Positron Emission Tomography Studies of Abnormal Glucose Metabolism in Schizophrenia

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Abstract

Schizophrenia, a devastating disease characterized by a combination of various types of disturbed behaviors, thoughts, and feelings, may likewise be heterogeneous in etiology. Recent advances in neuroscience and psychopharmacology have suggested a wide array of competing mechanisms that may be involved in schizophrenia, including but not limited to deficits in one or more neurotransmitters and second messenger systems (e.g., dopamine, serotonin, gamma-aminobutyric acid, glutamate, and noradrenalin), neurodevelopmental defects in brain circuitry, and viral infection. Psychiatric genetic studies indicate that schizophrenia is a disorder with multifactorial inheritance. Since cerebral metabolic activity reflects regional brain work for all neurotransmitter systems, imaging metabolism directly with fluorodeoxyglucose and indirectly with blood flow and hemoglobin oxygen saturation can provide information about the functional neuroanatomy of a deficit in individual patients and allow patients to be grouped into more homogeneous subgroups for intensive study. This review summarizes metabolic imaging studies in schizophrenia over the past decade.

Key words: Deoxyglucose, frontal lobe, thalamus, striatum, receptor ligands, brain imaging.

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Functional imaging studies of schizophrenia have focused on a variety of brain structures in searching for possible abnormalities. Favored targets have included the frontal lobes, the basal ganglia, the thalamus, and the temporal lobes. Although some evidence of abnormal function has been found for each structure, no primary site for schizophrenia has yet been identified. An alternative approach may be to look at relationships among brain centers rather than to search for any one abnormal site. Schizophrenia may be a disorder characterized primarily by problems in connectivity, that is, a dysfunction in normal brain circuitry. Both animal and postmortem human studies have provided information and hypotheses about brain circuitry. Functional brain imaging provides one way of testing these hypotheses in living normal subjects and patients with schizophrenia.

Techniques such as positron emission tomography (PET) with fluorodeoxyglucose (FDG), oxygen (O)15 blood flow, functional magnetic resonance imaging (fMRI), and single photon emission computed tomography (SPECT) can be used to examine the relationship between brain function in key anatomical regions and behavioral performance or response to drugs. The fact that functional brain imaging can bring together disparate neurochemical, neuroanatomical, and behavioral approaches makes it key in the effort to understand schizophrenia. With the advent of PET scanners capable of spatial resolution in the 4- to 5-mm range, psychiatric researchers can view both individual gyri of the cortex and discrete portions of the thalamus and basal ganglia, regions of great importance in understanding the neural systems involved in psychotic thought or response to medication. Complementing PET's improved spatial resolution is the short time resolution provided by fMRI, which makes it possible to dissect the components of cognitive operations that last mere seconds. This review focuses on the now extensive research literature on regional cerebral metabolism in schizophrenia, with an emphasis on multistructure patterns of change in activity and interrelationships.

Circuitry and Fronto-Striatal-Thalamic Dysfunction

Regional cerebral blood flow (rCBF) studies of schizophrenia by Ingvar and Franzén (1974) found a relative

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functional reduction in the frontal compared with the occipital lobes. Relative hypofrontality in schizophrenia has been observed both in some of the earliest published PET studies (Buchsbaum et al. 1982; Farkas et al. 1984) and in current reports (for reviews of the more than 40 PET and rCBF studies, see Williamson 1987; Buchsbaum 1990; Andreasen et al. 1992, 1997; Chua and McKenna 1995; Buchsbaum and Hazlett 1997*b*). Findings of hypofrontality have not been confined to PET studies with FDG or rCBF, but instead have been demonstrated for phosphomonoesters with magnetic resonance spectroscopy (Pettegrew et al. 1991; Williamson et al. 1991; Shioiri et al. 1994; Kato et al. 1995) and SPECT with technetium-99m-*d,l*-hexamethylpropylaneamine oxime (^{99}m Tc–HMPAO) (Hawton et al. 1990; Rubin et al. 1994; Vita et al. 1995). Although the frontal lobe is unlikely to be the primary site of schizophrenia and hypofrontality has not been found in all samples (e.g., Gur et al. 1995), abnormal findings have been frequent enough to suggest the value of a wider focus on the role of the frontal lobe, not in isolation, but as part of the fronto-striatal-thalamic circuitry. Chua and McKenna (1995) conclude that "schizophrenia shows complex alterations in regional patterns of activity rather than any simple deficit in prefrontal function" (p. 563). Andreasen et al. (1997), in reporting their most recent PET blood flow finding of decreased perfusion in prefrontal regions, note that "schizophrenia is characterized by dysfunctional regions in prefrontal cortex" but also "involves an imbalance in circuits distributed throughout the brain" (p. 1734). The prominent attentional deficits that characterize schizophrenia, as well as the impairment of executive function, memory, and perceptual processing, suggest disturbances in the linkages between the frontal lobe and other areas. Many authors have stressed the role of fronto-striatal-thalamic loops in sensory gating or modulation (Penney and Young 1983; Alexander et al. 1986) and subsequent sensory overload with attendant cognitive disorganization and psychotic symptoms (Crosson and Hughes 1987; Swerdlow and Koob 1987; Braff et al. 1992; Pantelis et al. 1992; Weinberger 1993).

Knowledge of the extensive interconnections between the prefrontal cortex and the striatum, as well as the ventral anterior and dorsomedial nuclei of the thalamus, and the role of the thalamus in regulating sensory input comes primarily from animal studies, where in vivo injections and post-mortem sectioning are possible. There are, however, fundamental differences between the prefrontal cortex of the rat and man: According to Fuster (1989), "The great expansion of the presylvian (prearcuate) area is one of the most remarkable developments of mammalian evolution" (p. 4). Even the rhesus monkey has a proportionately smaller prefrontal region with marked differences in gyrification. The principal sulcus of the monkey appears as two sulci in man, and the interspecies functional correspondence of this region is uncertain (Fuster 1989). Thus, while it is tempting to suggest that abnormal fronto-striatal-thalamic connections may account for schizophrenic phenomenology, clear demonstrations of functional deficits in subregions of the prefrontal cortex and in connectivity must come from normal subjects and living patients.

Factor-analytic studies of metabolic data have tended to confirm frontal/cingulate/striatal/thalamic covariation (e.g., Szabo et al. 1992; Friston et al. 1993; Schröder et al. 1994, 1995, 1996), consistent with the loop models derived from animal studies indicating cortico-cortico connectivity (especially from right to left) as more prominent in humans than in rats or even primates. Recent studies indicating metabolic reductions in the cingulate gyrus in schizophrenia (see the review in Haznedar et al. 1997) also suggest the clear need for more extensive human brain-imaging studies to understand regional interaction among the areas most closely associated with both medial and lateral prefrontal cortex. In this article, we first review the findings on the individual components of the circuit.

Frontal Lobe. Table 1 summarizes the right fronto-occipital and frontal/whole slice data in 25 PET FDG studies that report mean data from regions of interest (ROIs). (We calculated the ratios and/or *t* values from tables or figures if the authors did not supply the data in the text.) In some cases, only one of the ratios could be calculated from the published data. In 16 of 22 studies for which a fronto-occipital ratio was available, the ratios were lower in subjects with schizophrenia than in normal ones, and this difference was statistically significant in 7 studies. In 15 of 18 studies in which a frontal/whole slice ratio was available, ratios were lower in subjects with schizophrenia than in normal ones, and this difference was significant in 8 of them. It is important to note that hypofrontal function is typically quantitative and seems to reflect both diminished frontal and increased occipital activation (figure 1). In an 18-year followup of the original patients of Ingvar and Franzén (1974), Cantor-Graae et al. (1991) found hypofrontality stable, and not an artifact of age or cortical atrophy (see also DeLisi et al. 1985; Wolkin et al. 1992; Buchsbaum and Hazlett 1997*a*).

