Role of PET in the Investigation of Neuropsychiatric Disorders

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KEYWORDS

- PET
- Psychiatric disorders
- Depression
- Obsessive-compulsive disorder
- Neurotransmitter
- Schizophrenia

PET, along with an array of radiotracers, is used to study many physiologic and pathologic states throughout the body. Its applications in studying the brain, as a research and as a diagnostic clinical tool, have revealed some important findings. Specific psychiatric disorders in which PET studies may influence the management of patients include mood and anxiety disorders, attention deficit disorder, schizophrenia, and obsessive compulsive disorder (OCD).1

The only approved radiopharmaceutical for clinical PET imaging is fluorodeoxyglucose (FDG), which measures the cerebral metabolic rate for glucose (Fig. 1). There are several other tracers, however, that might be particularly useful in the study of psychiatric disorders. Specifically, tracers that bind to various receptors of neurotransmitter systems, such as serotonin, dopamine, and opiate, may play an important role in the study of psychiatric disorders.2–9 Other physiologic processes, such as blood flow and amino acid metabolism, might also be relevant. This review of the literature describes the application of PET imaging in the evaluation of a variety of common psychiatric disorders.

DEPRESSION

The most common finding on PET imaging in depressed patients (Fig. 2) is a global dysfunction as demonstrated by decreased cerebral blood flow (CBF)10 and decreased cerebral metabolism.11 Some studies have indicated that decreased CBF might correlate with the degree of depression. In one group,12,13 patients with depression had whole-brain decreases in blood flow, with the left anterior cingulate gyrus and the left dorsolateral prefrontal cortex (PFC) particularly affected. Depressed patients who also had cognitive impairment had decreased regional CBF (rCBF) in the left medial frontal gyrus and increased rCBF in the cerebellar vermis compared with depressed patients without cognitive dysfunction. Decreased activity in a localized area in the PFC ventral to the genu of the corpus callosum has been demonstrated in familial bipolar depressives and familial unipolar depressives.14 Even during non–rapid eye movement sleep, depressed patients have decreased frontal and limbic metabolic activity in association with posterior cortical increases.15

An FDG-PET study by Kumar and colleagues16 showed that patients with late-age onset of depression have decreased metabolism throughout the cortex and even in many subcortical structures. These decreases were of the same or greater magnitude compared with patients with Alzheimer disease. Alzheimer disease patients, however, more likely had the typical temporoparietal hypometabolism pattern on PET images whereas the depression patients tended to have more global hypometabolism.

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Depressed patients with concomitant anxiety symptoms demonstrated specific metabolic changes with increased activity in the right para-hippocampal and left anterior cingulate regions and decreased activity in the cerebellum, left fusiform gyrus, left superior temporal, left angular gyrus, and left insula. The investigators concluded that anxiety symptoms are associated with changes in specific brain regions that partially overlap with those in primary anxiety disorders and differ from those associated with depression.

Recent studies have also evaluated treatment-related effects in patients with depression. On pretreatment scans, lower metabolism in the left ventral anterior cingulate gyrus, ventrolateral PFC, orbitofrontal cortex (OFC), and midbrain has been associated with a better treatment response to paroxetine. Similarly, other studies have shown that increased metabolism in the ventral anterior cingulate was associated with nonresponse to selective serotonin reuptake inhibitor (SSRI) treatment or cognitive behavioral therapy. There is decreased activity in limbic and striatal areas and increased activity in the dorsal cortical areas (including the prefrontal, parietal, anterior, and posterior cingulated areas) associated with improvements in clinical symptoms. In a study of sleep deprivation, high pretreatment metabolic rates and overall post-treatment decreases in metabolic rates in the medial PFC and anterior cingulated gyrus (particularly on the right) were associated with those

![Fig. 1. Normal FDG-PET scan from a healthy individual without any neuropsychiatric disorder. There is uniform distribution of metabolism throughout the cortical and subcortical structures.](image-url)
depression patients who responded well to sleep deprivation therapy.\textsuperscript{22,23} In a recent study of nucleus accumbens deep brain stimulation, those patients who responded to the treatment had decreased metabolism in the amygdala and nucleus accumbens.\textsuperscript{24}

