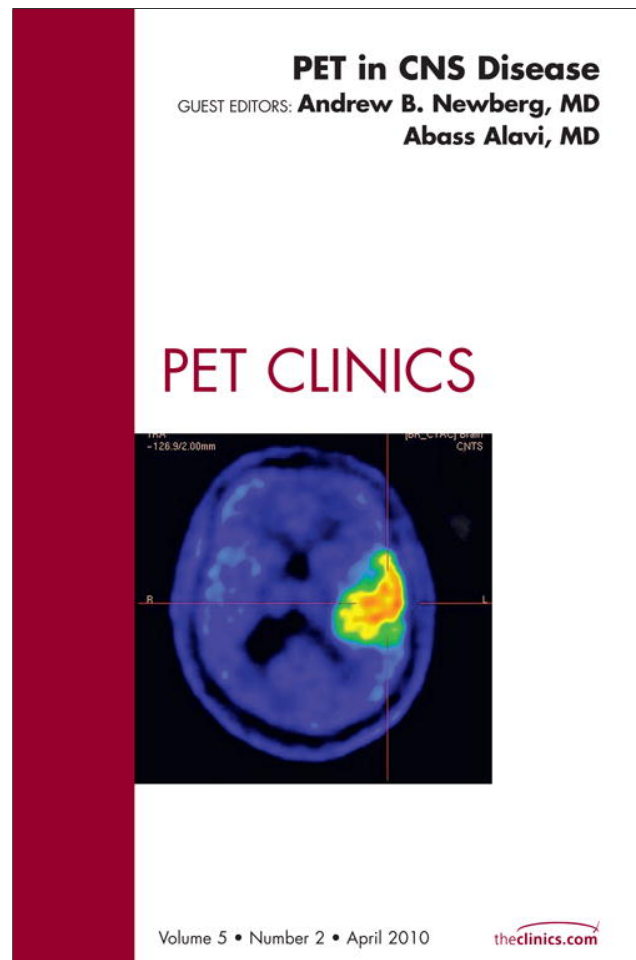


Provided for non-commercial research and education use.
Not for reproduction, distribution or commercial use.



This article appeared in a journal published by Elsevier. The attached copy is furnished to the author for internal non-commercial research and education use, including for instruction at the authors institution and sharing with colleagues.

Other uses, including reproduction and distribution, or selling or licensing copies, or posting to personal, institutional or third party websites are prohibited.

In most cases authors are permitted to post their version of the article (e.g. in Word or Tex form) to their personal website or institutional repository. Authors requiring further information regarding Elsevier's archiving and manuscript policies are encouraged to visit:

<http://www.elsevier.com/copyright>

Role of PET in the Investigation of Neuropsychiatric Disorders

Andrew B. Newberg, MD*, Abass Alavi, MD

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.

Division of Nuclear Medicine, Department of Radiology, Hospital of the University of Pennsylvania, 110 Donner Building, 3400 Spruce Street, Philadelphia, PA 19104, USA

* Corresponding author.

E-mail address: Andrew.newberg@uphs.upenn.edu

PET Clin 5 (2010) 223–242

doi:10.1016/j.cpet.2010.03.003

1556-8598/10/\$ – see front matter © 2010 Elsevier Inc. All rights reserved.