Hypofrontality has tended to be associated with the intensity of negative symptoms in FDG–PET (Wolkin et al. 1992; Siegel et al. 1993; Schröder et al. 1994, 1995), SPECT (Andreasen et al. 1992), and rCBF–PET (Friston et al. 1992) studies. The finding by Warkentin et al. (1990) of greater hypofrontality in patients who are not acutely exacerbated and of hyperfrontality by Szechtman et al. (1988) in acute patients may also be evidence that

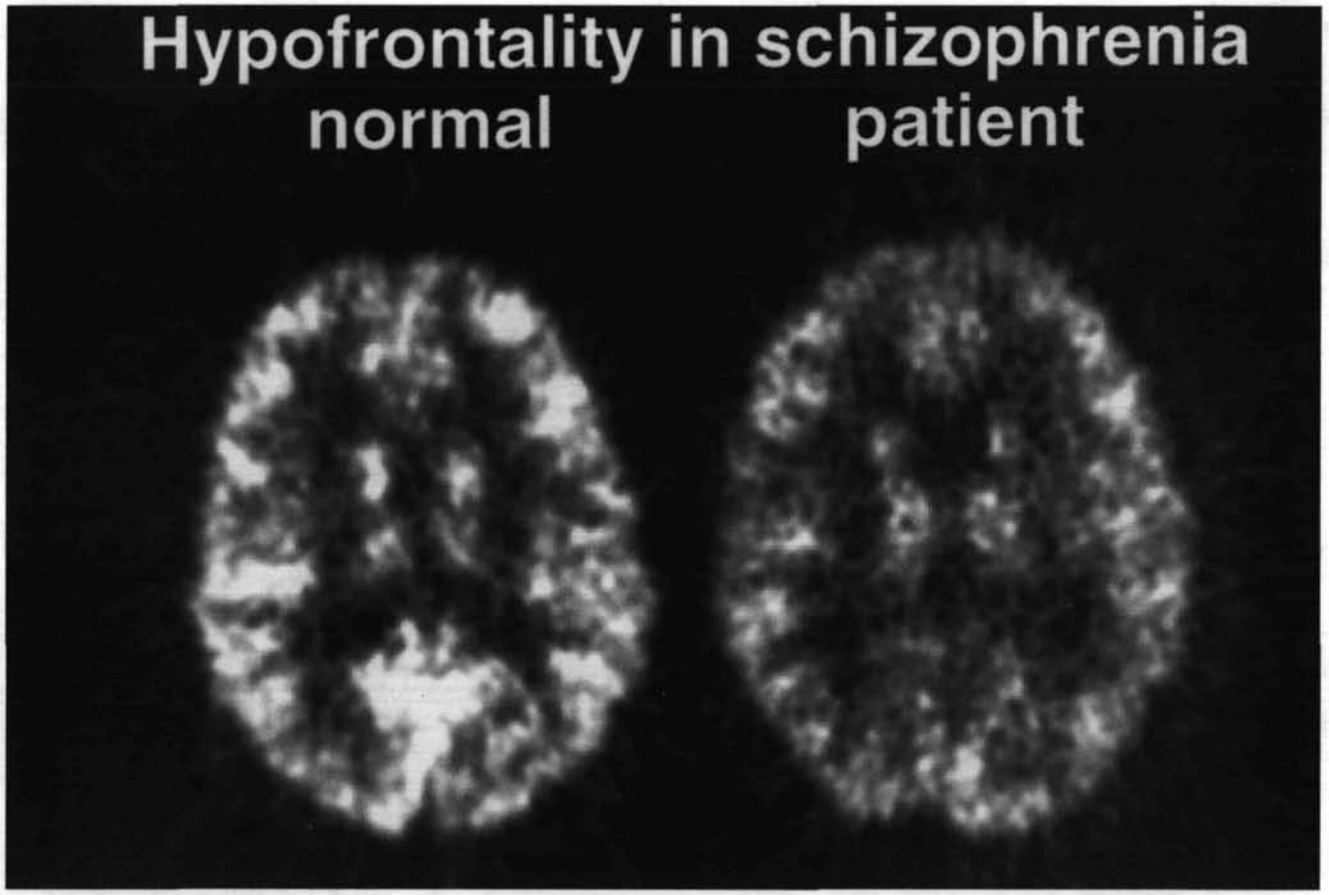
Table 1. Comparison of positron emission tomography studies in schizophrenia

Study	Frontal/occipital ratio			Frontal/whole ratio			Site in brain	No. of patients	Sensory condition	Medication status
	N	S	*p*	N	S	*p*				
Buchsbaum et al. (1982)	1.14	1.05	<0.05[1]	1.12	1.06	<0.05	Superior ventricle	8	Eyes closed	Off
Buchsbaum et al. (1984*a*)	1.08	1.02	<0.05	1.14	1.09	<0.05	Superior ventricle	16	Shocks	Off
Farkas et al. (1984)[2]	1.14	1.07	<0.05[3]	1.11	1.05	NT	Superior ventricle	11	Open room	6 On
Sheppard et al. (1983)[4]	1.1	1.0	NS	—	—	—	OM + 6 cm	12	Eyes closed	6 On[5]
Jernigan et al. (1985)[6]	1.10	1.03	NS	1.03	0.98	NS	Midventricle	6	Auditory	Off
Wolkin et al. (1985)	1.09	1.04	NS	1.08	1.04	<0.05	Midventricle	10	Eyes open	Off
Kling et al. (1986)[7]	0.79	0.74	NS	0.97	0.92	<0.05	"High"	6	Eyes open	On
Wiesel et al. (1985)[8]	—	—	—	1.16	1.12	NT	Brodmann 9, 10	13	Eyes closed	Off
Wolkin et al. (1988)	1.10	1.04	<0.03	—	—	—	Midventricle	13	Eyes open	Off
Volkow et al. (1986)	0.91	0.90	NT[9]	1.01	0.98	NT	Frontal lobe	18	Eyes open	On
Szechtman et al. (1988)	1.06	1.23	<0.01[10]	0.97	1.02	NS	Superior ventricle	12	Eyes closed	On
Szechtman et al. (1988)	1.06	1.31	<0.01[11]	0.97	1.08	<0.05	Superior ventricle	5	Eyes closed	Off
Gur et al. (1987)	1.08	1.08	NS	0.77	0.72	NT	Frontal lobe	12	Eyes open	Off[12]
Kishimoto et al. (1987)	1.09	0.92	NT[13]	—	—	—	Brodmann 10	20	Eyes closed	On
Cohen et al. (1989)	1.05	1.01	<0.03	—	—	—	Midventricle	16	Auditory	Off
Cleghorn et al. (1989)	1.07	1.14	<0.01	—	—	—	Midventricle	8	Eyes closed	Off
Buchsbaum et al. (1990)	1.00	0.97	NS[14]	1.12	1.06	<0.05	Midventricle	13	CPT	Off
Buchsbaum et al. (1992*a*)	1.07	1.01	<0.02	—	—	—	Prefrontal	18	CPT	Off[15]
Tamminga et al. (1992)	1.21	1.32	NT[16]	1.34	1.31	NS	Multiple slice	12	Eyes closed	Off
Siegel et al. (1993)	0.97	0.93	<0.05	—	—	—	Superior frontal	70	CPT	Off[17]
Biver et al. (1995)	—	—	—	1.17	1.13	<0.01	Multiple slice	15	Eyes closed	Off[18]
Gur et al. (1995)	0.90	0.87	NT[19]	—	—	—	Multiple slice	20	Eyes open	Off
Bertolio et al. (1996)	—	—	—	1.18	1.14	NT	Orbital frontal[20]	8	Eyes closed	On
Al-Mousawi et al. (1996)	0.88	0.95	NT	1.04	0.96	<0.01	Midfrontal	17	Eyes closed	On
Jacobsen et al. (1997)	1.20	1.22	NT[21]	1.04	0.99	<0.05	Ventricle "C level"	16	CPT	Off
Wong et al. (1997)[22]	—	—	—	1.18	1.26	NS	Superior ventricle	14	Eyes closed	On

Note.—Analysis for right hemisphere, midventricular or supraventricular slice when available. Fronto/occipital ratio calculated if occipital data were available. N = normal subjects; S = subjects with schizophrenia; OM = orbitomeatal line; CPT = Continuous Performance Test (Nuechterlein et al. 1983); not significant (NS) = $p > 0.05$; NT = not tested.

