Positron emission tomography (PET) has a potentially unique position in the study of psychiatric and neuropsychiatric disorders. The mechanisms by which regional pathologic changes disrupt normal psychologic functioning and the relationships between mental events and brain physiology are now open to empirical study. Although progress has been made in revealing the functional anatomy of human cognition, PET has not, as yet, clarified the pathologic processes underlying the major psychiatric disorders. This failure may mean that the processes mediating psychiatric disorders are beyond the resolution of PET or, alternatively, that the design of PET studies of psychiatric disorders is not sufficiently refined.

The primary focus of PET studies up to the present has been the investigation of neurologic disorders. In the application of PET to psychiatric research it is important to bear in mind essential differences between psychiatric and neurologic disorders. Psychiatric illness involves the disorganization of internal experience as opposed to the breakdown of primary sensorimotor function. Arguably PET methodologic strategies that have proved fruitful in the study of neurologic disorders, where there are fixed pathologic features, may be inappropriate to the study of psychiatric disorders. In psychiatric disorders, with no fixed pathologic features, abnormalities are likely to be "functional," involving disturbed neural integration. Therefore novel strategies or augmentation of existing methods will be necessary in the investigation of these disorders.

The choice of appropriate PET methods for data acquisition and analysis in studies of psychiatric disorders has still to be established. The normal responsivity of psychiatric patients to psychologic and physical stressors makes scan conditions critical. It can be argued that state metabolic scans should be augmented during the performance of cognitive tasks or during specific pharmacologic manipulations. Most PET studies reported to date have been performed under resting conditions and this may partially explain the lack of consistent findings. The absence of standardized approaches to PET analysis in circumstances where little is known concerning regional pathologic characteristics is a further drawback and has led to an excess reliance on ratio data. This type of approach can often be misleading because such relative values have been shown to be highly sensitive to ambient conditions. The seemingly arbitrary region of interest reported in the literature emphasizes need for standardized methods of region of interest definition or the exploration of alternative approaches.

As well as issues of study design, careful patient selection and characterization are fundamental in psychiatric studies. Lack of homogeneity can render relationships between cognitive groups and PET measures extremely elusive. Homogeneity is difficult to achieve using cross-sectional assessments, which are standard in psychiatric research. Such methods need to be augmented by either longitudinal assessments with the use of genetic or other such biologic markers.
psychiatric abnormalities. Particularly striking is the remitting nature of many psychiatric disorders, which emphasizes the need for appropriate studies in relation to clinical state. This article examines findings from PET studies of patients with psychiatric and neuropsychiatric disorders and highlights areas of current and future interest. Most studies have concerned the psychotic disorders, schizophrenia and affective disorders, and consequently the greater emphasis in this article will address findings in these areas.

SCHIZOPHRENIA

Schizophrenia is the most prevalent and disabling psychotic disorder and is characterized by a wide age of onset, symptoms such as hallucinations, delusions, disordered thinking (positive symptoms), and impoverished motivation and feeling (negative symptoms). A genetic predisposition is well established, although beyond this there is much uncertainty regarding etiology, which may be multifactorial. Schizophrenia is defined phenotypically and may subsume a number of clinical syndromes. PET studies of schizophrenia date from 1980 and vary according to the group studied and the image used. The most extensively used PET imaging techniques have been measurements of cerebral blood flow, metabolism, and receptor binding in normal vs. abnormal brains by comparison with controls. Patients have been classified according to standardized diagnostic criteria and this approach assumes regional dysfunction features common to clinically defined syndromes of schizophrenia. No such relationship between regional pathologic changes has been found.

Some early studies of regional cerebral blood flow (rCBF) in schizophrenia using xenon inhalation techniques suggested a relative decrease in several brain regions. Despite methodologic problems with these pioneering studies, associations emerged between abnormal patterns of perfusion and specific symptoms. In general, patients with predominant frontal rCBF tended to be the most mute, mute, and indifferent. This pattern of hypofrontality therefore is a finding antedating 1980 and remains important and controversial. Hypofrontality, a relative reduction in prefrontal cortical blood flow or metabolism, has been most often reported using PET. Despite this, there remains controversy regarding its reproducibility, specificity, sensitivity to the confounding effects of drugs, and dependence on cognitive state over time. Three studies using deoxyglucose as a metabolic tracer, which yielded contradictory results, will be considered.

