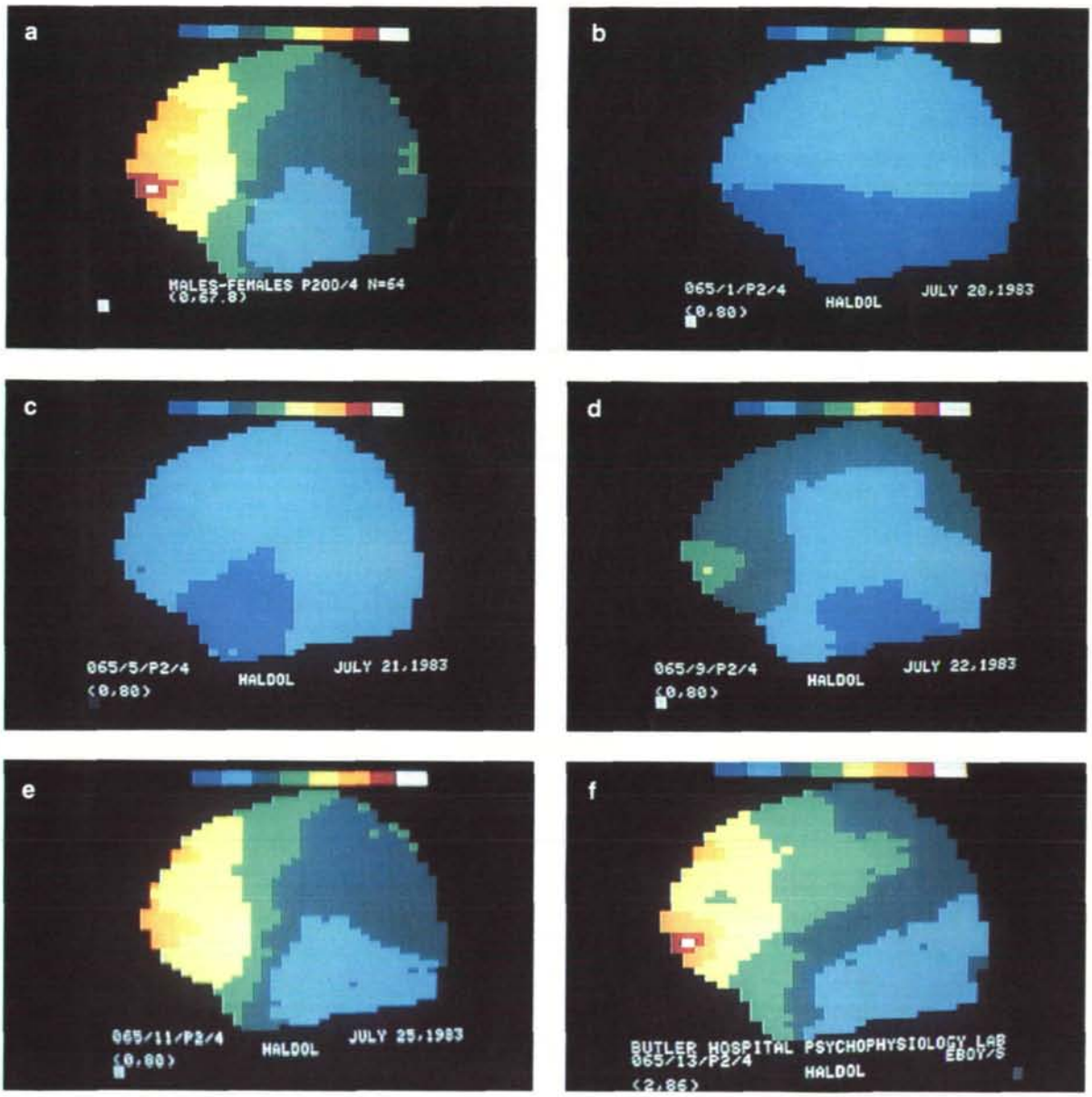

Figure 16*a–f*. Evoked potential topography and drug response

(a) The distribution of visual P_{200} evoked potential (EP) amplitude is shown for a group of 64 normal men and women. Largest amplitudes are over frontal regions and smallest over temporal lobe. The same EP map is shown for a schizophrenic patient off medication *(b)*, 1 hour after a first dose of haloperidol *(c)*, 24 hours on medication *(d)*, 4 days on medication *(e)*, and 7 days on medication *(f)*. Note increasing amplitudes in frontal lobes (Haier & Braden, submitted for publication)