[1]Linear trend analysis of variance.
[2]Right and left combined, calculated from tables 1-3 in Farkas et al. (1984).
[3]Analysis of covariance.
[4]Ratio calculated by authors to only 1 significant figure after the decimal.
[5]Six patients not > 7 days off medication.
[6]Automated analysis.
[7]Frontal/whole slice different by *t*-test.
[8]Occipital data not given in report; frontal areas calculated from Brodmann areas 9 and 10 data.
[9]Right frontal rate for schizophrenia patients (35.4) lower than for normal subjects (40.0) by *t*-test, $p < 0.01$.
[10]One-way analysis of variance for normal subjects; schizophrenia patients medicated 4-14 years.
[11]Never-medicated schizophrenia patients; data from figure 4 in Szechtman et al. (1988).
[12]Off medication > 7 days.
[13]Means calculated by weighted averages from table 4 in Kishimoto et al. (1987).
[14]Group by anteroposterior position significant.
[15]All never-medicated.
[16]Ratios of right superior frontal/occipital region.
[17]Contains 18 never-medicated subjects from Buchsbaum et al. (1992*a*).
[18]Twelve of 15 patients were never medicated.
[19]Ratios calculated from right frontal/occipital regions (excluding "medial" areas) in table 2 in Gur et al. (1995).
[20]Right orbitofrontal (personal communication).
[21]Calculated from table 1 in Jacobsen et al. (1997), level "C", ratio of anterior frontal to parietal-occipital.
[22]Patient group without repetitive violent history.

Figure 1. Positron emission tomography scans in a normal volunteer (left) and a never-medicated schizophrenia patient (right) who performed a serial verbal memory task during uptake of the tracer ^{18}fluoro-2-deoxyglucose



In contrast to the volunteer, the patient showed relatively diminished metabolism in the right inferior and orbitofrontal cortex, together with an active occipital region. Medial frontal lobe and cingulate regions also show diminished metabolic activity in the patient. Both images are scaled relative to their own maximum and minimum to allow direct comparison of fronto-occipital relationships.

negative, not positive, symptoms are associated with hypofrontality. The frontal lobe has also shown significant change during mood-induction experiments in normal subjects (Schneider et al. 1994, 1995; George et al. 1995), but methods for evaluating intensity of mood induction in patients with schizophrenia, whose ability to recognize and report emotional states may be compromised, have not yet been fully developed. Hypofrontality in the FDG–PET scans of patients with schizophrenia compared with normal controls was found during an acoustic startle paradigm (Hazlett et al. 1998), thus suggesting that levels of arousal may be important in understanding diminished frontal activity.

Differences in measurement methods, psychological condition, and exact data presentation make it difficult to summarize PET studies of schizophrenia, but the overall findings are similar to those shown with the lower-resolution xenon blood flow methods first reported by Ingvar and Franzén (1974) in their pioneering studies and reviewed by Weinberger and Berman (1988).

Striatum. An abnormality in the metabolic rate of the caudate and putamen would be consistent with a dysfunction in the fronto-striatal-thalamic circuit, as well as consistent with the dopamine (DA) hypothesis of schizophrenia, post-mortem DA receptor (D_2)-binding data, and the regional effects of neuroleptics. Since the first PET report of reduced basal ganglia metabolism in patients with schizophrenia (Buchsbaum et al. 1982), most investigators have found significantly decreased metabolic rates in the basal ganglia in unmedicated patients (table 2).

Most studies have failed to find significant differences between subjects with schizophrenia and normal subjects in functional asymmetry in the basal ganglia (Buchsbaum et al. 1987*a*; Resnick et al. 1988; Szechtman et al. 1988; Gur et al. 1995). Some studies, however, have

Table 2. Metabolic rate in basal ganglia

Author	Micromoles		Relative			Sample		ROI method	Sensory condition	Medication status
	N	S	N	S	p	Normals	Patients			
Buchsbaum et al. (1982)[1]	–	–	1.03	0.94	$p < 0.05$	6	8	Stereo box	Eyes closed	Off
Wolkin et al. (1985)										
Caudate	32.2	31.5	0.97	1.06	NS	8	10	ROI on CT	Eyes open	Off
Lentiform	38.7	36.7	1.16	1.23	NS	8	10			
Kling et al. (1986)	–	–	0.93	1.03	NS	6	6	PET outline	Eyes open	On
Buchsbaum et al. (1987)										
Caudate	19.6	20.5	1.06	0.97	$p < 0.05$[2]	24	21	Stereo box	Somatosensory	Off
Putamen	22.1	24.0	1.22	1.14	NS					
Wiesel et al. (1987*b*)										
Caudate	21.1	19.5	0.94	0.98	$p < 0.05$[3]	9	15	ROI on CT[4]	Eyes closed	Off
Lentiform	25.9	21.6	1.15	1.09	$p < 0.05$[3]					
Resnick et al. (1988)										
Caudate	21.7	18.5	1.00	1.00	$p < 0.05$[4]	18	20	Stereo ROI	Eyes open	Off
Lenticular	24.1	22.1	1.11	1.20	NS					
Szechtman et al. (1988)[5]	–	–	0.87	0.88	NS	10	5	Algorithm	Eyes closed	Off
Gur et al. (1987)[6]	22.0	19.5	1.07	1.11	NT[7]	12	12	ROI	Eyes open	Off
Cohen et al. (1989)[8]	–	–	1.02	1.02	NS	27	16	Visual placement	CPT	Off
Wik et al. (1989)	25.5	14.5	–	–	$p < 0.05$[7]	5	5	ROI on CT[4]	Eyes closed	Off
Chronic sample	–	–	1.15	1.07	NT	7	11			
Acute sample	–	–	1.15	1.09	NT	7	6			
Buchsbaum et al. (1992*a*)										
Caudate	28.4	22.7	1.26	1.16	$p < 0.05$	18	20	Stereo	CPT	Never
Anterior putamen	28.8	24.8	1.26	1.25	$p < 0.05$[9]					
Tamminga et al. (1992)										
Caudate	11.7	10.4	1.4	1.3	NS	12	12	Visual placement	Eyes closed	Off
Siegel et al. (1993)										
Caudate[10]	23.9	22.2	1.30	1.25	$p < 0.05$	30	70	Stereo	CPT	Off
Gur et al. (1995)	29.7	32.3	1.19	1.34	NS	42	20	ROI on MRI	Eyes open	Off
Al-Mousawi et al. (1996)	–	–	1.03	1.06	NS	10	17	ROI	Eyes closed	On

Note.—N = normal subjects; S = patients with schizophrenia; ROI = region of interest; not significant (NS) = $p > 0.05$; CT = computed tomography; PET = positron emission tomography; NT = not tested; CPT = Continuous Performance Test (Nuechterlein et al. 1983); MRI = magnetic resonance imaging.

[1]Midventricular slice, dorsal portion of basal ganglia.
[2]Significant reduction in relative metabolic rate only.
[3]Micromole glucose significantly lower; our calculation of relative data not tested statistically.
[4]Micromole glucose is significantly lower; relative is not significant (NS); means of left and right are given.
[5]Data from figure 4 in Szechtman et al. (1988).
[6]Data from figure 3 in Gur et al. (1987); contains caudate, putamen, and thalamus.
[7]*T*-test on left and right sides.
[8]Patients described in Cohen et al. (1987); left and right averaged.
[9]Analysis of variance $p < 0.05$ for caudate absolute and relative metabolic rate and putamen absolute rate only; left and right average.
[10]Middorsoventral level, right and left averaged, $p < 0.05$ for relative data. Includes subjects in Buchsbaum et al. (1992*a*).

suggested a possible right-sided abnormality: Wolkin et al. (1985) found a higher metabolic rate in the left lentiform nucleus than in the right in normal subjects, a difference that was not observed in patients with schizophrenia. Gur et al. (1995) reported greater right metabolic rate differences than left ones in first-episode patients than in previously treated ones. Buchsbaum et al. (1987*a*) reported that the effect of neuroleptic treatment was greater on the right than on the left, consistent with the findings of Early et al. (1987) of increased relative flow on the left in schizophrenia, which the latter interpreted as suggesting dysfunction on the right. Similarly, Potkin et al. (1994) reported a relative increase in metabolic rate in the basal ganglia, especially on the right side, in patients with schizophrenia who were treated with clozapine in a double-blind, placebo-controlled crossover PET study. The findings of a study by Bracha (1987) of asymmetric rotational behavior suggesting a dopaminergic overactivity on the right in unmedicated patients with schizophrenia may be consistent with these right-sided findings.