DeLisi et al studied patients with chronic schizophrenia and matched controls. The patients met strict DSM-III criteria for schizophrenia and were medication free for at least 2 weeks prior to the study. Patients had significantly lower anterior to posterior ratios (eight of the nine patients had ratios less than 1). Cerebral atrophy as determined by CAT scan was not associated with this aberrant metabolic pattern. Gur et al in two communications described abnormalities of the subcortical-cortical metabolic gradient in schizophrenic patients who were medication free for at least a week. The duration of illness varied from 3 to 17 years. No evidence for hypofrontality was found. Finally, Szechtman et al in a controlled study examined whether neuroleptic treatment duration influenced the regional distribution of metabolism in patients meeting Research Diagnostic Criteria (RDC) for schizophrenia. The patient group was dichotomized according to treatment duration. Both groups had a greater anterior to posterior ratio than control subjects, although this was less evident in the group with the longest neuroleptic exposure.

As in much other work on schizophrenia, the basic findings with PET are often not reproduced. Explanations for these apparently inconsistent results include the confounding effects of treatment and illness duration as well as differences in scanning procedure and in image analysis. An important consideration is the relative preponderance of positive and negative symptoms in the groups studied, which may reflect differing etiologies and pathologies. In this context Liddle has described three subsyndromes of schizophrenia which include a syndrome of “psychomotor poverty” characterized by negative symptoms (flat affect, poverty of speech and spontaneous movement). Based on a comparison of signs and symptoms in focal brain lesions, it is suggested that this syndrome is associated with impaired dorsolateral prefrontal cortical (DLPFC) function. The prediction that hypofrontality is associated with negative symptoms, within any patient group, has received independent support from PET studies. DeLisi et al reported that the only significant correlations between relative hypofrontality and symptom ratings were for emotional withdrawal, disorientation, distractibility, and helplessness or hopelessness. Kishomoto et al discriminated among three distinct types of metabolic pattern in chronic schizophrenic patients. Hypofrontal patients tended to show flat, blunted affect and a hypoparietal group, delusions and hallucinations. Because diagnostic criteria place an emphasis on delusions and hallucinations (positive symptoms), psychomotor poverty syndromes (negative symptoms) are likely to...
be underselected in some study protocols and therefore hypofrontality will be a variable finding across studies.

The possible relationships between negative symptoms, hypofrontality, and putative abnormalities of the mesocortical dopaminergic system have been addressed from a number of perspectives. Animal studies using autoradiography have shown increased frontal and anterior cingulate metabolic response to the dopaminergic agonist apomorphine. Corresponding dopaminergic challenge in humans has yet to be established, although initial studies have been reported. Wolkin et al. reported decreased frontal, temporal, and striatal glucose metabolism in schizophrenic and control subjects following d-amphetamine (0.5 mg/kg orally). Gerard et al. report a reversible hemodynamic hypofrontality in young schizophrenic patients. Hypofrontality was seen in chronic patients whose disease had evolved over more than 2 years, and this pattern disappeared during exacerbation of the symptoms. In a subgroup who had not been treated for several weeks a weak dose of a dopaminergic agonist restored near-normal frontality. The investigators conclude, "This [dopamine hypersensitivity] may reflect either the role of neuroleptic washout or a primitive dopaminergic depletion as proposed by some authors in the chronic form of schizophrenia." This is consistent with a study of patients, characterized by short duration of illness, before and after medication. In a medication-free state, patients had asymmetric basal ganglia uptake, left greater than right. Following dopamine receptor blockade consequent upon treatment, this asymmetry was abolished, but a left prefrontal cortical reduction in glucose uptake became evident.

