

## Positron Emission Tomography in Psychiatric and Neuropsychiatric Disorders

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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 psychological 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 responsiveness of psychiatric patients to psychological and physical stressors makes scanning conditions critical. It can be argued that rest state metabolic scans should be augmented by studies during the performance of cognitive tasks or during specific pharmacologic manipulations. Most PET studies reported to date have been required under resting conditions and this may partially explain the lack of consistent findings. The absence of standardized approaches to PET image analysis in circumstances where little is known concerning regional pathologic characteristics is another 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 selection reported in the literature emphasizes the need for standardized methods of region of interest definition or the exploration of alternative approaches.

As well as issues of study design, equal attention must be applied to patient selection and characterization. Homogeneity of the patient group is fundamental in psychiatric studies. Lack of homogeneity can render relationships between the 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 supplemented by either longitudinal assessments or the use of genetic or other such biologic markers.

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ing and remitting nature of many psychiatric disorders emphasizes the need for appropriate designs of 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 major psychiatric disorders, schizophrenia and affective disorders, and consequently the greater part of this article will address findings in these conditions.

## SCHIZOPHRENIA

Schizophrenia is the most prevalent and disabling psychotic disorder and is characterized by an early age of onset, symptoms such as hallucinations, delusions, disordered thinking (positive symptoms), and impoverished motivation and feelings (negative symptoms). A genetic predisposition is established, although beyond this there is much controversy regarding etiology, which may be multiple. Schizophrenia is defined phenomenologically and may subsume a number of clinical syndromes.

PET studies of schizophrenia date from 1980 and vary according to the group studied and the technique used. The most extensively used PET strategies have been measurements of cerebral blood flow, metabolism, and receptor binding in patients by comparison with controls. Patients have been classified according to standardized diagnostic systems and this approach assumes regional pathologic features common to clinically defined syndromes of schizophrenia. No such relationship with 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 frontal regions.<sup>1-3</sup> Despite methodologic problems with these pioneering studies, associations emerged between abnormal patterns of perfusion and specific symptoms. In general, patients with the lowest frontal rCBF tended to be the most withdrawn, mute, and indifferent. This pattern of hypofrontality therefore is a finding antedating PET and remains important and controversial.

Hypofrontality, a relative reduction in prefrontal cortical blood flow or metabolism, has been widely reported using PET.<sup>4-7</sup> Despite this, there is continuing controversy regarding its reproducibility, specificity, sensitivity to the confounding effects of drugs, and dependence on cognitive state and symptoms. Three studies using deoxyglucose as a metabolic tracer, which yielded contradictory results, will be considered.

DeLisi et al<sup>8</sup> studied patients with chronic schizophrenia and matched controls. The patients met strict DSM-II 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<sup>9,10</sup> in two communications described abnormalities of the subcortical 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<sup>11</sup> 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<sup>12</sup> 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<sup>13</sup> reported that the only significant correlations between relative hypofrontality and symptom ratings were for emotional withdrawal, disorientation, distractibility, and helplessness or hopelessness. Kishimoto et al<sup>14</sup> 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.<sup>15</sup> Corresponding dopaminergic challenge in humans has yet to be established, although initial studies have been reported. Wolkin et al<sup>16</sup> report decreased frontal, temporal, and striatal glucose metabolism in schizophrenic and control subjects following d-amphetamine (0.5 mg/kg orally). Geraud et al<sup>17</sup> 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."<sup>17</sup> This is consistent with a study of patients, characterized by short duration of illness, before and after medication.<sup>18</sup> 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,<sup>19</sup> using displacement of <sup>11</sup>C 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<sup>20</sup> and criticisms of methods of data analysis have been expressed.<sup>21</sup>

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 sensorimotor activation. Regional deficits measured with PET can be seen as a common concomitant of clinical and neuropsychologic symptoms. This approach depends on first establishing the functional anatomy of relevant cortical and subcortical regions in normal subjects. Weinberger et al<sup>22</sup> have reported findings that imply physiologic dysfunction of 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 but 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 the particular complex task involving a visual, abstract, and motor component is regionally specific is controversial.

Other, more simple, activation study designs have been reported. Cohen et al<sup>23</sup> studied cerebral function during an auditory discrimination task designed to emphasize sustained attention. A direct relationship was found between metabolic rate in the prefrontal cortex and accuracy of performance. In schizophrenics lower flow was found in the prefrontal cortex, which was unrelated to task performance. Warkentin et al,<sup>24</sup> again using a xenon inhalation measurement of rCBF, 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 <sup>11</sup>C-deoxyglucose as a PET tracer, Volkow et al<sup>25</sup> studied patients with chronic schizophrenia using a smooth pursuit eye tracking activation task. Both at baseline and during activation, patients displayed absolute and relative frontal 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 point 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<sup>26</sup> have extended their xenon inhalation technique, in conjunction with Wisconsin Card Sort, to studies of motor



otic twins concordant and discordant for schizophrenia. Their findings suggest that the neurophysiologic defect in prefrontal function is greater for the schizophrenic twin in a discordant pair. Furthermore, lifetime neuroleptic medication did not explain differences in hypofrontality in the concordant pairs. This finding, which needs replication with PET, may suggest that hypofrontality is not directly mediated by the genotype.