Temporal Lobe. Table 3 summarizes 18 FDG–PET studies on the temporal lobe. For relative data, most comparable across studies, 10 of 15 studies showed lower values in the temporal lobes of patients with schizophrenia combined across hemispheres, although only 5 were statistically significant. Left temporal metabolic rates were found to be significantly greater than right ones in several studies (Gur et al. 1987, 1995; DeLisi et al. 1989; Buchsbaum et al. 1992*a*); but right exceeded left in Wiesel et al. (1987*b*), and the extent of this left lateralization was correlated with Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1962) hallucination scores (DeLisi et al. 1989); a composite BPRS rating including emotional withdrawal, conceptual disorganization, mannerisms and posturing, grandiosity, suspiciousness, hallucinations, unusual thought content, and blunted affect (Gur et al. 1989); and poorer verbal memory recall on a separate session (Mozley et al. 1996). These findings suggest that temporal activity that is greater on the left than on the right, perhaps combined with lower temporal activity overall, is associated with characteristic schizophrenic symptoms involving not only hallucinations, but thought and affective symptoms as well. Verbal and spatial task effects were found to be important in determining differences in laterality between schizophrenia and normal groups in rCBF studies (Gur et al. 1985, 1994). These, however, need to be repeated with current high-resolution PET methods.

Thalamus. Studies (see figure 2) have shown metabolism in the thalamus of patients with schizophrenia to be lower in previously medicated (Wiesel et al. 1987*b*) and never-medicated patients (Buchsbaum et al. 1996), lower in deficit patients only (Tamminga et al. 1992), unchanged (Kling et al. 1986; Buchsbaum et al. 1987*a*; Wiesel et al. 1987*b*; Szechtman et al. 1988; Wik et al. 1989; Siegel et al. 1993; Gur et al. 1995), or higher (Resnick et al. 1988). MRI findings have suggested that the size of the thalamus is diminished as well (Andreasen et al. 1994; Buchsbaum et al. 1996).

Interregional Metabolic Correlations

FDG–PET allows the measurement of regional brain glucose metabolic rates (GMR) and has been useful in demonstrating physiological abnormalities in numerous psychiatric and neurological disorders. Previously, members of our group (Kessler et al. 1983; Clark et al. 1984, 1985; Wu et al. 1990; Katz et al. 1996) and other researchers (Wiesel et al. 1987*a*; Metter et al. 1988; Volkow et al. 1988; Horwitz 1990; Horwitz et al. 1991; Abercrombie et al. 1996; Baxter et al. 1996; Biver et al. 1996; Mallet et al. 1998) have studied the activity of brain circuits by correlating GMR between interconnected structures. This work is based on the assumption that significant correlations may reveal an important functional relationship between structures. Differences in intercorrelations between normal volunteers and patients with neuropsychiatric illness have suggested impairments in brain circuitry. Evidence for diminished dorsomedial thalamus versus limbic cortex metabolic correlation in patients with schizophrenia relative to normal volunteers was found in a study of 13 unmedicated patients (Wu et al. 1990). These data were analyzed to explore the Swerdlow and Koob model (1987) of brain circuitry, which placed less emphasis on frontal than on limbic cortex and therefore did not include frontal regions. In their response, Swerdlow and Koob (1990) note that the correlation method "provides insight into dynamic patterns of metabolic activity in related brain regions; this is a great advance over the information provided by simple analysis of absolute or relative regional metabolic rates" (p. 172).

Our recent study (Katz et al. 1996) is the first to examine intercorrelations of GMR in a group of never-medicated patients with schizophrenia. We hypothesized that as a result of impaired cortical function, decreased cortico-cortical, cortico-nigral, cortico-thalamic, and cortico-striatal excitatory glutamatergic tone would be present in patients with schizophrenia. Such a pattern would result in diminished cortico-cortical correlations, as well as correlations of cortical regions (particularly frontal) with midbrain, thalamic, and striatal areas. Similarly, a decreased striato-pallidal gamma-aminobutyric acid

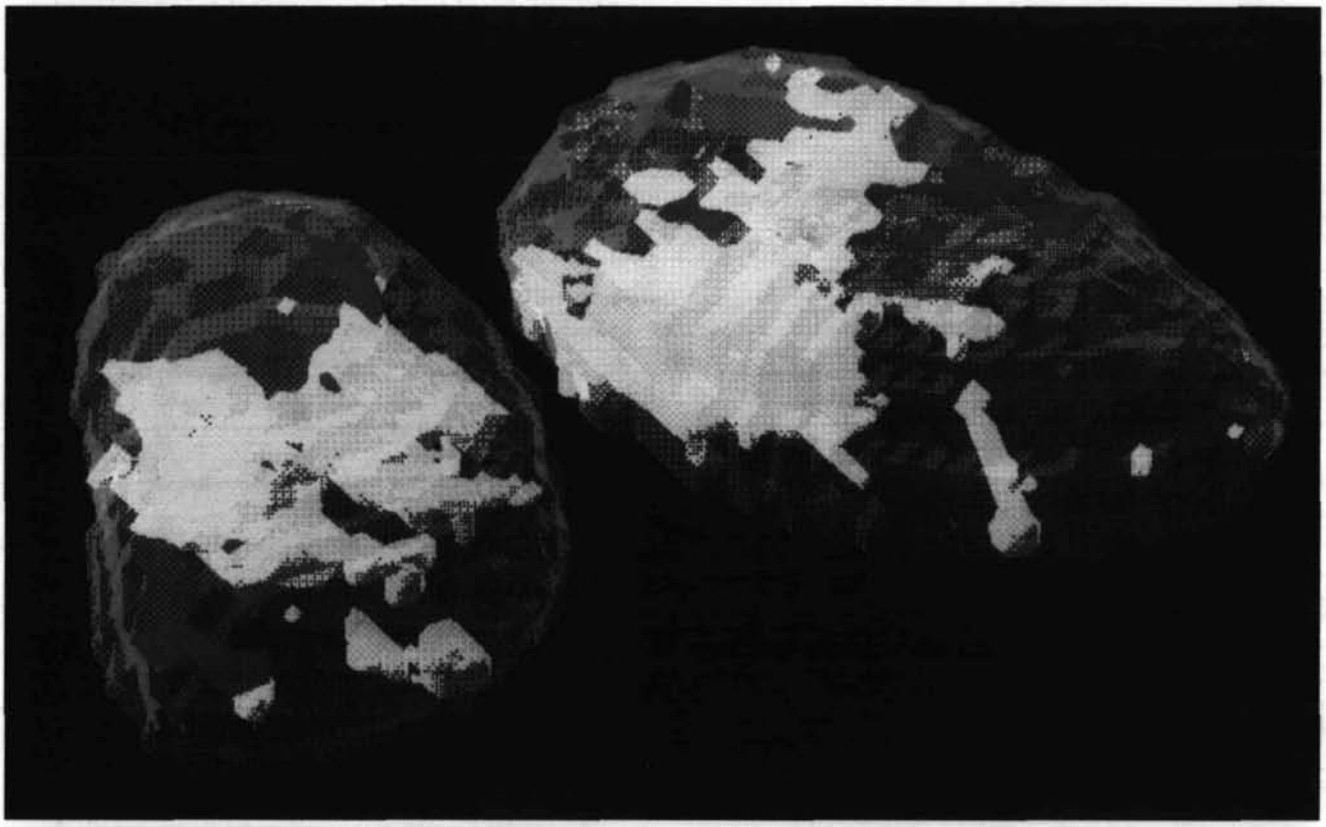
Table 3. Metabolic rate in whole temporal lobe