Basal ganglia changes in dopamine pharmacology have been reported from postmortem studies of schizophrenia patients, although the findings are confounded by possible drug effects. Increase in D2 receptors in unmedicated schizophrenic patients has partial support from the PET literature. Wong et al., using displacement of 11C N-methylspiperone by unlabeled haloperidol, studied D2 receptor density in normal, drug-naive, and treated schizophrenic subjects. A three-compartment model with irreversible radioligand binding was assumed. Significant increases in receptors were reported for both schizophrenic groups, with the increase being more evident in drug-treated patients. There is continuing debate over the reproducibility of these findings and criticisms of methods of data analysis have been expressed.

Making PET a behaviorally or pharmacologically specific technique is the object of activation paradigms. Behavioral specificity can be achieved by using PET in conjunction with cognitive or motor paradigms. Regional deficits measured with PET can be seen as a common concomitant of both clinical and neuropsychologic symptoms. The approach depends on first establishing the functional anatomy of relevant cortical and subcortical regions in normal subjects. Weinberger et al. reported findings that imply physiologic hypofrontality and increased metabolic rate in the prefrontal cortex in response to a specific cognitive challenge, the Wisconsin Card Sort. Using the xenon-133 inhalation technique, they reported that at rest patients had a relative not absolute reduction in dorsolateral prefrontal flow. During the cognitive activation, the patients showed evidence of impaired augmentation of the regional flow. These results have yet to be independently reproduced, and the likelihood that this complex task involving a visual, auditory, and motor component is regionally specific is controversial.

Other, more simple, activation studies have been reported. Cohen et al. studied cerebral blood flow during an auditory discrimination task designed to emphasize sustained attention. A direct relationship was found between metabolic rates in the prefrontal cortex and accuracy of performance. In schizophrenics lower flow was found in the prefrontal cortex, which was unrelated to performance. Warkentin et al. used a verbal fluency task as a cognitive challenge. The marked effect of the activation in normal subjects was seen in the left prefrontal area, but in the schizophrenic group this increase was attenuated.

The investigators conclude, "The controversy regarding frontal lobe dysfunction in schizophrenia is related to whether these areas are functionally challenged or not." Using 11C-deoxyglucose as PET tracer, Volkow et al. studied patients suffering from chronic schizophrenia using a smooth pursuit tracking activation task. Both at baseline and during activation, patients displayed absolute augmentation of prefrontal hypometabolism. Patients with negative symptoms had lower frontal, temporal, and parietal metabolic rates compared with those with positive symptoms across both conditions. Significant between-condition differences were observed solely in the positive group. During task performance, significant negative correlations between frontal lobe metabolism and symptom ratings appeared. This study therefore illustrates the evidence that activation studies may increase not only specificity, but also the sensitivity of PET.

Etiology has not been addressed by PET studies of schizophrenia. Berman et al. have used their xenon inhalation technique, in conjunction with Wisconsin Card Sort, to studies of regional...
Six twins concordant and discordant for schizophrenia. Their findings suggest that the neuroanatomic defect in prefrontal function is not directly mediated by the genotype. Furthermore, lifetime neuroleptic medication use may explain differences in hypofrontality in discordant pairs. This finding, which needs replication with PET, may suggest that hypofrontality behaviorally impairment, and regional cerebral blood flow (CRF) in schizophrenic, including depressives, with normal controls and failed to find differences across groups. Other studies of depressed and manic subjects also failed to find differences from controls.

A single study of depressed patients, using the xenon technique, has used an activation paradigm. Patients were studied in the resting state and during performance of both a verbal and a spatial task. Although no overall differences were apparent between groups during rest, differences emerged in the rCBF patterns of depressive and control subjects during cognitive activation. The depressed female patients had higher than normal flow in all states, whereas the depressed male patients had lower resting flow that became normal during cognitive activation.

The earliest study of affectively ill patients using PET compared regional cerebral metabolic rate of glucose (rCMRglu) values in schizophrenic, affective disorder, and control subjects using a somatosensory paradigm (subjects received 1/sec electric shocks to the right forearm) which attempted to control for the ambient state. The order of magnitude of these changes is indicated by an investigation that demonstrated a similarity in the metabolic rates for glucose between patients with depression and those with multi-infarct dementia. Only a single report to date has failed to find altered cerebral metabolism in depression. No differences were found in cerebral glucose utilization in a heterogeneous group of chronic psychiatric patients, including six depressives, and normal control subjects. The small sample size and the chronic population studied limit and complicate the interpretation of this study.