Another group used PET to study cerebral glucose metabolism in bipolar patients.\textsuperscript{25,26} The bipolar patients who were actively depressed had decreased global metabolism. As their depression improved, they had increases in their cerebral metabolism. In contrast, unipolar patients had normal global metabolic rates that did not correlate with clinical symptoms. These investigators also found a decreased caudate to hemispheric metabolic ratio in depressed unipolar patients, and this ratio increased as symptoms of depression improved. Buchsbaum and colleagues\textsuperscript{27} found a decreased anteroposterior gradient in bipolar depressed patients but not in unipolar patients. Also, a PET study by Phelps and colleagues\textsuperscript{11} reported similar decreases in global metabolism in bipolar patients in the depressive phase, although unipolar patients had global metabolism within normal limits.

Furthermore, bipolar patients in the hypomanic phase had normal glucose metabolism. More recent work has demonstrated that unipolar depression is associated with a pattern of prefrontal hypometabolism, whereas a cerebello-posterior cortical hypermetabolism may be observed in bipolar patients. Thus, in depressed patients, PET might be useful in distinguishing unipolar from bipolar patients, a distinction that would have significant implications for a patient’s treatment and prognosis.\textsuperscript{28}

The serotonin system has been explored particularly in patients with mood disorders because of the effectiveness of SSRIs, which are believed to aid depression by affecting the serotonergic system. The serotonin type 2A receptor does not seem to be affected in late life–onset depression, although there is a decrease in binding to this receptor type in patients with AD.\textsuperscript{29} There are typically decreases in serotonergic system, including 1A and 2A receptors in the limbic and neocortical areas.\textsuperscript{30–33} A review of serotonin type 2A imaging studies before 2003 of major depressive episodes, however, found a reduction in those depressed patients with recent antidepressant use and no

\textbf{Fig. 2.} FDG-PET scan of a patient with major depression showing global cortical decrease in metabolism relative to the subcortical structures.
change in those with no recent antidepressant use. The clinical improvement in depressed patients treated with paroxetine was also associated with an increase in the density of serotonin type 2A receptors in the frontal cortex. The reduction in serotonin type 1A receptor binding in depressed patients, however, was not changed by SSRI treatment or by electroconvulsive therapy. Also, depressed patients showed a significant reduction in available serotonin type 2A receptors in the brain after desipramine treatment. Serotonin transporter binding measured with \(^{11}\)C-DASB was reduced in the brain stem, thalamus, caudate, putamen, anterior cingulate cortex, and frontal cortex in patients with major depression.

Other receptor types have been studied in patients with mood disorders. Fluorodopa uptake in the left caudate was significantly lower in depressed patients with psychomotor retardation than in patients with high impulsivity and in comparison subjects. A recent study suggests that there is decreased dopamine D2 receptor binding in depression patients after successful electroconvulsive therapy. Some bipolar patients also have psychotic symptoms and had elevations in dopamine D2 receptor density likely associated with the psychotic symptoms and not the mood disorder. Finally, there seems to be decreased \(\gamma\)-aminobutyric acid (GABA)–A binding in the parahippocampus and superior temporal lobe in patients with depression, and the temporal lobe decrease correlated with hypothalamus-pituitary axis hyperactivity.

ANXIETY AND STRESS

PET has been used to attempt to gain a better understanding of the neurophysiologic mechanisms underlying stress and anxiety. In general, the hippocampus, the amygdala, and the PFC as part of the limbic system are believed to play important roles in the regulation of the hypothalamic-pituitary-adrenal axis. Riemann and colleagues studied patients with panic disorders using \(\text{H}_2\text{O}\) PET; these patients had increased rCBF in the right parahippocampal gyrus in lactate-vulnerable patients in a resting, nonpanic state, compared with controls (patients in whom intravenous infusion of sodium lactate can induce a panic attack). During a lactate-induced panic attack, the patients had increased rCBF bilaterally in the temporal poles, the claustrum, and the lateral putamen.