Author	Micromoles		Relative		p	Sample size		ROI method	Sensory condition	Medication status
	N	S	N	S		Normals	Patients			
Buchsbaum et al. (1982)[1]	–	–	1.02	0.99	NS[2]	6	8	Computer	Eyes closed	Off
Jernigan et al. (1985)	–	–	1.02	1.04	NS	6	6	Algorithm	Auditory	Off
Wolkin et al. (1985)	35.1	29.3	1.05	0.98	$p < 0.05$[3]	8	10	ROI on CT	Eyes open	Off
Gur et al. (1987)	22.1	18.7			$p < 0.05$	12	12	ROI	Eyes open	Off
Volkow et al. (1987)[1]	37.4	34.0	0.94	0.95	NS	12	18	ROI on CT	Eye tracking	On
Wiesel et al. (1987*b*)	25.8	20.8	1.15	1.04	$p < 0.05$[3]	9	15	ROI on CT	Eyes closed	Off
Szechtman et al. (1988)[4]	–	–	1.05	1.05	NS	10	5	Algorithm	Eyes closed	On
Cohen et al. (1989)[1]	–	–	1.05	1.03	$p < 0.05$	27	16	Inspection	Auditory	Off
DeLisi et al. (1989)	12.9	17.0	–	–	$p < 0.05$	18	17	Algorithm	Somatosensory	Off
Wik et al. (1989)										
Older sample	26.0	14.0	–	–	$p < 0.05$	5	5	ROI on CT	Eyes closed	Off
Younger sample	26.0	25.0	–	–	NS	5	5			
Buchsbaum et al. (1990)[1,5]	20.4	17.2	1.00	1.02	$p < 0.05$	18	13	Algorithm	Visual	Off
Buchsbaum et al. (1992*a*)[6]	16.0	14.1	0.66	0.65	$p < 0.05$	18	20	Algorithm	CPT	Never
Tamminga et al. (1992)[7]	53.9	46.9	1.22	1.06	NS	12	12	Visual	Eyes closed	Off
Siegel et al. (1993)[8]	18.1	17.4	0.95	0.97	NS	30	70	Stereo	CPT	Off
Gur et al. (1995)[1]	28.1	29.8	1.13	1.08	NS	42	22	ROI on MRI	Eyes open	Off
Al-Mousawi et al. (1996)[1,9]	–	–	0.96	0.97	NT	10	17	ROI	Eyes closed	On
Jacobsen et al. (1997)[1]	–	–	1.01	0.97	NS	26	16	ROI	CPT	Off
Wong et al. (1997)[9]	–	–	1.08	0.95	$p < 0.02$	16	14	ROI	Eyes closed	On

Note.—N = normal subjects; S = schizophrenia subjects; ROI = region of interest; NS = not significant (p value > 0.05); CT = computed tomography; MRI = magnetic resonance imaging; NT = not tested.

[1]Left and right areas combined.
[2]Analysis of variance with anteroposterior position; slice level and group significant; followup t test significant only for frontal lobe.
[3]T test on micromole data, our calculation of relative data on slice or whole brain metabolic rate.
[4]From their figure 5, temporoposterior cortex, left plus right.
[5]Table 6 in Buchsbaum et al. (1990), mid-posterior, micromoles, $t = 2.07$, $p < 0.05$, relative data, p = NS.
[6]Table 5 in Buchsbaum et al. (1992*a*), inferior region left and right combined, t test.
[7]Lateral superior, mid, and inferior temporal combined.
[8]Left and right combined; patients showed $p < 0.05$ diminished right more than left asymmetry.
[9]Anterior inferior region bilaterally.

Figure 2. Three-dimensional view of thalamus



The thalamus is a brain region which is a major cortical relay from the limbic system and has many important frontal lobe connections. Here, the outlines for the thalamus in the right and left hemispheres have been traced on serial magnetic resonance imaging (MRI) sections of 32 normal subjects and 27 unmedicated schizophrenic patients, and the MRI outlines coregistered to glucose metabolic images from positron emission tomography. The orientation of the brain is that of standing slightly behind the subject. The white areas indicate regions that have significantly lower relative metabolic rates in schizophrenia patients compared with controls using the method of Shihabuddin et al. (1998). This methodology allows investigators to examine subcomponents (e.g., the mediodorsal nucleus region) of the thalamus as well as other key areas that are dysfunctional in schizophrenia with anatomical accuracy.

(GABA) or GABAergic tone in schizophrenia would be expected to decrease the amplitude of the predicted normal pattern of negative striato-pallidal correlations, while disinhibition of pallido-thalamic activity would be expected to result in a more prominent negative correlation.

The largest normal–schizophrenia difference was in the correlation between GMR in the anterior thalamus and the frontal cortex, a key element in the thalamo-cortical-striatal circuit suggested to be abnormal in several models of schizophrenia (see Katz et al. 1996). Correlations between the frontal lobe and other regions were also greater in normal subjects than in patients with schizophrenia: normal subjects had three correlational paths from the frontal cortex (to the temporal cortex, the ventral anterior thalamus, and the dorsomedial thalamus) with significantly higher correlations than patients with schizophrenia did. These findings are perhaps consistent with other findings of frontal cortical dysfunction in schizophrenia.

Factor analysis based on correlational patterns also confirms regional interrelationships (Szabo et al. 1992; Friston et al. 1993; Schröder et al. 1994, 1995, 1996) consistent with the loop models discussed above, although in some cases with very small sample sizes (e.g., $n = 6$ in Friston et al. 1993). Recently, the technique called diffusion tensor imaging has permitted direct assessment of the large axon bundles stretching from the prefrontal cortex to the striatum. This anatomical technique demonstrated significantly reduced diffusion anisotropy in the white matter in these areas (Buchsbaum et al. 1998). In addition, coregistered FDG–PET on these same patients showed similar patterns of diminished interregional correlation, thus providing support for the inferences drawn about white matter connectivity from analysis of metabolic regional correlation coefficients.

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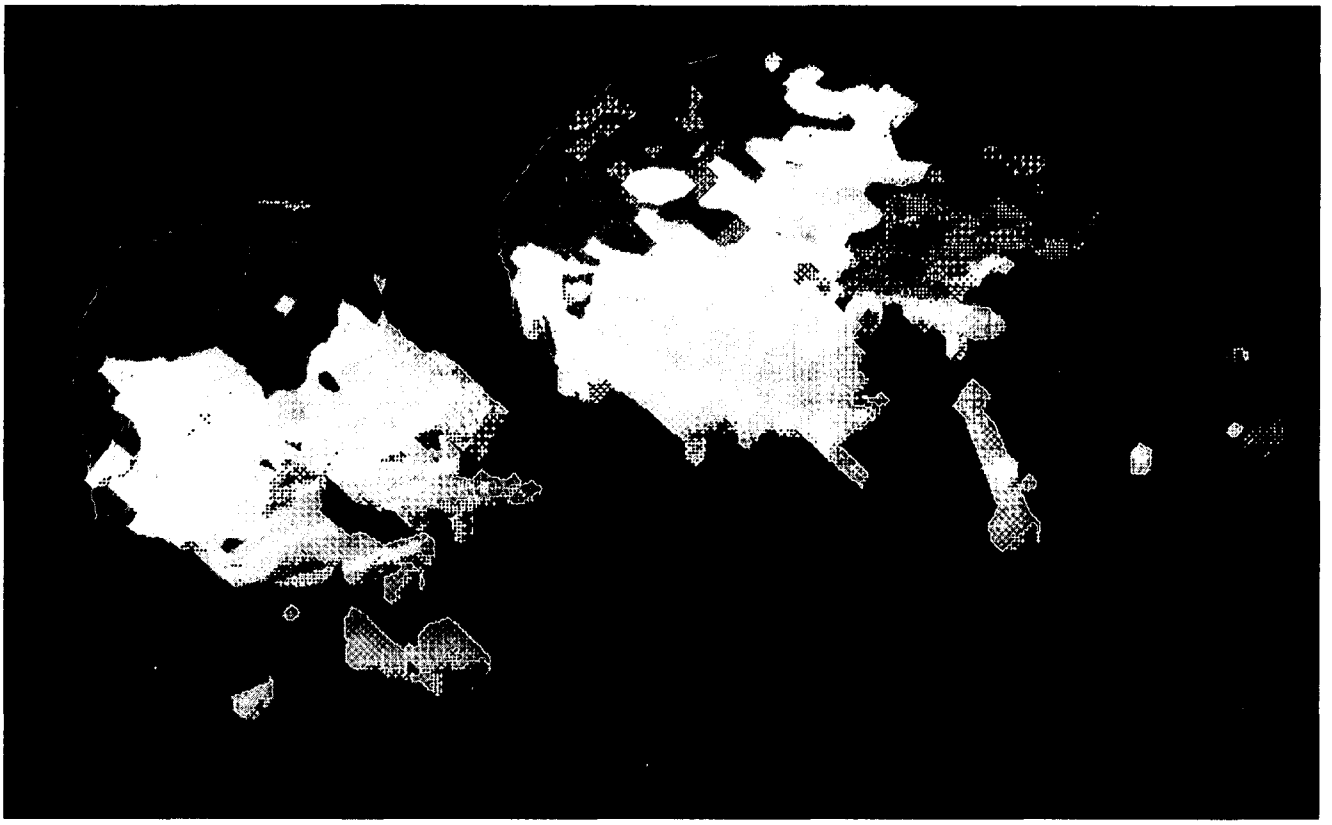

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Diagnostic Specificity

Functional imaging methods have not revealed patterns of hypoactivity or hyperactivity highly specific to schizophrenia. The relatively lower metabolic rates in the frontal lobe found in schizophrenia have also been reported in 27 studies of patients with affective disorder (Ketter et al. 1996), with perhaps even greater uniformity than in schizophrenia. Unlike affective disorder, which has been characterized by metabolic patterns reminiscent of schizophrenia, obsessive-compulsive disorders may constitute an opposite or mirror image of schizophrenia: high activity in both the frontal cortex and the basal ganglia (Baxter et al. 1987; see review in Cottraux et al. 1996 and Buchsbaum et al. 1997*a*). Successful treatment of both schizophrenia and obsessive-compulsive disorder has been associated with a normalizing effect on metabolism in the basal ganglia (Baxter et al. 1992; Buchsbaum et al. 1992*c*; Shihabuddin et al. 1998), although the changes are in opposite directions (i.e., treatment-related increases in metabolism in schizophrenia and decreases in obsessive-compulsive disorder).