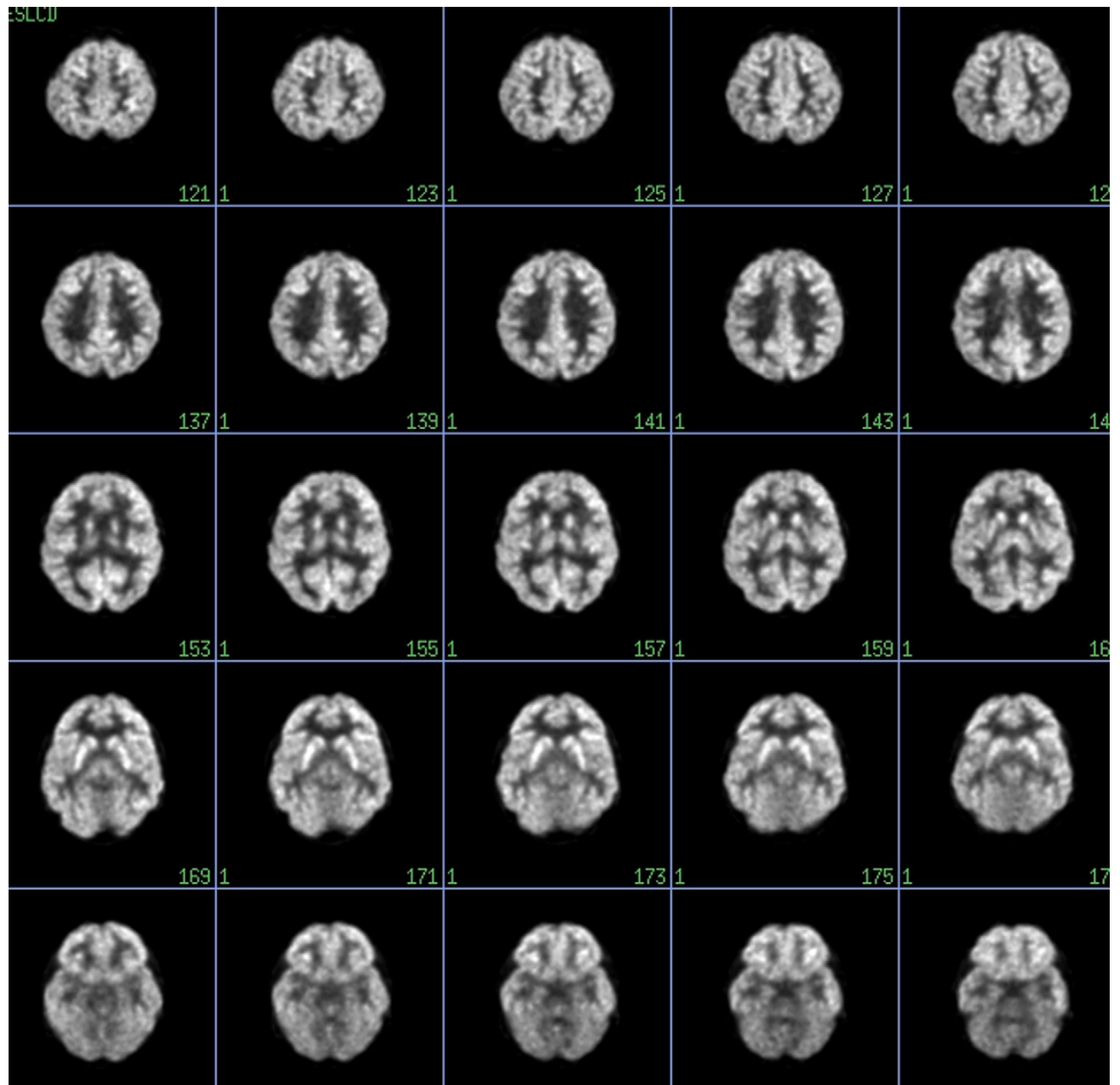


Fig. 1. Normal FDG-PET scan from a healthy individual without any neuropsychiatric disorder. There is uniform distribution of metabolism throughout the cortical and subcortical structures.

Depressed patients with concomitant anxiety symptoms demonstrated specific metabolic changes with increased activity in the right parahippocampal and left anterior cingulate regions and decreased activity in the cerebellum, left fusiform gyrus, left superior temporal, left angular gyrus, and left insula.¹⁷ 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.^{18,19} 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.²⁰ 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.²¹ 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