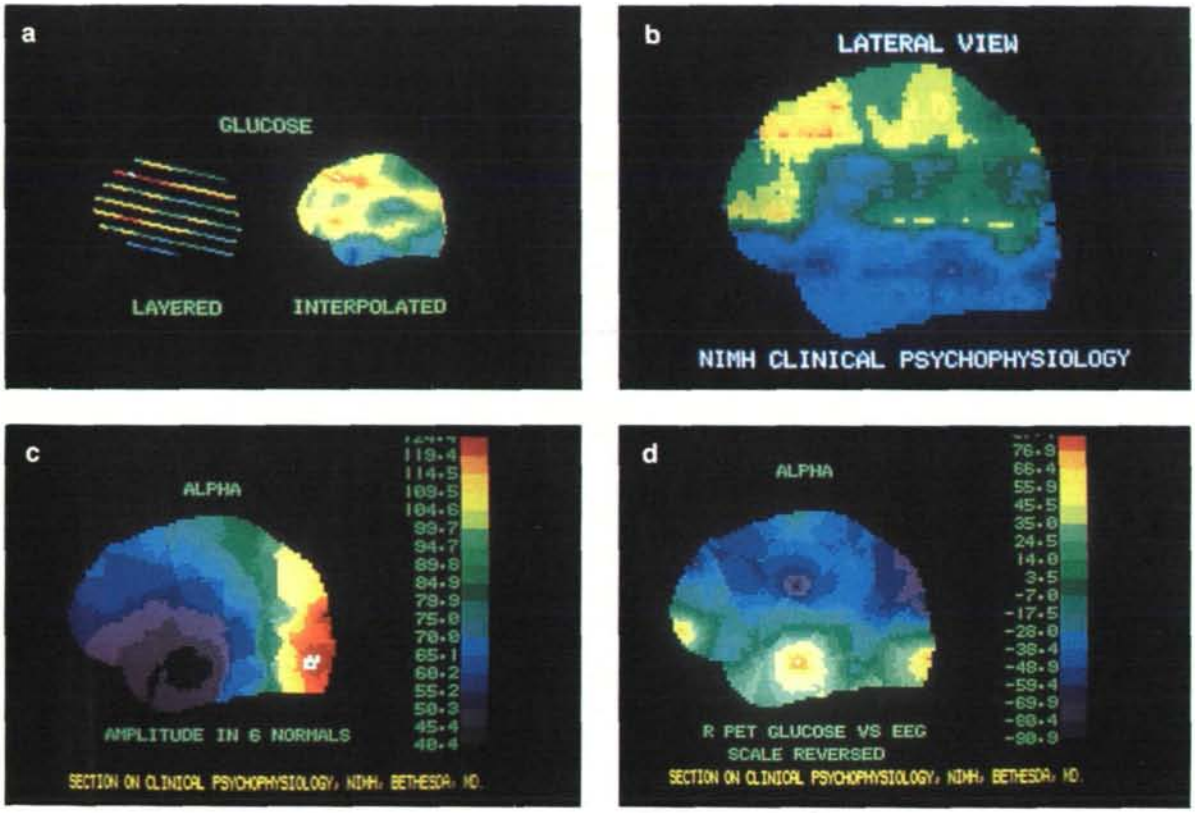

Figure 17*a–d*. Relationship between electroencephalographic (EEG) alpha and glucose metabolism

(a) Positron emission tomography (PET) slice edges representing cortical metabolic rate are peeled from consecutive PET slices and conformed to lateral view EEG map (Buchsbaum et al. 1984*b*). *(b)* Lateral view of glucose metabolic rate constructed as in *(a)*. Note similarity to cerebral blood flow images in figure 13. Frontal lobes show highest rates of glucose metabolism with lower rates in the posterior regions. *(c)* Alpha activity in 6 volunteers resting with eyes closed; scale is microvolts $\times 10$. *(d)* Map of correlation between glucose metabolic rate and alpha activity shows high metabolic rate coupled to low alpha levels. Scale is correlation coefficient $\times 100$, with scale reversed so that high values are negative. This reveals that for the occipital and temporal regions, high alpha is associated with low metabolic rate, consistent with the usual psychophysiological interpretation of alpha as an idling brain rhythm.

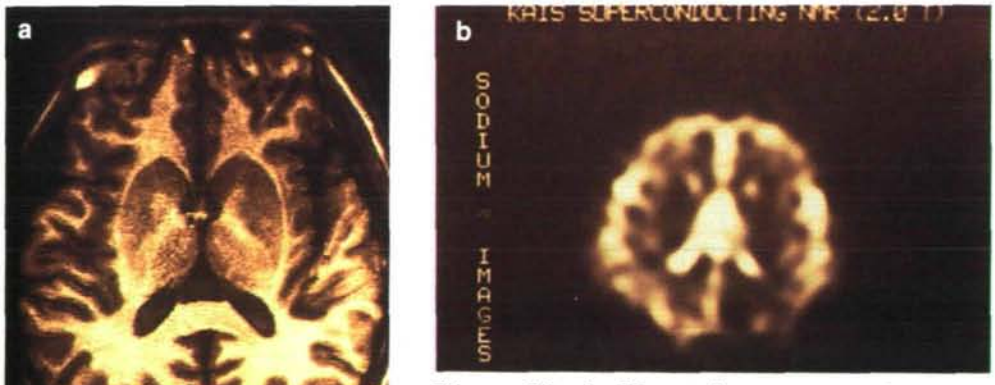

Figure 18a–b. Magnetic resonance imaging (MRI)

(a) Horizontal section through the basal ganglia reveals high level of anatomical detail in the basal ganglia. *(b)* First images of Sodium-23 in the human head reveal potential of MRI for physiological imaging. (Photo courtesy Z. Cho.)

brain in the area of deficit to reveal the differences between normals and patients. Tasks performed by patients in brain areas other than the one used by normals may prove revealing of adaptation to deficit by brain area, neurotransmitter, and cognitive strategy.