Two major methodological problems limit the usefulness of these cross-disorder comparisons: ROI size and medication status. Many studies have assessed function in large, often geometrically defined areas covering a heterogeneous combination of Brodmann's areas of the frontal cortex. Patients with schizophrenia, mostly young males, are difficult to compare with the mostly female and older patients with affective disorder, especially when studies involve different imaging parameters. The effects of current or past exposure to different psychotropic drugs in the various diagnostic groups are also difficult to gauge. Schizotypal, schizoaffective, psychotic depression, and atypical psychoses patients are often excluded from imaging studies, although these are the very patients for whom diagnostic specificity issues might be of greatest importance. Response to medication may be more closely tied to frontal and striatal metabolic rate than to behavioral spectrum symptoms.

Effects of Medication

Effects on Striatal Function. Not surprisingly, the metabolic changes in response to neuroleptics can be especially marked in the striatum. We found a significant increase in metabolic rate in the putamen in eight patients with schizophrenia who were scanned both before and after neuroleptic treatment (Buchsbaum et al. 1987*a*). In contrast, no cortical area showed a statistically significant medication-related increase, although there was a trend ($p < 0.10$) toward increased metabolic rates. In the same study, significant correlations were found between metabolic changes in the basal ganglia after medication and improvement on the BPRS. Neuroleptic-related increases in the metabolic rate in the basal ganglia were also found in most other studies (Cohen et al. 1988, 1998; Wik et al. 1989; Cleghorn et al. 1991*a*, 1991*b*; Buchsbaum et al. 1992*b*, 1992*c*; Potkin et al. 1994; Holcomb et al. 1996; Wolkin et al. 1996), but not in all of them (e.g., Resnick et al. 1988). Neuroleptics may differ in their effects on the metabolic rate in the striatum as well (Bartlett et al. 1991; Buchsbaum et al. 1992*b*, 1992*c*; Potkin et al. 1994; see discussion below). One interpretation of PET studies of response to drugs is that neuroleptic action in the brain may closely reflect the striato-thalamo-cortical neural circuitry rather than a direct effect in different areas (Holcomb et al. 1996). Because there is high D_2 receptor density in the striatum, neuroleptics increase synaptic activity, which may be reflected by increased glucose metabolism. Augmented GABAergic connection from the striatum, in turn, may increase synaptic activity, thereby resulting in increased thalamic metabolism. Finally, thalamic glutamatergic efferents to the frontal and cingulate cortex may be overinhibited and, as a result, the cortex may receive reduced excitatory signals and consequently show reduced metabolic activity.

To shed light on response to neuroleptic treatment in schizophrenia, some studies have examined the effects of neuroleptic challenge on regional glucose metabolism in healthy human subjects. In a single-dose challenge study, Bartlett et al. (1994) found that relative putamen metabolic rates increased 12 hours after intramuscular administration of 5 mg of haloperidol to normal men. In a more recent study with similar methodology, Bartlett et al. (1996) found no significant regional glucose changes 2 hours after haloperidol was administered. By contrast, the DA agonists amphetamine (Wolkin et al. 1987, 1994) and apomorphine (Cleghorn et al. 1989) decreased striatal metabolic rate.

Taken together, several studies indicate that the most common pattern of striatal activity in drug-free schizophrenia is characterized by relatively low rates in the striatum, particularly the putamen. With neuroleptic treatment, the decreased activity in the striatum noted in the drug-free state tends to normalize. Conversely, administering DA agonists results in an abnormal "schizophrenia-like" reduction (although there may be differences in response in normal subjects and patients with schizophrenia [Cleghorn et al. 1991*a*, 1991*b*]). Individual differences have been found in the tendency of unmedicated patients with schizophrenia to show reduced striatal metabolism. Not all patients, of course, show such an abnormality. In this context, it is interesting to note that

the subgroup of patients with low off-medication striatal metabolic rates were found most likely to improve after neuroleptic medication was initiated (Buchsbaum et al. 1992*c*). In this study, 25 patients entered a double-blind, placebo-controlled crossover trial with haloperidol; 80 percent of responders and nonresponders were correctly identified by their striatal metabolic rate in the placebo condition. A recent study by Cohen et al. (1998) found that "high basal ganglia rates . . . predicted poor treatment response to neuroleptics" (p. 36).

Even with standard neuroleptics, which have been studied for many years, it is not possible to predict which patients will develop tardive dyskinesia. Unfortunately, once this condition becomes clinically apparent, it is largely irreversible. A *predictor* of vulnerability to tardive dyskinesia would therefore be of great clinical importance. Recent PET studies have suggested that an increased metabolic rate in the caudate nucleus can predict the subsequent appearance of tardive dyskinesia on multiyear followup (Szymanski et al. 1996) and is associated with current risk (Shihabuddin et al. 1998). Higher metabolic rates in the globus pallidus have also been associated with tardive dyskinesia (Pahl et al. 1995). Taken together, these studies suggest that FDG–PET may be a potential clinical tool for predicting tardive dyskinesia and possibly choosing between typical and atypical neuroleptics with their differential potential risks for the disorder.

Effects on Fronto-Striatal-Thalamic Circuits. Decreases in frontal cortex and cingulate were found with haloperidol (Holcomb et al. 1996), fluphenazine (Cohen et al. 1997), and clozapine (Potkin et al. 1994; Cohen et al. 1997). It is interesting to note that the *N*-methyl-D-aspartate antagonist ketamine, an agent that produces an acute psychotic state, increased prefrontal metabolic rates (Breier et al. 1997). Thalamic metabolism increased after haloperidol (Holcomb et al. 1996) but decreased after clozapine (Potkin et al. 1994). As previously discussed, this pattern of effects in descending order—striatum, thalamus, and cortex—might be related to the circuits linking the three (Alexander et al. 1986). Alexander et al. viewed the basal ganglia as a mechanism to concentrate information from the cortex and provide a cortex–basal ganglia–thalamus–cortex regulatory loop. Haloperidol might work at least partly by diminishing an abnormally active ventral tegmental area and substantia nigra dopaminergic pathways inhibiting the basal ganglia. If so, it might be expected that the neuroleptic-related metabolic effects would be greatest in the striatum and then diminished and diffused in successively later stages of the circuit. Alexander et al. (1986) stressed the separate motor and association circuits; and they proposed a lateral-orbitofrontal pathway in which the ventromedial striatum and the anterior and medial dorsal thalamus might be linked to attentional performance and maintenance of attentional set. This set of structures seems consistent both with the findings of low inferior frontal and ventral striatal values in unmedicated and never-medicated patients with schizophrenia (tables 1 and 2), as well as with the pattern of greatest striatal metabolic change in response to neuroleptics and successively lesser effects in thalamus and cortex reviewed earlier.

Bartlett et al. (1994) did not find significant relative metabolic rate changes in the thalamus of normal volunteers treated with haloperidol, a finding that possibly suggests circuit differences. Nevertheless, neuroleptic effects in the thalamus may be found in studies with a longer exposure that is more comparable to actual treatment. In addition, Resnick et al. (1988) suggest that long intervals off medication are associated with higher thalamic metabolic rates. Components of the motor loop, including the supplementary motor area and the ventrolateral thalamus, appear neither to differ between normal subjects and patients with schizophrenia nor to be affected by clozapine. However, amphetamine's effect in lowering the metabolic rate of the temporal cortex (Wolkin et al. 1987, 1994) suggests that agonists and antagonists could have different downstream effects or differential effects in normal volunteers and patients with schizophrenia (see also table 3).