In patients with generalized anxiety disorder, there are lower metabolic rates in basal ganglia and white matter and increased metabolism in the left inferior occipital lobe, right posterior temporal lobe, and the right precentral frontal gyrus. In one study, benzodiazepine therapy resulted in decreases in metabolic rates for cortical areas, limbic system, and basal ganglia. A related study showed decreases in metabolism in the visual cortex and increases in the basal ganglia and thalamus. An FDG-PET study found that the PFC is activated in response to psychosocial stress, and distinct prefrontal metabolic glucose patterns are linked to endocrine stress measures, such as cortisol levels. Patients with simple phobias might also be expected to have changes in cerebral metabolism or blood flow. Mountz and colleagues, however, did not find any changes in these patients in the resting state or when exposed to a phobic stimuli compared with controls. This finding conflicts with the reports of anxiety response in normal patients (discussed previously). Elucidation of the mechanisms underlying anxiety is needed.

Several studies have used PET imaging to evaluate the effects of practices and interventions that might attenuate stress and anxiety. Brain imaging studies suggest that willful acts and tasks that require sustained attention are initiated via activity in the PFC, particularly in the right hemisphere. There is evidence to suggest that during meditation practices, there are frontal lobe increases (Fig. 3), which have been hypothesized to help modulate activity in the anterior cingulate and limbic structures, possibly resulting in lowering perceived levels of stress, anxiety, and depression.

In terms of neurotransmitter systems, recent PET studies have demonstrated reduced serotonin type 1A receptor binding in patients with panic disorder and social anxiety disorder but not in posttraumatic stress disorder (PTSD). A PET study using \(^{11}\)C-raclopride to measure the dopaminergic tone during Yoga Nidra meditation demonstrated a significant increase in dopamine levels during the meditation practice. The authors hypothesized that this increase may be associated with the gating of cortical-subcortical interactions that leads to an overall decrease in readiness for action associated with this particular type of meditation. Stressors also are shown related to a release of dopamine using PET imaging. Future studies will be necessary to elaborate on the role of dopamine in stress and anxiety.

POSTTRAUMATIC STRESS DISORDER

A few studies have explored cerebral changes associated with PTSD. A case report of a subject exposed to war-related sounds before and after treatment with an SSRI showed that before treatment, trauma reminders resulted in decreased
rCBF in the insula, prefrontal, and inferior frontal cortices. There was also increased activity in the cerebellum, precuneus, and supplementary motor cortex. These findings normalized after SSRI administration, suggesting that the anxiolytic effect of such medications for PTSD could be mediated by prefrontal and paralimbic cortices, areas typically involved in memory, emotion, attention, and motor control. An FDG-PET study of 15 patients showed that PTSD was associated with diminished activity in the cingulate gyri, precuneus, insula, hippocampus PFC, occipital lobe, and verbal areas. This same study showed increased activity in the fusiform gyrus, superior temporal lobe, and cerebellum in PTSD patients. The amygdala and the thalamus showed normal metabolic activity in this cohort. The investigators suggest that the metabolic pattern was comparable to that in patients with personality disorders of the borderline type.

A different study explored rCBF changes associated with the recollection and imagery of traumatic events in trauma-exposed individuals with and without PTSD. This study showed that the traumatic condition was associated with increases in OFC and anterior temporal poles compared with the neutral condition and that these increases were greater in the PTSD group. rCBF decreases in both anterior frontal regions and the left inferior frontal regions were greater in the PTSD group. A follow-up study by the same group showed that the PTSD group had CBF decreases in the medial frontal gyrus when patients recalled traumatic in comparison with neutral stimulus. CBF changes in medial frontal gyrus were inversely correlated with CBF changes in the amygdala. Symptom
severity was positively correlated to CBF in the right amygdala and negatively correlated to CBF in medial frontal gyrus.

Another study explored the association with cocaine and alcohol abuse with PTSD. Such patients had significantly higher rCBF in the right amygdala and the left parahippocampal gyrus than control patients during an auditory continuous performance task. The investigators concluded that the amygdala’s attention and fear function suggests that increased amygdala rCBF may be related to clinical features of PTSD. Cocaine use may be associated with increased amygdala rCBF in these PTSD patients. Therefore, the amygdala and frontal cortex attention systems may be reciprocally related and their relative contributions associated with processing of neutral stimuli that are perturbed in patients with cocaine and alcohol abuse in association with PTSD.