For receptor imaging, interpretation of the meaning of the isotope concentration numbers obtained remains an important methodological problem. Artifacts of previous and current neuroleptic exposure will need to be explored as part of these investigations.

For EEG imaging, interpretation of the physical source of signals remains a major methodological issue, although task selection is also critical.

For all imaging approaches to schizophrenia, the problem of biological heterogeneity needs consideration. Clinical response to neuroleptics, catecholamine measures in cerebrospinal fluid, blood, and urine, and neuroendocrine challenge tests have all indicated that considerable individual differences occur among schizophrenics. PET studies, because of their expense and technical complexity, tend to have especially small sample sizes and thus may be initially disappointing in schizophrenia. The varied data of tables 1 and 2 are typical of many biological markers. These important early studies develop the technology and prepare the research teams for the larger sample size studies to come. This later cohort of studies can address the individual who responds to neuroleptics, has low cerebrospinal fluid homovanillic acid, dilated ventricles, attentional deficits, paranoid symptoms, low platelet monomine oxidase, or other markers of a biologically homogeneous grouping. From such studies, functional brain imaging may develop as the clinician's tool to select and monitor drugs, to predict outcome, and guide rehabilitation and educational psychotherapies.

References

Abenson, M.H. EEGs in chronic schizophrenia. *British Journal of Psychiatry*, 116:421–425, 1970.

Andreasen, N.; Nasrallah, H.A.; Dunn, V.; Olson, S.C.; Grove, W.M.; Ehrhardt, J.C.; Coffman, J.A.; and Crossett, J.H.W. Structural abnormalities in the frontal system in schizophrenia. *Archives of General Psychiatry*, 43:136–144, 1986.

Ariel, R.N.; Golden, C.J.; Berg, R.A.; Quaife, M.A.; Dirksen, J.W.; Forsell, T.; Wilson, J.; and Graber, B. Regional cerebral blood flow in schizophrenics. *Archives of General Psychiatry*, 40:258–263, 1983.

Asarnow, R.F.; Steffy, R.A.; MacCrimmon, D.J.; and Cleghorn, J.M. An attentional assessment of foster children at risk for schizophrenia. *Journal of Abnormal Psychiatry*, 6:267–275, 1977.

Baron, J.C.; Lebrun-Grandie, Ph.; Collard, Ph.; Crouzel, C.; Mestelan, G.; and Bousser, M.G. Noninvasive measurement of blood flow, oxygen consumption, and glucose utilization in the same brain regions in man by positron emission tomography: Concise communication. *The Journal of Nuclear Medicine*, 23:391–399, 1982.

Baron, J.C.; Maziere, B.; Loc'h, C.; Sgouropoulos, P.; Bonnet, A.M.; and Agid, Y. Progressive supranuclear palsy: Loss of striatal dopamine receptors demonstrated in vivo by positron tomography. *Lancet*, I: 1163–1164, 1985.

Baxter, L.R.; Phelps, M.E.; Mazziotta, J.C.; Schwartz, J.M.; Gerner, R.H.; Selin, C.E.; and Sumida, R.M. Cerebral metabolic rates for glucose in mood disorders (studies with positron emission tomography and fluorodeoxyglucose F 18). *Archives of General Psychiatry*, 42:441–447, 1985.

Benes, F.M.; Davidson, J.; and Bird, E.D. Quantitative cytoarchitectural studies of the cerebral cortex of schizophrenics. *Archives of General Psychiatry*, 43:31–35, 1986.

Brownell, G.L.; Budinger, T.F.; Lauterbur, P.C.; and McGeer, P.L. Positron tomography and nuclear magnetic resonance imaging. *Science*, 215:619–626, 1982.

Buchsbaum, M.S. The middle evoked response components and schizophrenia. *Schizophrenia Bulletin*, 3:93–104, 1977.

Buchsbaum, M.S.; Awsare, S.V.; Holcomb, H.H.; DeLisi, L.E.; Hazlett, E.; Carpenter, W.T., Jr.; Pickar, D.; and Morihisa, J.M. Topographic differences between normals and schizophrenics: The N120 evoked potential component. *Neuropsychobiology* 15:1–6, 1986*a*.

Buchsbaum, M.S.; Cappelletti, J.; Coppola, R.; Rigal, F.; King, A.C.; and van Kammen, D.P. New methods to determine the CNS effects of antigeriatric compounds: EEG topography and glucose use. *Drug Development Research*, 2:489–496, 1982*a*.

Buchsbaum, M.S.; DeLisi, L.E.; Holcomb, H.H.; Cappelletti, J.; King, A.C.; Johnson, J.; Hazlett, E.; Dowling-Zimmerman, S.; Post, R.M.; Morihisa, J.; Carpenter, W.T., Jr.; Cohen, R.; Pickar, D.; Weinberger, D.R.; Margolin, R.; and Kessler, R.M. Anteroposterior gradients in cerebral glucose use in schizophrenia and affective disorders. *Archives of General Psychiatry*, 41:1159–1166, 1984*a*.