Some of the important problems in understanding practical clinical pharmacology in schizophrenia include the mixed action of neuroleptics on more than a single type of receptor (e.g., Hyttel et al. 1985) and the heterogeneity of response of different patients to different medications. FDG uptake patterns may help explain these variations.

Early PET studies of neuroleptic effects (e.g., Buchsbaum et al. 1987*a*; Resnick et al. 1988) tended to lump together patients treated with a variety of conventional neuroleptic drugs. Because no clear-cut pattern of the superior efficacy of one typical neuroleptic over another had emerged, it was perhaps assumed in the early PET studies that the metabolic effects of these agents would be more or less equivalent. However, clinical lore suggests that individual patients may show systematic differences in their responses to one or another of the so-called typical neuroleptics. This is not surprising since these agents show many differences in their pharmacological profiles. Indeed, as shown in more recent studies, regional patterns of FDG uptake between haloperidol and thiothixene (Bartlett et al. 1991), clozapine and thiothixene (Buchsbaum et al. 1992*b*), clozapine and haloperidol (Potkin et al. 1994), and clozapine and fluphenazine (Cohen et al. 1997) differ significantly. More systematic

attempts to relate differences in drug-free metabolic patterns to metabolic changes arising from a variety of different neuroleptic agents may help clarify responder/nonresponder status.

Other Effects on Metabolic Rate. In addition to PET studies of typical and atypical neuroleptics, which are important for their DA- and serotonin (5-HT)-related actions, other drug classes also merit further study. Regional effects of benzodiazepines on metabolism (Buchsbaum et al. 1987*b*; de Wit et al. 1991) may allow imaging of GABA interactions in medication response or subtype. Regional effects of antidepressants (e.g., Buchsbaum et al. 1986; Baxter et al. 1989), which tend to enhance metabolism in frontal regions, may be examined as predictors of response to additive trials of antidepressants in schizophrenia. FDG–PET may reveal patterns similar to activation of the proto-oncogene c-*fos* in neurons in autoradiography studies (see the review by Duncan and Stumpf 1991). The prevalence of FDG pattern abnormalities in schizophrenia, the consistency of neuroleptic and DA agonist effects on abnormal patterns of metabolism, and the documented effects of drugs in other classes suggest the usefulness of FDG imaging as a guide in the future psychopharmacology of schizophrenia. Most investigators approach schizophrenia as a neuropsychiatric disorder reflecting dysfunction in several structures of the brain circuits (e.g., Mega and Cummings 1994). A number of transmitters, receptors, and second messengers that can be manipulated pharmacologically are involved. Thus, as the functional and chemical architecture of key circuits is revealed, FDG–PET may be particularly useful in examining the effectiveness of circuit-specific pharmacological interventions in schizophrenia.

Genetic Studies

PET studies of identical quadruplets (Nora, Iris, Myra, and Hester Genain) who were concordant for schizophrenia revealed significant hypofrontality (Buchsbaum et al. 1984*b*). The differential responses of these quadruplets to neuroleptics were noteworthy. Nora and Hester had a modest clinical response, Iris had a minimal response, and Myra actually deteriorated on medication and was discharged off medication (DeLisi et al. 1984). All four tended to have higher metabolic rates in the striatum than our concurrent normal control subjects. If we examine metabolic rates in the right inferior putamen, which was selected in a recent sample of 25 patients with schizophrenia as the best predictor of neuroleptic response (Buchsbaum et al. 1992*c*), the quadruplets showed values (Nora, 1.17; Iris, 1.25; Myra, 1.41; and Hester, 1.22) that paralleled individual differences in drug response (DeLisi et al. 1984). Myra, the quad with the highest value, showed the poorest response (worse on medication), and Nora, the quad with lowest value, showed the best neuroleptic response. In an rCBF study of monozygotic twin pairs who were psychiatrically normal, discordant for schizophrenia, and concordant for schizophrenia, Berman et al. (1992) found lower flow in the prefrontal cortex in the affected twin than in the normal cotwin in discordant pairs. The difference was significant only when the twins were studied during the performance of the Wisconsin Card Sorting Test (WCST; Heaton 1981), not when resting or doing number matching. Within concordant pairs, the authors found that the cotwin with a higher lifetime history of neuroleptic treatment was more hyperfrontal in six of eight twin pairs, suggesting to the authors that "long-term neuroleptic treatment does not play a major role in hypofrontality" (Berman et al. 1992, p. 927). No significant differences between nonaffected cotwins of patients with schizophrenia and twins from psychiatrically normal pairs were found. Thus, Berman et al. found that rCBF findings were more related to clinical diagnosis than to genetic relationship.

Clark et al. (1988) found metabolic rate correlations in normal twin pairs that supported some genetic effects. Many more PET studies in larger numbers of both monozygotic and dizygotic twin pairs are needed before any firm conclusions can be drawn.

Tasks in Functional Imaging

Since the early blood flow studies of Ingvar and Franzén (1974) that revealed hypofrontality while patients performed Raven's matrices (Raven et al. 1983) or picture naming, tasks have been widely used to control psychological activity and activate structures considered salient for schizophrenia. Weinberger et al. (1986) found lower prefrontal flow during rest and diminished activation with the WCST. Blood flow studies with this test have demonstrated greater task-associated activation in the frontal lobe in normal subjects than in patients with schizophrenia (Weinberger et al. 1986; Catafau et al. 1994; Parellada et al. 1994; Berman et al. 1995) and schizotypal personality disorder (Buchsbaum et al. 1997*b*), and normal studies showing its regional activation further support this link (Rezai et al. 1993). Correlations between relative metabolic rate in the frontal lobe and scores on the Continuous Performance Test (CPT; Nuechterlein et al. 1983) support using this task as well in assessing frontal function (Siegel et al. 1995). Other studies (e.g., Paulman et al. 1990; Sagawa et al. 1990; Deicken et al. 1995; Ross et al. 1995) have confirmed correlations between resting hypo-

frontality and performance at another session on frontal lobe tasks.

Consistent with the wide range of neuropsychological deficits seen in schizophrenia, table 1 does not reveal a clear trend toward greater patient–normal differences with any one task. This might suggest a deficit in executive function common across tasks, but it is not entirely inconsistent with findings of deficits of frontal function even in the absence of experimenter-imposed tasks—a condition imprecisely termed "rest." While it could be argued that imaging under "resting" conditions makes comparability across studies more feasible, an activation task may be no more or less problematic than the resting state. In a recent article, Andreasen et al. (1995, p. 1577) termed the so-called resting state "random episodic silent thinking (REST)," reviewed which cognitive activities may be activated in rest, and presented data on which brain areas could be associated. The views of Weinberger on the need for task-based assessment are also well known (e.g., Weinberger and Berman 1988). Many recent PET studies used tasks (e.g., Dolan et al. 1995; Silbersweig et al. 1995), and a recent FDG neuroleptic study demonstrated high test-retest reliability with a single attentional task (Holcomb et al. 1996). Adequate sample sizes for statistical power for task activation, estimated to be approximately $n = 16$ in a power-analysis study (Andreasen et al. 1996), are important, but only 7 of 21 PET studies of the frontal lobe had a sample this large.

Armamentarium of Functional Imaging Techniques

The functional imaging techniques using FDG, O15, and receptor ligands with PET, HMPAO and receptor ligands with SPECT, xenon with surface detectors, fMRI and quantitative topographic electroencephalographic (EEG)/evoked potentials (EP) have complementary power to reveal specific aspects of brain function. For identifying the neuroanatomy of psychological deficit in schizophrenia, spatial and time resolution, a variety of control tasks, and delineation of underlying neurochemical pathways are important priorities. In the cognitive realm, deficits in attention, memory, lateralization, information capacity, executive function, and sensory filtering are among the major contenders. Hypotheses based on neural systems have included a large number of brain areas, among them the frontal and temporal lobes, dorsal and ventral striatum, cingulate gyrus and hippocampus, globus pallidus, thalamus, cerebellum, and brain stem. Hypotheses based on pharmacological response have featured the neurotransmitter systems for DA, 5-HT, and glutamate. If nothing else, brain-imaging technology has deemphasized theories that postulate whole brain abnormalities and black box behavioral theories as well. Nevertheless, the lists of cognitive functions and potential anatomical substrates to be matched constitute a dauntingly complex effort. Hypotheses that begin by linking large brain areas with broad areas of cognitive function (e.g., temporal lobe and lateralization deficits or frontal lobe and executive function) can find experimental support with the full list of imaging techniques, while narrowly focused hypotheses may best be testable with only a single technique (e.g., excess number of DA receptors in the striatum with PET radioligands).