SCHIZOPHRENIA

PET has been widely used in the study of the functional abnormalities in schizophrenia. It has been suggested that schizophrenia is most commonly associated on PET scans (Fig. 4) with frontal lobe dysfunction, although other studies did not report such a finding. One study showed that the degree of frontal hypometabolism correlated with negative symptoms as opposed to positive symptoms, although other studies have found an association between positive symptoms and decreased frontal activity. A refinement of the proposed hypothesis for the underlying cause of dysfunction in schizophrenia ascribes the hypofrontal pattern to those schizophrenic patients with a predominance of negative symptoms. These patients tend to be older and have a long history of neuroleptic therapy. Alternatively, younger patients with predominantly positive symptoms usually have not demonstrated the hypofrontal pattern to the same extent. It may also be that the frontal lobe activity changes during the course of the disorder and is more prominent in the acute setting or that frontal lobe changes may vary with specific symptoms in individual patients. There are other areas that may also be affected in schizophrenia, including hypometabolism in the anterior cingulate cortex, striatum, and thalamus. Liddle and colleagues proposed 3 syndromes of symptoms in schizophrenics with corresponding PET patterns of rCBF: (1) patients with psychomotor poverty syndrome and diminished word-generating ability have decreased perfusion of the dorsolateral PFC; (2) patients with the disorganization syndrome have impaired inhibition of inappropriate responses and have increased rCBF of the right anterior cingulate gyrus; and (3) patients with the reality distortion syndrome have increased perfusion in the medial temporal lobe at a locus that is activated in normal subjects during the internal monitoring of eye movements.

More recent work has tried to establish specific networks of structures related to the clinical manifestations of schizophrenia. For example, there is a correlation between the anterior thalamus and the frontal cortex, a key element in the thalamocortical-striatal circuit suggested as abnormal in some models of schizophrenia. The findings from this study also showed that schizophrenics

![FDG-PET scan of patient with schizophrenia showing a mild global decrease, particularly in the frontal regions (arrows), consistent with some of the reported findings in the literature.](image-url)
have lower correlations between the frontal lobe activity and that in other structures consistent with frontal cortical dysfunction.

Several PET studies have been performed to determine whether or not left hemispheric dysfunction can be detected in schizophrenics. In some studies, patients with schizophrenia at rest had increased perfusion and metabolism in the left hemispheric cerebral cortex relative to the right. 88–90 Also, the severity of the symptoms of schizophrenia correlated with the degree of hyperactivity of the left hemisphere and not with the degree of hypofrontality. This concurs with a study by Sheppard and colleagues, 91 which found increased blood flow to the left hemisphere using 15O-H2O PET. Also, Early and colleagues 92 found increased CBF in the left globus pallidus in patients with schizophrenia. Cleghorn and colleagues, 65 however, did not find any significant difference in laterality between schizophrenics and controls. A more recent study showed that patients lack asymmetry in caudate dopamine transporter binding, which conforms with the concept of disrupted brain lateralization in schizophrenia. 93

Cerebral activation studies have improved the understanding of the cognitive and affective deficits associated with schizophrenia. FDG-PET studies, in which a subject underwent specific frontal lobe activation tests of sustained attention by continuous performance tasks, found decreased activation of the frontal lobes in schizophrenic patients compared with controls. 94,95 DeLisi and colleagues 96 found that schizophrenic patients had higher left temporal lobe metabolic rates compared with controls when there was sensory stimulation of the right arm. Another study 97 compared PET and electroencephalogram findings in schizophrenic and control subjects performing various simple and complex motor tasks. Although no changes were observed in the schizophrenic or control groups during simple motor tasks, the schizophrenic group had decreased activation in the supplementary motor and the contralateral sensorimotor cortices during complex motor tasks compared with controls. During a continuous performance task, schizophrenics showed negative correlations of task performance with anterior cingulate activity, suggesting that overactivity of that region, which is involved in mental effort and whose metabolic rate is typically lower in schizophrenic patients, may also result in the impairment of task performance in these patients. 98 Patients with schizophrenia also fail to activate the anterior cingulate gyrus during selective attention performance. 99