Buchsbaum, M.S.; Ingvar, D.H.;

Kessler, R.; Waters, R.N.; Cappelletti, J.; van Kammen, D.P.; King, A.C.; Johnson, J.L.; Manning, R.G.; Flynn, R.W.; Mann, L.S.; Bunney, W.E., Jr.; and Sokoloff, L. Cerebral glucography with positron tomography: Use in normal subjects and in patients with schizophrenia. *Archives of General Psychiatry*, 39:251–259, 1982*b*.

Buchsbaum, M.S.; Kessler, R.; King, A.; Johnson, J.; and Cappelletti, J. Simultaneous cerebral glucography with positron emission tomography and topographic electroencephalography. In: Pfurtscheller, G.; Jonkman, E.J.; and Lopes da Silva, F.H., eds. *Brain Ischemia: Quantitative EEG and Imaging Techniques: Progress in Brain Research*. Amsterdam: Elsevier Science Publishers, 1984*b*. pp. 263–269.

Buchsbaum, M.S.; King, A.C.; Cappelletti, J.; Coppola, R.; and van Kammen, D.P. Visual evoked potential topography in patients with schizophrenia and normal controls. *Advances in Biological Psychiatry*, 9:50–56, 1982*c*.

Buchsbaum, M.S.; Mirsky, A.F.; DeLisi, L.E.; Morihisa, J.; Karson, C.R.; Mendelson, W.B.; King, A.C.; Johnson, J.; and Kessler, R. The Genain quadruplets: Electrophysiological, positron emission and x-ray tomographic studies. *Psychiatry Research*, 13:95–108, 1984*c*.

Buchsbaum, M.S.; Rigal, F.; Coppola, R.; Cappelletti, J.; King, A.C.; and Johnson, J. A new system for gray-level surface distribution maps of electrical activity. *Electroencephalography and Clinical Neurophysiology*, 53:237–242, 1982*d*.

Buchsbaum, M.S.; Wu, J.C.; DeLisi, L.E.; Holcomb, H.H.; Hazlett, E.; Cooper-Langston, K.; and Kessler, R. Positron emission tomography studies of basal ganglia and somatosensory cortex neuroleptic drug effects: Differences between normal controls and schizophrenic patients. *Biological Psychiatry*, in press.

Buchsbaum, M.S.; Wu, J.; DeLisi, L.E.; Holcomb, H.; Kessler, R.; Johnson, J.; King, A.C.; Hazlett, E.; Langston, K.; and Post, R.M. Frontal cortex and basal ganglia metabolic rates assessed by positron emission tomography with (^{18}F) 2-deoxyglucose in affective illness. *Journal of Affective Disorders*, 10:137–152, 1986*b*.

Bustany, P.; Henry, J.F.; Rotrou, J.; Singnoret, P.; Cabanis, E.; Zarifian, E.; Ziegler, M.; Derlon, J.M.; Crouzel, C.; Soussaline, F.; and Comar, D. Correlations between clinical state and PET measurement of local brain protein synthesis in Alzheimer's dementia, Parkinson's disease, schizophrenia and gliomas. In: Greitz, T.; Ingvar, D.H.; and Widen, L., eds. *The Metabolism of the Human Brain Studied with Positron Emission Tomography*. New York: Raven Press, 1985. pp. 241–250.

Chabrol, H.; Guell, A.; Bes, A.; and Moron, P. Cerebral blood flow in schizophrenic adolescents. *American Journal of Psychiatry*, 143:130, 1986.

Coffman, J.A.; Barfknecht, C.F.; Neff, N.; Hunter, W.; and Dunn, V. "Benzodiazepine Receptor Site Imaging by Magnetic Resonance Techniques." Presented at the Annual Meeting of the American College of Neuropsychopharmacology, Maui, HI, December 9–13, 1985.

Comar, D.; Zarifian, E.; Verhas, M.; Soussaline, F.; Maziere, M.; Berger, G.; Loo, H.; Cuche, C.; Kellershohn, C.; and Deniker, P. Brain distribution and kinetics of ^{11}C-chlorpromazine in schizophrenics: Positron emission tomography studies. *Psychiatry Research*, 1:23–29, 1979.

Davis, G.C.; Buchsbaum, M.S.; and Bunney, W.E., Jr. Research in endorphins and schizophrenia. *Schizophrenia Bulletin*, 5:244–250, 1979.

Davis, G.C.; Buchsbaum, M.S.; van Kammen, D.P.; and Bunney, W.E., Jr. Analgesia to pain stimuli in schizophrenics and its reversal by naltrexone. *Psychiatry Research*, 1:61–69, 1979.

DeLisi, L.E.; Holcomb, H.H.; Cohen, R.M.; Pickar, D.; Carpenter, W.T., Jr.; Morihisa, J.; King, A.C.; Kessler, R.; and Buchsbaum, M.S. Positron emission tomography in schizophrenic patients with and without neuroleptic medication. *Journal of Cerebral Blood Flow and Metabolism*, 5:201–206, 1985.

Devous, M.D.; Raese, J.D.; Herman, J.H.; Paulman, R.G.; Gregory, R.R.; Rush, A.J.; Chehabi, H.H.; and Bonte, F.J. "SPECT Determination of Regional Cerebral Blood Flow in Schizophrenic Patients at Rest and During a Mental Task." Presented at the 32nd Annual Meeting of the Society of Nuclear Medicine, Houston, TX, June 2, 1985.