In conclusion, PET studies of schizophrenia suggest a pattern of hypofrontality in some groups of patients diagnosed as schizophrenic. Hypofrontality is best correlated with a clinical psychomotor disorder syndrome with predominantly negative symptoms. The functional state at the time of scanning can greatly change the nature of the findings, and this is best exemplified by studies using activation paradigms. Much work needs to be done to refine and develop activation strategies both cognitive and pharmacologic. Their combined use offers the possibility of linking abnormal neuro-transmission, behavioral impairment, and regional pathologic changes in schizophrenia.

### AFFECTIVE DISORDERS

The etiology of affective disorders is still unknown. The most widely accepted viewpoint posits functional disturbances of neural networks in critical brain centers concerned with mood regulation. Abnormal neural transmission in monoaminergic pathways has been implicated by the advent of potent antidepressant drugs. No specific monoaminergic system abnormality in affective disorders has yet been identified using indirect methods. This failure has frequently been attributed to the lack of direct measures of brain function *in vivo*.

Compared with studies of schizophrenia, there are relatively few PET studies of affective patients and most of those reported have focused on the measurement of cerebral blood flow (CBF) and metabolism. Early studies used the xenon inhalation technique. These will be discussed as a preliminary to a consideration of PET studies.

Studies of CBF in affective disorders, using the xenon inhalation technique, have suggested generalized decreases in CBF in depressed patients. Mathew et al<sup>27</sup> studied 13 young patients of an age- and sex-matched control group. The patients met RDC for depression and had a medication washout period of 2 weeks. A generalized decrease in cerebral blood flow was reported in the patients compared with control subjects. An inverse relationship was observed between blood flow and an index of illness severity. The principal findings were replicated by a number of sepa-

rate investigators, who likewise reported decreased CBF in depressed compared with control subjects.<sup>28,29</sup> Uytendhoef et al<sup>30</sup> 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<sup>31</sup> 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<sup>32</sup> and depressed patients alone<sup>33</sup> 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.<sup>34</sup> 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 across subjects.<sup>35</sup> The affective patients showed a reduced anteroposterior gradient in glucose metabolism compared with control subjects. 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.<sup>36</sup> Only a single report to date has failed to find altered cerebral metabolism in depression.<sup>37</sup> No differences were found in cerebral glucose utilization in a heterogeneous group of chronic psychiatric patients, including six chronic 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 <sup>18</sup>F deoxyglucose as a metabolic tracer has been reported.<sup>38-40</sup> In the first of these, unipolar and bipolar patients were studied under a variety of con-



ditions. The unipolar group were scanned in a drug-free baseline state, following administration of methylphenidate and when euthymic on follow-up. The bipolar patients were studied either in a manic or depressed phase and when euthymic on follow-up. An interesting observation was that the bipolar depressed patients in the resting state had lower hemispheric metabolic rates for glucose than either control subjects, unipolar depressed or bipolar manic patients. A subgroup of unipolar depressed patients were identified who had metabolic asymmetries, most prominent in the posteroinferior frontal areas. In this latter group a positive clinical response to methylphenidate was associated with normalization of metabolic asymmetries, whereas an absent clinical response was associated with persistence of asymmetries.

In a subsequent communication on an enlarged series of patients, including unipolar depressives, bipolar depressives, a bipolar mixed group, a manic group, and a control group, the bipolar depressed and the mixed bipolar patients were reported as displaying lower supratentorial whole-brain glucose metabolic rates than any of the comparison groups.<sup>39</sup> Patients with unipolar depression had significantly lower metabolic ratios of caudate nucleus to whole hemisphere values than either the other patient groups or control subjects. The data further suggested, like the xenon studies, that global hypometabolism in the depressed bipolar patients was state dependent because the metabolic rates "normalized" when patients were euthymic or in a manic phase.

The possibility of a common pathophysiologic basis for the behavioral expression of depression was investigated in a study that examined cerebral metabolic rates in a heterogeneous group of depressives, patients with obsessive compulsive disorders with or without major depression, and normal control subjects.<sup>40</sup> A significant lowering of metabolic rates for glucose in the left dorsal anterolateral prefrontal cortex was reported in patients with primary depression, unipolar and bipolar, by comparison with other groups. Similar results, although less marked, were obtained for the right dorsal anterolateral prefrontal cortex. Obsessive compulsive patients with depression displayed lower metabolic values in the same regions as patients with primary depression. Glucose metabolic rates in the left anterolateral prefrontal cortex correlated significantly with severity ratings of depression. Following clinical response to medication, the metabolic pattern became normal. The investigators concluded that the findings suggested a left anterolateral prefrontal cortex abnormality in major depression.