Schizophrenia patients with negative symptoms had a lesser activation in the left hemisphere during word generation with compensatory changes in the right hemisphere. 100 Schizophrenia is also associated with attenuated right thalamic and right prefrontal activation during the recognition of novel visual stimuli and with increased left prefrontal cortical activation during impaired episodic recognition of previously seen visual stimuli. 101 Similarly, patients with schizophrenia fail to activate cortical-cerebellar-thalamic-cortical circuitry during recall of well-learned and novel word lists. 102 Frontal cortex function during memory retrieval is more impaired in schizophrenic patients. 103,104 Volkow and colleagues 105 found that with eye-tracking tasks, schizophrenic patients had lower correlations between anterior and posterior cortical areas and between the thalamus and neocortical areas compared with controls. These results suggest a marked derangement in the pattern of interactions between various brain regions in schizophrenics. The results of most of these activation studies suggest abnormal thalamic and PFC function in schizophrenia, 106 although another study showed a cingulate gyrus–parietal lobe dysfunction underlying impairment of working memory processes during a random number generation task in schizophrenia. 107 There has also been evidence of hippocampal dysfunction during episodic memory retrieval in schizophrenia. 108 Schizophrenic patients have also failed to show graded, memory task–related decreases in activity in the left superior temporal and inferior parietal gyrus, which is typically seen in control subjects. 109,110

In addition to the metabolic and blood flow studies, PET imaging of the dopamine system in schizophrenic patients has been an important advance. 111,112 This is particularly useful because the dopaminergic system has been implicated in the pathophysiology of this disorder as well as the site of action for neuroleptic drugs, the primary therapeutic modality considered effective in these patients. Early studies reported no differences in dopamine receptor density or affinity in the basal striatum between schizophrenics and controls. 113–115 Other studies, however, reported an increased density of dopamine receptors in neuroleptic naive and previously treated but drug-free schizophrenic patients. 116,117 The same group 118 found increases in dopamine activity in patients with manic depressive psychosis suggesting that increased dopamine activity might be a feature of psychotic illness in general and may not be specific to schizophrenia. A recent study using 18F-fallypride showed that in schizophrenic subjects there is increased dopamine D2 receptor levels in the substantia nigra and there was
a significant correlation of symptoms of disorganized thinking and nonparanoid delusions with the right temporal cortex binding. In a review article by Howes and colleagues, 6 of 8 studies using 18F-fluorodopa found elevated striatal dopamine uptake in patients with schizophrenia. A recent study also suggests that there is elevated striatal dopamine uptake in patients withprodromal symptoms of schizophrenia as well as in those with frank schizophrenia. These findings suggest that striatal dopamine overactivity predatesthe onset of schizophrenia. Another study demonstrated that depressive symptoms in neuroleptic-naive, first-admission schizophrenia patients have low presynaptic dopamine function. There has been no evidence of a change in serotonin receptors in patients with schizophrenia, although some investigators have reported a decrease in the frontal lobes in neuroleptic-naive patients.

PET studies have also evaluated the effects of therapeutic interventions in patients with schizophrenia. Early studies reported a general increase in glucose metabolism, particularly in the left temporal lobe, after neuroleptic treatment, but there was no change in the anteroposterior gradient. Schizophrenic patients who responded to haloperidol treatment typically had a "normalizing" effect on metabolic activity in the striatum, with the metabolic rate when they were receiving haloperidol higher than that when they were receiving placebo. Nonresponders were more likely to show a worsening of hypofrontality and an absence of change in the striatum during the treatment condition. Another study corroborated this finding, in that a haloperidol challenge caused widespread decreases in absolute metabolism in nonresponsive patients but not the responsive patients. Studies have shown that there is a high dopamine D2 receptor occupancy, particularly in the basal ganglia, in early treatment with neuroleptics, and that this occupancy was dose dependent and associated not only with the therapeutic effect but also with side effects, such as hyperprolactinemia and extrapyramidal signs. Upregulation of dopamine D2 receptors has also been associated with a regional increase of blood flow and metabolism in the basal ganglia. Furthermore, the D2 receptor occupancy has been shown to decrease as the drug levels decreased on withdrawal of treatment. Patients who are resistant to neuroleptic therapy have similar D2 receptor blockade compared with patients who respond clinically to therapy. In addition to D2 receptor blockade with antipsychotic drugs, Sedvall and colleagues found that there is also blockade of the D1 receptors (D1 receptor activity was measured with 11C-SCH 23900). This is particularly true with the drug clozapine, which shows almost the same amount of D1 as D2 receptor occupancy. The data suggest that traditional and novel antipsychotics with high affinity for dopamine D2 receptors are associated with a substantial increase in D2 receptor binding. The current data in humans corroborate the animal data that implicate D2 receptor-mediated mechanisms in motor hyperactivity.