Doran, A.R.; Pickar, D.; Boronow, J.; Breier, A.; Wolkowitz, O.M.; and Goodwin, F.K. "CT Scans in Schizophrenic Patients, Medical and Normal Controls." Presented at the Annual Meeting of the American College of Neuropsychopharmacology, Maui, HI, December 9–13, 1985.

Duff, T.A. Topography of scalp recorded potentials evoked by stimulation of the digits. *Electroencephalography and Clinical Neurophysiology*, 49:452–460, 1980.

Duffy, F.H., ed. *Topographic Mapping of Brain Electrical Activity*. Boston: Butterworths, 1986.

Dyksen, M.; Patlak, C.S.; Dobben, G.D.; Pettigrew, K.D.; Bartko, J.J.; Burns, E.M.; Davis, J.; and Regier, D.A. Rapid dynamic CT scanning to distinguish schizophrenic from nor-

mal subjects. *Psychiatry Research*, 20:165–175, 1987.

Erlenmeyer-Kimling, L., and Cornblatt, B. Attentional measures in a study of children at high risk for schizophrenia. *Journal of Psychiatric Research*, 14:93–98, 1978.

Farde, L.; Ehrin, E.; Eriksson, L.; Greitz, T.; Hall, H.; Hedstrom, C.G.; Litton, J.E.; and Sedvall, G. Substituted benzamides as ligands for visualization of dopamine receptor binding in the human brain by positron emission tomography. *Proceedings of the National Academy of Sciences, U.S.A.*, 82:3863–3867, 1985.

Farde, L.; Hall, H.; Ehrin, E.; and Sedvall, G. Quantitative analysis of D_2 dopamine receptor binding in the living human brain by PET. *Science*, 231:258–259, 1986.

Farkas, T.; Reivich, M.; Alavi, A.; Greenberg, J.H.; Fowler, J.S.; MacGregor, R.R.; Christman, D.R.; and Wolf, A.P. The application of [^{18}F] 2-deoxy-2-fluoro-D-glucose and positron emission tomography in the study of psychiatric conditions. In: Passonneau, J.V.; Hawkins, R.A.; Lust, W.D.; and Welsh, F.A., eds. *Cerebral Metabolism and Neural Function*. Chapter 44. Baltimore: Williams & Wilkins Company, 1980. pp. 403–408.

Farkas, T.; Wolf., A.P.; Jaeger, J.; Brodie, J.D.; Christman, D.R.; and Fowler, J.S. Regional brainglucose metabolism in chronic schizophrenia: A positron emission transaxial tomographic study. *Archives of General Psychiatry*, 41:293–300, 1984.

Fink, M. EEG profiles and bioavailability measures of psychoactive drugs. *Modern Problems of Pharmacopsychiatry*, 8:76–98, 1974.

Garnett, E.S.; Firnau, G.; and Nahmias, C. Dopamine visualized in the basal ganglia of living man. *Nature*, 305:137–138, 1983.

Goldberg, E. Akinesia, tardive dysmentia and frontal lobe disorder in schizophrenia. *Schizophrenia Bulletin*, 11:255–263, 1985.

Golden, C.J.; Graber, B.; Coffman, J.; Berg, R.A.; Newlin, D.B.; and Bloch, S. Structural brain deficits in schizophrenia. *Archives of General Psychiatry*, 38:1014–1017, 1981.

Grillon, C., and Buchsbaum, M.S. Computed EEG topography of response to visual and auditory stimuli. *Electroencephalography and Clinical Neurophysiology*, 63:42–53, 1986.

Guenther, W., and Breitling, D. Predominant sensorimotor area left hemisphere dysfunction in schizophrenia measured by brain electrical activity mapping. *Biological Psychiatry*, 20:515–532, 1985.

Gur, R.E.; Gur, R.C.; Skolnick, B.E.; Caroff, S.; Obrist, W.D.; Resnick, S.; and Reivich, M. Brain function in psychiatric disorders. *Archives of General Psychiatry*, 42:329–334, 1985.

Haier, R.J., and Braden, W. "Serial Evoked Potential Topography in Schizophrenia and Depression." Submitted for publication.

Ingvar, D.H. Functional landscapes of the dominant hemisphere. *Brain Research*, 107:181–197, 1976.

Ingvar, D.H., and Franzen, G. Abnormalities of cerebral blood flow distribution in patients with chronic schizophrenia. *Acta Psychiatrica Scandinavica*, 50:425–462, 1974.

Itil, T. Qualitative and quantitative EEG findings in schizophrenia. *Schizophrenia Bulletin*, 3:61–79, 1977.

Jacquy, J.; Charles, P.; Piraux, A.; and Noel, G. Relationship between the electroencephalogram and the rheoencephalogram in the normal young adult. *Neuropsychobiology*, 6:341–348, 1980.

Jernigan, T.L.; Sargent, T.; Pfefferbaum, A.; Kusubov, N.; and Stahl, S.M. ^{18}Fluorodeoxyglucose PET in schizophrenia. *Psychiatry Research*, 16:317–329, 1985.