In contrast to these preliminary reports a detailed series of studies of affective patients using F deoxyglucose as a metabolic tracer has been reported. In the first of these, unipolar and bipolar patients were studied under a variety of con-

**AFFECTIVE DISORDERS**

The etiology of affective disorders is still uncertain. The most widely accepted viewpoint posits neural disturbances of neural networks in critical brain centers concerned with mood regulation. Normal neural transmission in monoaminergic systems has been implicated by the advent of psychotropic drugs. No specific monoaminergic system abnormality in affective disorders has been identified using indirect methods. This feature has frequently been attributed to the lack of direct measures of brain function in vivo.

Disorders of CBF in affective disorders, using xenon inhalation technique, have suggested that decreases in CBF in depressed patients have been replicated by a number of separate investigators, who likewise reported decreased CBF in depressed compared with control subjects. Uytdehoef et al reported changes of a different kind in a study of unipolar and bipolar patients, the latter while in remission. Significant left frontal hyperperfusion and right posterior hypoperfusion were seen in the depressive compared with control subjects. This pattern was not observed in the euthymic bipolar patients, suggesting that alterations in rCBF in depression might be state dependent. These findings were not replicated in a number of other reports. Gustafson et al compared a heterogeneous group of patients, including depressives, with normal controls and failed to find differences across groups. Other studies of depressed and manic subjects also failed to find differences from controls.
jeers. The data further suggested, like the xenon
jor depression.

The bipolar patients were studied either in a
manic or depressed phase and when euthyrnic on

or without major depression, and normal control subjects. A significant lowering of
metabolic rates for glucose in the left dorsal
anterolateral prefrontal cortex was reported in pa-

patients with primary depression, unipolar and bi-
polar, by comparison with other groups. Similar re-
sults, although less marked, were obtained for the
dorsal anterolateral prefrontal cortex. Obsessive
compulsive patients with depression displayed
lower metabolic values in the same regions as pa-

tients with primary depression. Glucose metabolic
rates in the left anterolateral prefrontal cortex cor-
related significantly with severity ratings of depres-
sion. Following clinical response to medication, the
metabolic pattern became normal. The investiga-
tors concluded that the findings suggested a left
anterolateral prefrontal cortex abnormality in ma-
jor depression.

In conclusion, PET, and early studies using xe-
on, of affectively ill patients are consistent in-
ly detecting decreased cerebral metabolism, greatest in
inferior frontal region, during the depressed

No theoretical framework has been articulated to
accommodate these findings with conventional
theories of monoaminergic function in depression.

The findings have considerable face validity since
mood changes are a frequent concomitant of intel-
tal state pathologic states. Although the findings
suggest decreased frontal metabolism are reminiscent
of those reported in schizophrenic patients, due to
anatomic resolution of early PET techniques, they
don not exclude subtle focal differences between nosologically distinct patient groups.

OBSESSIONAL DISORDERS

Obsessional compulsive disorders (OCD)
among the most disabling nonpsychotic psycho-
disorders and occur in pure form or as severe
phenomena in other psychiatric disorders, par-
icularly depression, and in primary neurosis.

This association with neurologic dysfunction and the similarities between intrusive ideation
in OCD and intrusive motor acts, such as tics, led
to the hypothesis that OCD may be secondary
dysfunction in basal ganglia or related structures.

This hypothesis is now amenable to direct
test by PET.