The atypical antipsychotic, quetiapine, results in a transiently high D2 occupancy, which decreases to low levels by the end of the dosing interval, which may account for its lower incidence of extrapyramidal side effects. Quetiapine and clozapine have a lower incidence of extrapyramidal side effects in part because of their lower striatal D2 binding, whereas their antipsychotic effect may be mediated by preferential binding in the temporal cortex. Another study using 11C-raclopride, however, found that with risperidone and olanzapine, striatal D2 occupancy predicted response in terms of positive psychotic symptoms but not for negative symptoms. PET has also been used to evaluate other new drugs, such as amoxapine and olanzapine, which have a profile similar to that of other atypical antipsychotics with a higher occupancy of serotonin receptors compared with D2 receptors. PET imaging has demonstrated gender differences related to the effects with antipsychotic medications with women having a reduction in cingulated gyrus metabolism compared with men with clozapine and fluphenazine. In men, fluphenazine was associated with a greater elevation in basal ganglia metabolic rates than was clozapine whereas women demonstrated nearly equal increases in fluphenazine and clozapine.

**OBSESSIVE-COMPULSIVE DISORDER**

Several studies have used FDG-PET to investigate patients with OCD. Early results (Fig. 5) have generally shown that OCD patients have increased cerebral metabolism in the orbital region of the frontal cortex and the caudate nuclei compared with controls. There has not been a consistent observation, however, of increased activity in the caudate. One study also found increased metabolism in the cingulate gyrus of OCD patients compared with controls. PET has been used to explore the effects of different types of therapy in OCD. Another study demonstrated that higher glucose metabolism in the OFC was associated with greater improvement with behavioral therapy and a worse outcome with fluoxetine treatment.
Behavior therapy responders also had significant bilateral decreases in caudate metabolism. Furthermore, patients who responded to paroxetine had significantly lower metabolic rates in the right anterolateral OFC and right caudate nucleus and lower pretreatment metabolism in the left and right OFC predicted greater improvement with treatment. These results suggest that subjects with differing patterns of metabolism preferentially respond to behavioral therapy versus medication. In patients with OCD, behavioral therapy responders have been shown to have significant bilateral decreases in caudate glucose metabolic rates compared with poor responders. This study, as well as others, also suggests that there is a prefrontal cortico-striato-thalamic network that mediates the symptoms of OCD. Neuroimaging studies have also revealed important findings in OCD. A study that used 11C-MDL found a significant reduction of serotonin type 2A receptor availability in the frontal polar, dorsolateral, and medial frontal cortex as well as in the temporoparietal association cortex in OCD patients. There was also a significant correlation between serotonin type 2A receptor availability in the OFC and dorsolateral frontal cortex and clinical severity of OCD. In addition, this same study used 11C-raclopride PET and found a significant reduction of uptake in the whole striatum, possibly reflecting endogenous dopaminergic hyperactivity. Furthermore, the reduction in 11C-raclopride binding is improved by treatment with fluvoxamine with concomitant improvement in symptoms. Another study showed that OCD was associated with decreased serotonin transporter binding in the insular cortex as measured by 11C-DASB PET imaging. This finding suggests the potential role of the serotonergic system in the pathophysiology of OCD.

ALCOHOLISM

Studies of alcoholic patients with PET have generally found decreased whole-brain metabolic activity. A study by Wik and colleagues used CT and FDG–PET to examine patients with alcoholism. They found that alcoholic patients had reductions of 20% to 30% in cortical and subcortical brain regional metabolism compared with controls. Although the hypometabolism was diffusely distributed, the parietal areas were disproportionately affected. Other studies have reported frontal lobe hypometabolism. Also, studies have reported metabolic deficits in the left hemisphere more often than in the right. A recent study suggests that there may be differences in the cerebral metabolism in women with alcoholism compared with men because women had less of a decrease in metabolism compared with men. Patients with chronic alcoholism and cerebellar degeneration had significantly reduced glucose metabolism in the superior vermis compared with controls. Volkow and colleagues reported that the decrease in metabolism in chronic alcoholics correlated with the time since they last consumed alcohol. There were decreases in frontal and parietal metabolism that did not follow this pattern, suggesting that these changes might be a long-term component of the effects of chronic alcoholism. Patients who remained abstinent or who had minimal alcohol during longitudinal follow-up, however, showed partial recovery of glucose metabolism in 2 of 3 divisions of the frontal lobes and improvement on neuropsychological
tests of general cognitive and executive functioning, whereas the patients who relapsed had further declines in these areas.\textsuperscript{163} Examining the metabolic changes associated with detoxification showed a significant increase in global and regional (primarily frontal lobe) measures predominantly within 16 to 30 days.\textsuperscript{164} Additional follow-up did not demonstrate additional changes suggesting that the effects of detoxification occur in the first 30 days.