Jones, S.C.; Alavi, A.; Christman, D.; Montanez, I.; Wolf, A.P.; and Reivich, M. The radiation dosimetry of 2-[F-18] Fluoro-2-deoxy-D-glucose in man. *Journal of Nuclear Medicine*, 23:613–617, 1982.

Kanazawa, Y.; Momozono, Y.; Ishikawa, M.; Yamada, T.; Yamane, H.; Haradahira, T.; Maeda, M.; and Kojima, M. Metabolic pathway of 2-deoxy-2-fluoro-D-glucose studied by F-19 NMR. *Life Sciences*, 39:737–742, 1986.

Kessler, R.M.; Ellis, J.R., Jr.; and Eden, M. Analysis of emission tomographic scan data: Limitations imposed by resolution and background. *Journal of Computer Assisted Tomography*, in press.

Kety, S.S.; Woodford, R.B.; Harmel, M.H.; Freyhan, F.A.; Appel, K.E.; and Schmidt, C.F. Cerebral blood flow and metabolism in schizophrenia: The effects of barbiturate semi-narcosis, insulin coma and electroschock. *American Journal of Psychiatry*, 104:765–770, 1948.

Kishimoto, H.; Kuwahara, H.; Takazu, O.; Ohno, S.; Hama, Y.; Sato, C.; Ishii, T.; Nomura, Y.; Fujita, H.; Miyauchi, T.; Yokoi, S.; and Iio, M. The three subtypes of chronic schizophrenia using ^{11}C-glucose positron emission tomography (PET). *Psychiatry Research*, in press.

Kling, A.S.; Metter, E.J.; Riege, W.H.; and Kuhl, D.E. Comparison of PET measurement of local brain glucose metabolism and CAT measurement of brain atrophy in chronic schizophrenia and depression. *American Journal of Psychiatry*, 143:175–180, 1986.

Kuhl, D.E.; Metter, E.J.; Riege, W.H.; and Hawkins, R.A. Patterns of cerebral glucose utilization in dementia. In: Greitz, T.; Ingvar, D.H.; and Widen, L., eds. *The Metabolism*

of the Human Brain Studied With PET. New York: Raven Press, 1985. pp. 419–432.

Largen, J.W.; Calderon, M.; and Smith, R.C. Asymmetries in the densities of white and gray matter in the brains of schizophrenic patients. *American Journal of Psychiatry,* 140:1060–1062, 1983.

Largen, J.W.; Smith R.C.; Calderon, M.; Baumgartner, R.; Ru-Band, L.; Schoolar, J.C.; and Ravichandran, G.K. Abnormalities of brain structure and density in schizophrenia. *Biological Psychiatry,* 19:991–1013, 1984.

Lifshitz, J., and Gradijan, J. Relationships between measures of the coefficient of variation of the mean absolute EEG voltage and spectral intensities in schizophrenic and control subjects. *Biological Psychiatry,* 5:149–163, 1972.

Lifshitz, J., and Gradijan, J. Spectral evaluation of the electroencephalogram: Power and variability in chronic schizophrenics and control subjects. *Psychophysiology,* 11:479–490, 1974.

Maser, J.D., and Keith, S.J. CT scans and schizophrenia—Report on a workshop. *Schizophrenia Bulletin,* 9:265–283, 1983.

Mathew, R.J.; Duncan, G.C.; Weinman, M.L.; and Barr, D.L. Regional cerebral blood flow in schizophrenia. *Archives of General Psychiatry,* 39:1121–1124, 1982.

Mazziotta, J.C.; Phelps, M.E.; Plummer, D.; and Kuhl, D.E. Quantitation in positron emission computed tomography: Five physical-anatomical effects. *Journal of Computer Assisted Tomography,* 5:734–743, 1981.

Mchedlishvili, G. Physiological mechanisms controlling cerebral blood flow. *Stroke,* 11:240–248, 1980.

Moore, R.Y., and Bloom, F.E. Central catecholamine neuron systems: Anatomy and physiology of dopamine systems. *Annual Review of Neuroscience,* 1:129–169, 1978.

Morihisa, J.M.; Duffy, F.H.; and Wyatt, R.J. Brain electrical activity mapping (BEAM) in schizophrenic patients. *Archives of General Psychiatry,* 40:719–728, 1983.

Morihisa, J.M., and McAnulty, G.B. Structure and function: Brain electrical activity mapping and computed tomography in schizophrenia. *Biological Psychiatry,* 20:3–19, 1985.

Morstyn, R.; Duffy, F.H.; and McCarley, R.W. Altered topography of EEG spectral content in schizophrenia. *Electroencephalography and Clinical Neurophysiology,* 56:263–271, 1983.

Nelson, T.; Lucignani, G.; Atlas, S.; Crane, A.M.; Dienel, G.A.; and Sokoloff, L. Reexamination of glucose-6-phosphatase activity in the brain *in vivo:* No evidence for a futile cycle. *Science,* 229:60–62, 1985.

Nuechterlein, K.H. Signal detection in vigilance tasks and behavioral attributes among offspring of schizophrenic mothers and among hyperactive children. *Journal of Abnormal Psychology,* 92:4–28, 1983.