In conclusion, PET, and early studies using xe-

non, of affectively ill patients are consistent in finding decreased cerebral metabolism, greatest in the inferior frontal region, during the depressed state. No theoretical framework has been articulated to accommodate these findings with conventional theories of monoaminergic function in depression. The findings have considerable face validity in that mood changes are a frequent concomitant of frontal lobe pathologic states. Although the findings of decreased frontal metabolism are reminiscent of those reported in schizophrenic patients, the poor anatomic resolution of early PET techniques do not exclude subtle focal differences between the nosologically distinct patient groups.

### OBSESSIONAL DISORDERS

Obsessional compulsive disorders (OCD) are among the most disabling nonpsychotic psychiatric disorders and occur in pure form or as secondary phenomena in other psychiatric disorders, particularly depression, and in primary neurologic disorders. This association with neurologic disorders and the similarities between intrusive ideations in OCD and intrusive motor acts, such as tics, have led to the hypothesis that OCD may be secondary to dysfunction in basal ganglia or related systems. This hypothesis is now amenable to direct testing by PET.

Baxter et al<sup>41</sup> compared metabolic rates for glucose in 14 patients with OCD, normal control subjects, and patients with primary depression. A significant increase in the metabolic rate in the orbital gyrus, a nonsignificant increase in the caudate nucleus, and a bilateral increase in caudate metabolism, specific to patients with OCD, were observed. Changes in the caudate to hemisphere metabolic ratio exclusive to medication-responsive OCD patients were also reported. In a further study, OCD patients with and without major depression were compared with normal control subjects. Metabolic rates in the OCD patients with depression were significantly lower in the left anterolateral prefrontal cortex compared with patients without depression, a metabolic pattern similar to that seen in patients with primary depression. A single study of five patients with Gilles de la Tourette syndrome, a condition invariably associated with obsessional phenomena, has also reported increased metabolism in the basal ganglia.<sup>42</sup>

PET studies therefore support the hypothesis that obsessional disorders are associated with functional changes in the basal ganglia and the frontal lobes. Because OCD is responsive to psycho-



pharmacologic treatment it 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 status of OCD, which has traditionally been classified as a neurotic disorder with a presumed psychologic etiology.

### ANXIETY AND PANIC DISORDERS

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

The relationship between panic disorder and anxiety has been investigated using PET.<sup>43</sup> Cerebral blood flow was measured in patients with a history of panic disorder and control subjects. Two groups of patients with PD were identified, namely, patients with positive and negative lactate response. Whole brain and hemispheric CBF was measured as well as specific brain regions, including the hippocampus and parahippocampal gyrus. No differences were found between groups for whole brain or hemispheric CBF, but the left to right CBF ratio differed in the parahippocampal gyrus 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 oxygen metabolism were found. The patients with PD also had higher whole brain oxygen metabolism.<sup>44</sup>

The relationship between anxiety, panic disorder, and normal anticipatory anxiety was investigated in a study of subjects at rest and during sodium lactate infusion.<sup>45</sup> During periods of lactate-induced anxiety, there were increases in CBF in the anterior temporal poles, insular cortex, claustrum, lateral putamen, the vicinity of the superior colliculus, and left anterior cerebellar vermis. There was no increase in rCBF in the non-panic and control subjects. A separate study measured rCBF in subjects while they anticipated a painful electric shock.<sup>45</sup> In these subjects anticipatory anxiety was associated with an increase in CBF in the temporal poles.

Both these latter studies suggest a common pathway for the expression of anxiety, involving structures in the temporal poles, and relate well to

recent conceptualizations of the pathophysiologic basis of anxiety.<sup>46</sup> Studies of patients with PD provide intriguing evidence that this condition has a biologic basis separate from generalized anxiety.

### NEUROPSYCHIATRIC DISORDERS

Psychiatric morbidity, both psychotic and non-psychotic, is common in primary neurologic illness. The application of PET to the study of such neuropsychiatric disorders should greatly extend our knowledge of brain-behavior relationships and clarify pathophysiologic mechanisms mediating primary psychiatric disorders. The mechanisms by which focal brain insults result in neuropsychologic impairment is open to study. Few PET studies, with notable exceptions, have extended their boundaries beyond either a primary neurologic or psychiatric perspective. A full review of PET in neuropsychiatric disorders is beyond the scope of this article: two studies will be considered as illustrative of the potential application of PET in neuropsychiatric research.

A wide range of clinical manifestations are recognized following isolated infarcts of the thalamus, including verbal and visual memory impairment, aphasia, neglect, and behavioral change. A clinicopathologic perspective might suggest that these impairments reflect a critical role for the thalamus in these diverse psychologic functions. However, findings from PET investigations of such patients with thalamic lesions provide a different viewpoint, suggesting that neuropsychologic impairment relates to remote physiologic effects rather than the direct pathologic effects of lesions. Baron et al<sup>47</sup> in a combined PET and neuropsychologic study of ten patients with single isolated unilateral lesions of the thalamus reported that nine of ten displayed significant and widespread ipsilateral cortical hypometabolism remote from the lesion. These patients also displayed a range of neuropsychologic impairments with a marked trend for deficits to be related to degree of cortical hypometabolism.

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<sup>48</sup> 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.

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