Baxter et al11 compared metabolic rates
of glucose in 14 patients with OCD, normal
subjects, and patients with primary depression.
A significant increase in the metabolic rate in
anterior orbital gyrus, a nonsignificant increase in the
orbital gyrus, and a bilateral increase in caudate
metabolism, specific to patients with OCD, was
observed. Changes in the caudate to hemi-
pheric metabolic ratio exclusive to medication-responsive
OCD patients were also reported. In a
study, OCD patients with and without
depression were compared with normal sub-
jects. Metabolic rates in the OCD patients
without depression were significantly lower in the
terolateral prefrontal cortex compared with pa-
ients without depression, a metabolic pattern
similar to that seen in patients with panic
depression. A single study of five pa-
tients with Gilles de la Tourette syndrome, a condi-
tion invariably associated with obsessional pha-
ses, has also reported increased metabolism in the
ganglia.12

PET studies therefore support the view
that obsessional disorders are associated with
pathologic states in the basal ganglia and pre-
lateral lobes. Because OCD is responsive to pa-


The pharmacologic treatment would be of interest to establish the effects such interventions might have on cerebral metabolism. The findings if established would have a major impact on the nosology of OCD, which has traditionally been regarded as a neurotic disorder with a presumed organic etiology.

### Anxiety and Panic Disorders

Recurrent, discrete, episodic, and spontaneous anxiety attacks are the principal features of panic disorder (PD). Its nosology is controversial. It is generally considered as a form of anxiety, although there is a viewpoint that PD is a separate neurologic entity with unique pathophysiologic characteristics. A feature of PD is that it may be induced in susceptible patients by sodium lactate infusion.

The relationship between panic disorder and anxiety has been investigated using PET. Cerebral blood flow was measured in patients with a history of panic disorder and control subjects. Two groups of patients with PD were identified, those with positive and negative lactate responders. Whole brain and hemispheric CBF was measured as well as specific brain regions, including the hippocampus and parahippocampal gyrus. Differences were found between groups for brain or hemispheric CBF, but the left to right CBF ratio differed in the parahippocampal areas of the lactate responders. In an extension of this study, with the addition of further patients with PD and control subjects, the finding was replicated and in addition asymmetries of blood volume and metabolism were found. The patient with PD also had higher whole brain oxygen metabolism.

Depression is a common accompaniment of Parkinson’s disease and may frequently antedate the onset of motor impairment. Its relationship to the disorder is controversial and has been conceptualized as a psychologic reaction to the motor disability. Mayberg et al have investigated the relationship between cerebral glucose metabolism and mood disorder in parkinsonian patients. Depressed parkinsonian patients had a significant decrease in rCMRglu in the orbital and inferior prefrontal cortex compared with nondepressed patients and control subjects. A significant corre-
lation emerged between ratings of mood severity and rCMRglu in these regions. It is tempting to speculate that the decreased metabolism was related to loss of extrastriatal ascending monoaminergic projections, since destruction of these pathways in primates is associated with decreased frontal metabolism.

**SUMMARY**

PET is potentially the most powerful tool yet available for the direct, in vivo investigation of the biologic basis of psychiatric and neuropsychiatric disorders. The fulfillment of its potential rests on the development of methodologies and study design appropriate to psychiatric disorders. To date, findings in both schizophrenia and affective disorder, using protocols largely based on resting state data acquisition, suggest altered regional metabolism. These approaches need to be extended, particularly by the application of protocols that utilize PET to obtain longitudinal data under controlled experimental situations. In two conditions traditionally ascribed to psychologic causes, OCD and PD, there is intriguing evidence of specific biologic abnormalities, which, if confirmed, would lead to a fundamental revision of their nosologic status. In neuropsychiatric disorders PET findings, although preliminary in nature, offer an alternative paradigm to traditional clinicopathologic correlations by suggesting that clinical impairments relate to physiologic effects at sites distant from structural lesions.

**REFERENCES**

1. Ingvar DH, Fransen G. Distribution of cerebral activity in chronic schizophrenia. Lancet 1974;2:1484–6
12. Liddle PF. The symptoms of chronic schizophrenia: examination of the positive negative dichotomy. Psychiatry 1987;151:145–51
20. Farde L, Wiesel FA, Hall H, et al. No D2 receptor increase in PET study of schizophrenia. Arch Gen Psychiatry 1987;44:671
22. Weinberger DR, Berman KF, Zec RF. Phasic dysfunction of the dorsolateral prefrontal cortex in schizophrenia: I. Regional cerebral blood flow evidence. Arch Gen Psychiatry 1986;43:114–24