Orzack, M.H., and Kornetsky, C. Attention dysfunction in chronic schizophrenia. *Archives of General Psychiatry,* 14:323–326, 1966.

Phelps, M.E.; Huang, S.C.; Hoffman, E.J.; Selin, C.; Sokoloff, L.; and Kuhl, D.E. Tomographic measurement of local cerebral glucose metabolic rate in humans with (F-18) 2-fluoro-2-deoxy-D-glucose: Validation of method. *Annals of Neurology,* 6:371–388, 1979.

Phelps, M.E.; Mazziotta, J.C.; and Huang, S-C. Study of cerebral function with positron computed tomography. *Journal of Cerebral Blood Flow and Metabolism,* 2:113–162, 1982.

Phelps, M.E., and Mazziotta, J.C. Positron emission tomography: Human brain function and biochemistry. *Science,* 228:799–809, 1985.

Pycock, C.J.; Kerwin, R.W.; and Carter, C.J. Effect of lesion of cortical dopamine terminals on subcortical dopamine receptors in rats. *Nature,* 286:74–77, 1980.

Raichle, M.E. Positron emission tomography. *Annual Review of Neuroscience,* 6:249–267, 1983.

Reivich, M.; Gur, R.; and Alavi, A. Positron emission tomographic studies of sensory stimuli, cognitive processes and anxiety. *Human Neurobiology,* 2:25–33, 1983.

Rosenthal, D. *The Genain Quadruplets.* New York: Basic Books, 1963.

Roth, W. Late event-related potentials and psychopathology. *Schizophrenia Bulletin,* 3:105–120, 1977.

Schneider, J.S. Basal ganglia role in behavior: Importance of sensory gating and its relevance to psychiatry. *Biological Psychiatry,* 19:1693–1710, 1984.

Sedvall, G.; Blomquist, G.; De Paulis, T.; Ehrin, E.; Eriksson, L.; Farde, L.; Greitz, T.; Hedstrom, C.G.; Ingvar, D.H.; Litton, J-E.; Nilsson, J.L.G.; Stone-Elander, S.; Widen, L.; Wiesel, F.A.; and Wik, G. PET studies on brain energy metabolism and dopamine receptors in schizophrenic patients and monkeys. In: Pichot, P.; Berner, P.; Wolf, R.; and Than, K., eds. *Psychiatry: The State of the Art.* New York: Plenum Publishing Company, 1984. pp. 305–312.

Shagass, C. Early evoked potentials. *Schizophrenia Bulletin,* 3:80–92, 1977.

Shagass, C.; Roemer, R.A.; Straumanis, J.J.; and Amadeo, M. Topography of sensory evoked potentials in depressive disorders. *Biological Psychiatry,* 15:183–207, 1980.

Sheppard, G.; Gruzelier, J.; Man-

chanda, R.; Hirsch, S.R.; Wise, R.; Frackowiak, R.; and Jones, T. ^{15}O-positron emission tomographic scanning in predominantly never-treated acute schizophrenic patients. *Lancet*, II:1448–1452, 1983.

Smith, R.C.; Baumgartner, R.; and Calderon, M. Magnetic resonance imaging studies of the brains of schizophrenic patients. *Psychiatry Research*, 20:33–46, 1987.

Smith, R.C.; Calderon, M.; Ravichandran, G.K.; Largen, J.; Vroulis, G.; Shvartsburd, A.; Gordon, J.; and Schoolar, J.C. Nuclear magnetic resonance in schizophrenia: A preliminary study. *Psychiatry Research*, 12:137–147, 1984.

Sokoloff, L. Relation between physiological function and energy metabolism in the central nervous system. *Journal of Neurochemistry*, 29:13–26, 1977.

Sokoloff, L. Relationships among local functional activity, energy metabolism, and blood flow in the central nervous system. *Proceedings from the Symposium Regulation of the Cerebral Circulation*, 40:2311–2316, 1981.

Sokoloff, L. The radioactive deoxyglucose method: Theory, procedure, and applications for the measurement of local glucose utilization in the central nervous system. In: Agranoff, B.W., and Aprison, M.H., eds. *Advances in Neurochemistry*, New York: Plenum Publishing Co., 1982. pp. 1–82.

Sokoloff, L. Rates of local, cerebral glucose utilization in the normal, conscious state. In: Sokoloff, L. *Metabolic Probes of CNS Activity in Experimental Animals and Man*. Sunderland, MA: Singver Assoc. Inc., 1984. pp. 28–71.

Sokoloff, L.; Reivich, M.; Kennedy, C.; Des Rosiers, M.H.; Patlak, C.S.; Pettigrew, K.D.; Sakurada, O.; and Shinohara, M. The ^{14}C deoxyglucose method for the measurement of local cerebral glucose utilization: Theory, procedure, and normal values in the conscious and anesthetized albino rat. *Journal of Neurochemistry*, 28:897–916, 1977.

Spohn, H.E., and Patterson, T. Recent studies of psychophysiology in schizophrenia. *Schizophrenia Bulletin*, 5:581–611, 1979.

Tolonen, U., and Sulg, I.A. Comparison of quantitative EEG parameters from four different analysis techniques in evaluation of relationships between EEG and CBF in brain infarction. *Electroencephalography and Clinical Neurophysiology*, 51:177–185, 1981.