For many psychological paradigms in schizophrenia, the current hypothesis is that of a continuing, traitlike deficit in a major cognitive function. For tasks that assess vigilance, set maintenance, suppression of irrelevant stimulus features, problem solving, or memory acquisition, FDG–PET's 30-minute uptake interval is long enough to include a statistically adequate behavioral sample of trials. Psychometrically sound assessment of attentional and memory deficits usually requires hundreds of stimulus presentations over many minutes (since errors may appear in only 10% of trials). This time interval more closely matches the uptake period of FDG than that of O15–PET or fMRI blood flow techniques, which image a brief interval of a few seconds. A particular advantage of FDG–PET is that its resolution is not limited by the reduced counting time and the three- to fourfold longer 8-mm path of the positron emitted by O15. However, O15–PET and fMRI may offer unique advantages in imaging states such as hallucinations that fluctuate minute by minute (e.g., Silbersweig et al. 1995) and in designs where multiple comparison conditions within a session (e.g., saying words out loud, reading silently, viewing nonverbal stimuli) are subtracted.

PET studies with receptor ligands obviously provide very important basic information about static features such as receptor density, but such studies have not yet imaged neurotransmitter release in a behavioral paradigm. Although nonspecific, FDG has advantages in exploring altered neurochemical function. Glucose use is the final common path for the bioenergetics of all neurochemical processes. FDG uptake parallels energy consumption (Sokoloff et al. 1977; see review in Hertz and Peng 1992), can be quantitatively determined with PET (Phelps et al. 1979), and is sensitive to both the effects of neuroleptic treatment and individual differences in pharmacological response. FDG uptake is thus "generally taken to represent the integrated neuronal activity of the terminals in that region" (Tamminga et al. 1988, p. 447). While DA receptor ligand studies are important, specific ligands for

D_3 and D_4 are not yet available, and it is difficult to assess brain areas with low concentrations of DA receptors; in a neuropharmacological experiment, metabolic change can be taken as indicating both direct and indirect effects of DA receptor change.

Deoxyglucose has been widely used in animal experiments to understand the functional neuroanatomy of new neuroleptics in the search for medications specific to a particular target structure with a concentration of a key receptor subtype. Deoxyglucose can indicate not only change in glucose use in a primary area, but also the complete functional changes of the antagonist in connected areas that may be far more widespread than the target receptors. In a series of deoxyglucose studies, Freo et al. (1991*a*, 1991*b*, 1992, 1993) investigated regional effects of 5-HT agonists and interpreted their data to indicate the 5-HT receptor subtype profile. Mitchell and Pratt (1991) used the metabolic change pattern to investigate the purported 5-HT_3 antagonist ondansetron and concluded that glucose changes indicated a pattern of limbic and sensory structure change not completely limited to high 5-HT_3 areas. Cascella et al. (1994) imaged the new neuroleptic savoxepin and found a pattern not unlike that of haloperidol, indicating the difficulty in developing a neuroleptic with purely limbic effects. Taken together, these studies suggest that 5-HT agonists have different patterns of functional effect and that these patterns cannot be entirely inferred from neurochemical or radiolabeled ligand studies. The potential for applying this fruitful animal methodology to humans is suggested by a body of FDG studies on differential drug response, but it has not yet been exploited with new high-resolution PET or MRI methods.

Documented test–retest reliability is important for imaging techniques. For FDG, estimates of reproducibility in normal and schizophrenic populations are provided in Bartlett et al. (1988, 1991) and indicate that reproducibility is comparable in normal subjects and subjects with schizophrenia (with most showing whole brain metabolic variability below 10%). When a scaling factor (relative metabolic rate) was used to correct for differences in whole brain metabolism across scans, the resulting regional changes for most subjects were below 1 percent, suggesting that the *proportion* of whole brain metabolism used regionally is stable over time.

A large statistical study using rCBF data also identified the ratio as the most desirable of four normalizing transformations (Gullion et al. 1996). For this reason, most imaging studies have included ratio to whole brain or structure-to-structure ratios. Stability over time may be further enhanced by using a task; Holcomb et al. (1993) found that FDG reliability in patients was increased by task performance, even in brain areas unrelated to it. Reliability studies are available for surface xenon measures (Roland 1981) and for quantitative EEG and EP measures (Buchsbaum 1976), but the day-to-day test–retest reliability of fMRI activation magnitude has been little assessed.

The pairing of certain imaging techniques may be especially advantageous. Thus, PET, which has relatively slow time resolution but relatively high spatial resolution, might be combined with EP mapping, which is limited to surface recordings of electrical activity but has the time resolution (5 to 100 ms) necessary to sort individual trials and examine response of neural components of rapidly occurring memory and attentive processes. PET FDG and fMRI might be paired to combine the high time resolution, many-task capability of fMRI, which has a mixed physiological signal without absolute units of activity, with the lower time resolution but more precisely known glucose metabolic rate in micromole units of PET FDG. Newer MRI techniques, such as diffusion tensor imaging, which permits the visualization of white matter pathways, also can be used in combination with PET FDG (Buchsbaum et al. 1998) to provide anatomical information to complement metabolic approaches to the study of brain circuitry.

Finally, the pairing of functional and anatomical imaging must receive greater emphasis in both subcortical and cortical area studies. The lateral displacement of the caudate from ventricular enlargement, the variable anterior-to-posterior placement of the cingulate gyrus, and the horizontal position of the tip of the temporal lobe are but a few of the individual variations in anatomical coordinates that may differ between normal subjects and patients with schizophrenia. While many investigators now have coregistered PET/MRI scans available, the information obtained from the MRI is often not exploited in commonly applied data-analytic approaches based on atlas-derived stereotaxic coordinates. For studies of normal subjects, there are advantages to using a universal atlas with a simple linear transformation, but extending this method into studies of patients with morphological abnormalities may create interpretation hazards. Even if a stereotaxic point is actually within a structure, it may not provide a representative value. A single coordinate in the center of the caudate may yield systematically higher metabolic rates than an ROI outlined on MRI or computed tomography. Visual placement of a box ROI on a functional image is typically on a regional peak, thus also providing an upward bias. Shrinkage of the basal ganglia with aging, chronic neuroleptic treatment, or the schizophrenic process might affect small central stereotaxically placed boxes less than the metabolic rate as outlined on MRI studies but still not reflect the metabolic rate of the total structure available with outlining.

Conclusion

This review focused primarily on FDG–PET. Compared with the other available techniques, FDG–PET has both advantages and disadvantages. The fact that many of the advantages have mirror-image disadvantages illustrates the need for studies using the full armamentarium of imaging techniques. Compared with O15–PET, FDG–PET has high spatial resolution, but low temporal resolution. O15's temporal resolution is itself bested by fMRI's, which is in turn vanquished by EP mapping and magnetoencephalography (MEG). Despite their superior temporal resolution, however, fMRI, EP mapping, and MEG approaches have limited ability to fully survey the brain; that is, they are confined to surface measurement or to particular slices. Compared with PET-ligand studies, FDG–PET cannot provide neurotransmitter-specific information about brain function. By the same token, however, FDG– PET can show the combined actions of many transmitters (consonant with the multineurotransmitter effects of most drugs) and of effects that occur in structures downstream of the initial receptor-binding effects of drug administration. Because the information gained is comparatively nonspecific, inferences must be made about the neurotransmitters involved. Although challenges with pharmacological agents and concurrently obtained biochemical measurements can be used to enhance the accuracy and sophistication of those inferences, FDG–PET will never be able to obtain the relative selectivity to a single transmitter provided by PET-radioligand approaches, which will undoubtedly improve as still more selective ligands are developed. But in this continuing cycle of invidious comparisons, it must be acknowledged that it would take a minimum of two separate scans with each of the multiple ligands to provide the same information provided by a single FDG scan.

The lesson to be drawn, it would appear, is that all of the imaging approaches have their uses, and primacy cannot be claimed for any one of them. The information to be gained from the full armamentarium of imaging techniques will perhaps lead to incremental progress in our understanding of schizophrenia.

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