Another study compared the effects of acute alcohol ingestion on brain metabolism in a group of chronic alcoholics and controls.\textsuperscript{165} Subjects in each group underwent FDG-PET studies at baseline and after the administration of ethanol (1 g per kg). The results showed hypometabolism, particularly in the occipital, prefrontal, and cerebellar cortices, after acute ingestion of alcohol. These areas also correspond to the areas of the highest density of benzodiazepine receptors, which may be clinically relevant because benzodiazepines are used for the treatment of alcohol withdrawal. Compared with controls, alcoholics had a more marked metabolic deficit after ethanol ingestion but had fewer clinical symptoms, suggesting a tolerance to alcohol.

Studies have also explored the effects of alcohol on various neurotransmitter systems within the brain. GABA-benzodiazepine receptor function is altered in alcoholics as demonstrated by decreased sensitivity to lorazepam administration in the thalamus, basal ganglia, OFC, and cerebellum and may account for the decreased sensitivity to the effects of alcohol and benzodiazepines in these subjects.\textsuperscript{162,166} For example, studies have shown low dopamine D2 receptor densities and less conclusive changes in the dopamine transporter densities among late-onset alcoholics and low presynaptic DA function observed in the left caudate of 2 patients, suggesting that this stage of alcoholism may be a heterogeneous disorder.\textsuperscript{167,168} One study reported reduced binding in the striatal monoaminergic presynaptic terminals in severe chronic alcoholic patients, suggesting that the damaging effects of severe chronic alcoholism on the central nervous system are more extensive than previously considered.\textsuperscript{169} A comparison of alcoholics with controls with a serotonergic challenge demonstrated activation of the basal ganglia circuits involving the orbital and prefrontal areas in controls but a blunted response among alcoholics.\textsuperscript{170} In a related study of alcoholic patients on disulfiram, there was decreased cerebral glucose metabolism and decreased flumazenil influx and distribution volume in patients receiving disulfiram, suggesting that this drug may be an important factor in the functional imaging studies of alcoholic patients.\textsuperscript{171}

**COCAINe ABUSE**

The use of cocaine has steadily increased over the past few decades and has reached an almost epidemic proportion. Cocaine is one of the most addictive and toxic abused drugs.\textsuperscript{172} PET studies have the potential of elucidating the mechanisms of the effects and the addictive properties of cocaine.\textsuperscript{173} Initial studies with $^{11}$C cocaine showed maximal uptake in the basal ganglia.\textsuperscript{174} This uptake was rapid, reaching peak concentration in 4 to 8 minutes after injection and a clearance half-life of 20 minutes. Preadministration of nomifensine, which blocks the presynaptic reuptake of dopamine and norepinephrine, was shown to block the uptake of cocaine in the basal ganglia in this study. Another study has shown that the euphoric effects of cocaine correspond directly to the concentration of the drug in the basal ganglia,\textsuperscript{175} corroborating the findings of the PET scan results.