Volkow, N.D.; Brodie, J.D.; Wolf, A.P.; Gomez-Mont, F.; Cancro, R.; Van Gelder, P.; Russell, J.A.G.; and Overall, J. Brain organization in schizophrenia. *Journal of Cerebral Blood Flow and Metabolism*, 6:441–446, 1986.

Wagner, H.N.; Burns, H.D.; Dannals, R.F.; Wong, D.F.; Langstrom, B.; Duelfer, T.; Frost, J.; Ravert, H.T.; Links, J.M.; Rosenbloom, S.B.; Lukas, S.E.; Kramer, A.V.; and Kuhar, M.J. Imaging dopamine receptors in the human brain by positron tomography. *Science*, 221:1264–1266, 1983.

Walker, E. Attentional and neuromotor functions of schizophrenics, schizoaffectives, and patients with other affective disorders. *Archives of General Psychiatry*, 38:1355–1358, 1982.

Walker, E., and Shaye, J. Familial schizophrenia: A predictor of neuromotor and attentional abnormalities in schizophrenia. *Archives of General Psychiatry*, 39:1153–1156, 1982.

Weinberger, D.R.; Berman, K.F.; and Zec, R.F. Physiologic dysfunction of dorsolateral prefrontal cortex in schizophrenia: I. Regional cerebral blood flow evidence. *Archives of General Psychiatry*, 43:114–124, 1986.

Weinberger, D.R.; Wagner, R.L.; and Wyatt, R.J. Neuropathological studies of schizophrenia: A selective review. *Schizophrenia Bulletin*, 9:193–212, 1983.

Widen, L.; Blomquist, G.; Greitz, T.; Litton, J.E.; Bergstrom, M.; Ehrin, E.; Ericson, K.; Eriksson, L.; Ingvar, D.H.; Johansson, L.; Nilsson, J.L.G.; Stone-Elander, S.; Sedvall, G.; Wiesel, F.; and Wik, G. PET studies of glucose metabolism in patients with schizophrenia. *American Journal of Neurology*, 4:550–552, 1983.

Wiesel, F-A.; Blomquist, G.; Greitz, T.; Nyman, H.; Schalling, D.; Stone-Elander, S.; Widen, L.; and Wik, G. In: Shagass, C.; Josiassen, R.C.; Bridger, W.H.; Weiss, K.J.; Stoff, D.; and Simpson, G.M., eds. *Biological Psychiatry 1985: Proceedings of the 4th World Congress of Biological Psychiatry*. New York: Elsevier Science Publishers, in press.

Wolf, A.P. Cyclotrons, radionuclides, precursors, and demands for routine versus research compounds. *Annals of Neurology*, 15:519–524, 1984.

Wolkin, A.; Jaeger, J.; Brodie, J.D.; Wolf, A.P.; Fowler, J.; Rotrosen, J.; Gomez-Mont, F.; and Cancro, R. Persistence of cerebral metabolic abnormalities in chronic schizophrenia as determined by positron emission tomography. *American Journal of Psychiatry*, 142:564–571, 1985.

Wong, D.F.; Wagner, H.N., Jr.; Tune, L.E.; Dannals, R.F.; Pearlson, G.D.; Links, J.M.; Tamminga, C.A.; Broussolle, E.P.; Ravart, H.T.; Wilson, A.A.; Toung, J.K.T.; Malat, J.; Williams, J.A.; O'Tuama, L.A.; Snyder, S.H.; Kuhar, M.J.; and Gjedde, A. Positron emission tomography reveals elevated D_2 dopamine receptors in drug naive schizophrenics. *Science*, 234:1558–1563, 1986.

Zubin, J.; Sutton, S.; and Steinhauer, S.R. Event-related potential and behavioral methodology in psychiatric research. In: Shagass, C., and Josiassen, R.C., eds. *Electrical Brain Potentials and Psychopathology*. Amsterdam: Elsevier Science Publishers, in press.

The Authors

Monte S. Buchsbaum, M.D., is Professor, and Richard J. Haier, Ph.D., is Associate Professor, Department of Psychiatry, University of California, Irvine, CA.

Schizophrenia: Questions and Answers

What is schizophrenia? What causes it? How is it treated? How can other people help? What is the outlook? These are the questions addressed in a booklet prepared by the Schizophrenia Research Branch of the National Institute of Mental Health.

Directed to readers who may have little or no professional training in schizophrenia-related disciplines, the booklet provides answers and explanations for many commonly asked questions of the complex issues about schizophrenia. It also conveys something of the sense of unreality, fears, and loneliness that a schizophrenic individual often experiences.

The booklet describes "The World of the Schizophrenic Patient" through the use of analogy. It briefly describes what is known about causes—the influence of genetics, environment, and biochemistry. It also discusses common treatment techniques. The booklet closes with a discussion of the prospects for understanding schizophrenia in the coming decade and the outlook for individuals who are now victims of this severe and often chronic mental disorder.

Single copies of *Schizophrenia: Questions and Answers* (DHHS Publication No. ADM 86–1457) are available from the Public Inquiries Branch, National Institute of Mental Health, Room 15C–05, 5600 Fishers Lane, Rockville, MD 20857.