PET studies of brain metabolism studies (Fig. 6) have shown that acute administration of cocaine in chronic cocaine abusers results in decreased metabolism in the cortical and subcortical structures.\textsuperscript{176} The extent of metabolic decrease correlated with the subjective evidence of the euphoria. In patients with chronic cocaine abuse, the duration since detoxification affects the cerebral glucose metabolism. Volkow and colleagues\textsuperscript{177} showed decreased frontal activity 8 days to 2 months after last cocaine use (more extensive decrement in the left compared with the right hemisphere) in chronic abusers compared with controls. Another study\textsuperscript{178} of the acute changes after withdrawal of the drug showed that 1 week after last cocaine use, these patients had hypermetabolism in the OFC and the basal ganglia compared with normal controls and those studied 1 month after last cocaine use. Furthermore, hypermetabolism in these regions correlated with the subjective craving for cocaine. A follow-up study also showed similar findings, particularly affecting the right hemisphere, but this study indicated that dopamine enhancement is not sufficient to increase metabolism in the frontal regions.\textsuperscript{179} The predominant correlation of craving within the right but not the left brain region suggests laterality of the addiction response. A similar pattern has been reported in patients with OCD,\textsuperscript{180} although it is not clear whether or not the ritualistic behavior in OCD is comparable with the addictive behavior of cocaine abusers. The OFC and basal ganglia, areas
involved in cocaine abuse, however, are also involved in a circuit regulating repetitive behavior.\textsuperscript{181} In terms of the actual craving for cocaine, one PET study showed a pattern of increased activity in limbic (amygdala and anterior cingulate) CBF and decreases in the basal ganglia while watching a video designed to induce craving\textsuperscript{182} whereas another study showed activation of the temporal insula (involved with autonomic control) and the OFC (involved with expectancy and reinforcement) during a craving stimulus.\textsuperscript{183}

PET receptor studies have attempted to determine the relationship between cocaine and dopamine receptors in the basal ganglia. For example, an $^{11}$C-raclopride PET study showed modest decreases in D2 receptor availability throughout the striatum in chronic cocaine even though there was no clear relationship between D2 receptor availability and cocaine-induced cocaine-taking behavior.\textsuperscript{184} Increased dopamine has been shown to play a role in cocaine’s euphoric properties, and a decrease in dopamine presynaptic activity plays a role in withdrawal and possibly addictive properties.\textsuperscript{185,186} Another study suggests that the thalamic dopamine pathways are also important in cocaine addiction.\textsuperscript{187} A recent study suggests that low D1 receptor availability in the ventral striatum in cocaine abusers was associated with the choice to self-administer cocaine, suggesting that low D1 receptor availability may be associated with an increased risk of relapse.\textsuperscript{188}

Cocaine has been shown to significantly block dopamine transporters.\textsuperscript{189} The levels of blockade were comparable across several different routes of administration, including intravenous, intranasal, and smoked. Smoked cocaine induced significantly greater self-reports of a high than the other routes, likely due to the speed at which the cocaine is delivered to the brain, because there was no difference in the overall dopamine transporter blockade. Another study demonstrated that cocaine abusers have an enhanced sensitivity to lorazepam, suggesting a disruption of GABA pathways that may reflect, in part, cocaine withdrawal.\textsuperscript{190} This same study noted that cocaine abusers also have intense sleepiness induced by lorazepam, suggesting potential clinical consequences of prescribing such medications to cocaine abusers.

\begin{figure}[h]
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\includegraphics[width=\textwidth]{fig6.png}
\caption{FDG-PET scan of patient with chronic cocaine abuse showing global cortical decrease in glucose metabolism, particularly in the temporal lobes (arrows).}
\end{figure}
ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

Attention-deficit/hyperactivity disorder (ADHD) is characterized by inattention, hyperactivity, or impulsivity that produces impairment across a variety of cognitive, behavioral, and interpersonal domains. One of the first FDG-PET studies on ADHD examined 25 treatment-naive patients and found global cerebral glucose hypometabolism, particularly in the premotor cortex and in the superior PFC. Two follow-up studies by the same group, however, did not find the same global or regional deficits. Two other PET studies did suggest that there are frontostriatal abnormalities associated with ADHD.

PET studies have shown that brain dopamine neurotransmission is disrupted in ADHD and that these deficits may underlie core symptoms of inattention and impulsivity. One PET study showed lower L-11C-DOPA use in adolescents with ADHD compared with control subjects, especially in subcortical regions. ADHD may also be associated with deficits in the reward and motivation centers of the brain. Several studies have demonstrated reduced dopaminergic activity in patients with ADHD, particularly in the subcortical structures and midbrain.

PET imaging has been used to assess a wide variety of psychiatric disorders. Most of these imaging results still lie in the realm of research, helping to understand the pathophysiology of different disorders, explore diagnostic criteria, and evaluate the effects of treatment. Future studies are needed to explore how the growing number of neurotransmitter ligands can be used in the study of psychiatric disorders. Ultimately, identifying and validating clinical applications will be necessary so that PET imaging continues to play a key role in the management of psychiatric disorders.

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