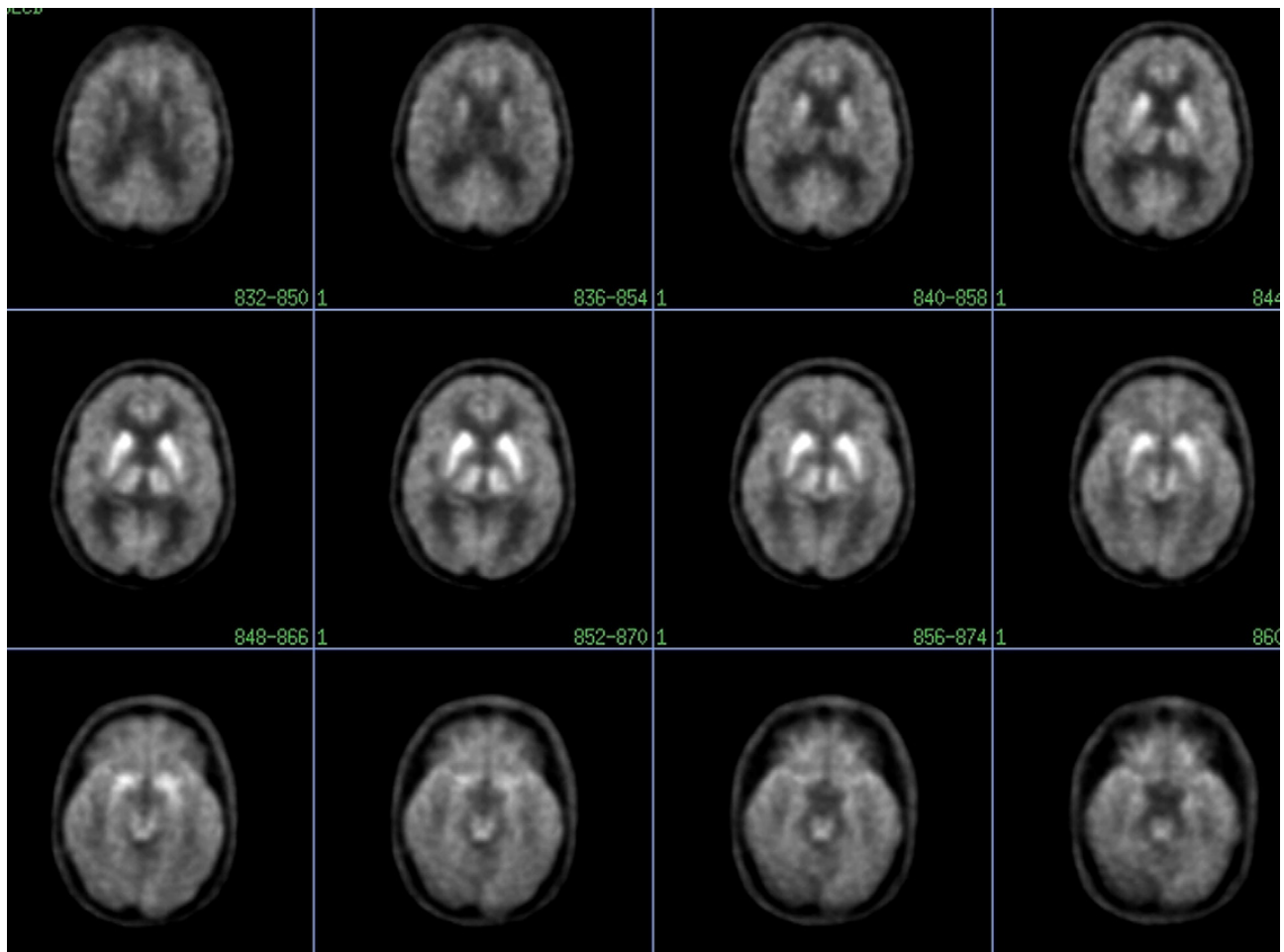


Fig. 2. FDG-PET scan of a patient with major depression showing global cortical decrease in metabolism relative to the subcortical structures.

depression patients who responded well to sleep deprivation therapy.^{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.²⁴

Another group used PET to study cerebral glucose metabolism in bipolar patients.^{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 colleagues²⁷ found a decreased anteroposterior gradient in bipolar depressed patients but not in unipolar patients. Also, a PET study by Phelps and colleagues¹¹ 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.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.²⁹ There are typically decreases in serotonergic system, including 1A and 2A receptors in the limbic and neocortical areas.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

change in those with no recent antidepressant use.³⁴ 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.^{35,36} The reduction in serotonin type 1A receptor binding in depressed patients, however, was not changed by SSRI treatment³⁷ or by electroconvulsive therapy.³⁸ Also, depressed patients showed a significant reduction in available serotonin type 2A receptors in the brain after desipramine treatment.³⁹ Serotonin transporter binding measured with ¹¹C-DASB was reduced in the brain stem, thalamus, caudate, putamen, anterior cingulate cortex, and frontal cortex in patients with major depression.⁴⁰

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.⁴¹ A recent study suggests that there is decreased dopamine D2 receptor binding in depression patients after successful electroconvulsive therapy.⁴² 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.⁴³ Finally, there seems to be decreased γ -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.⁴⁴

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. Rieman and colleagues⁴⁵⁻⁴⁷ studied patients with panic disorders using H₂O 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.⁴⁸ 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.²⁷ 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.⁴⁹

Patients with simple phobias might also be expected to have changes in cerebral metabolism or blood flow. Mountz and colleagues,⁵⁰ 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.⁵¹ There is evidence to suggest that during meditation practices, there are frontal lobe increases (Fig. 3),^{52,53} 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.⁵⁴

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).⁵⁵ A PET study using ¹¹C-raclopride to measure the dopaminergic tone during Yoga Nidra meditation demonstrated a significant increase in dopamine levels during the meditation practice.⁵⁶ 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.⁵⁷ 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

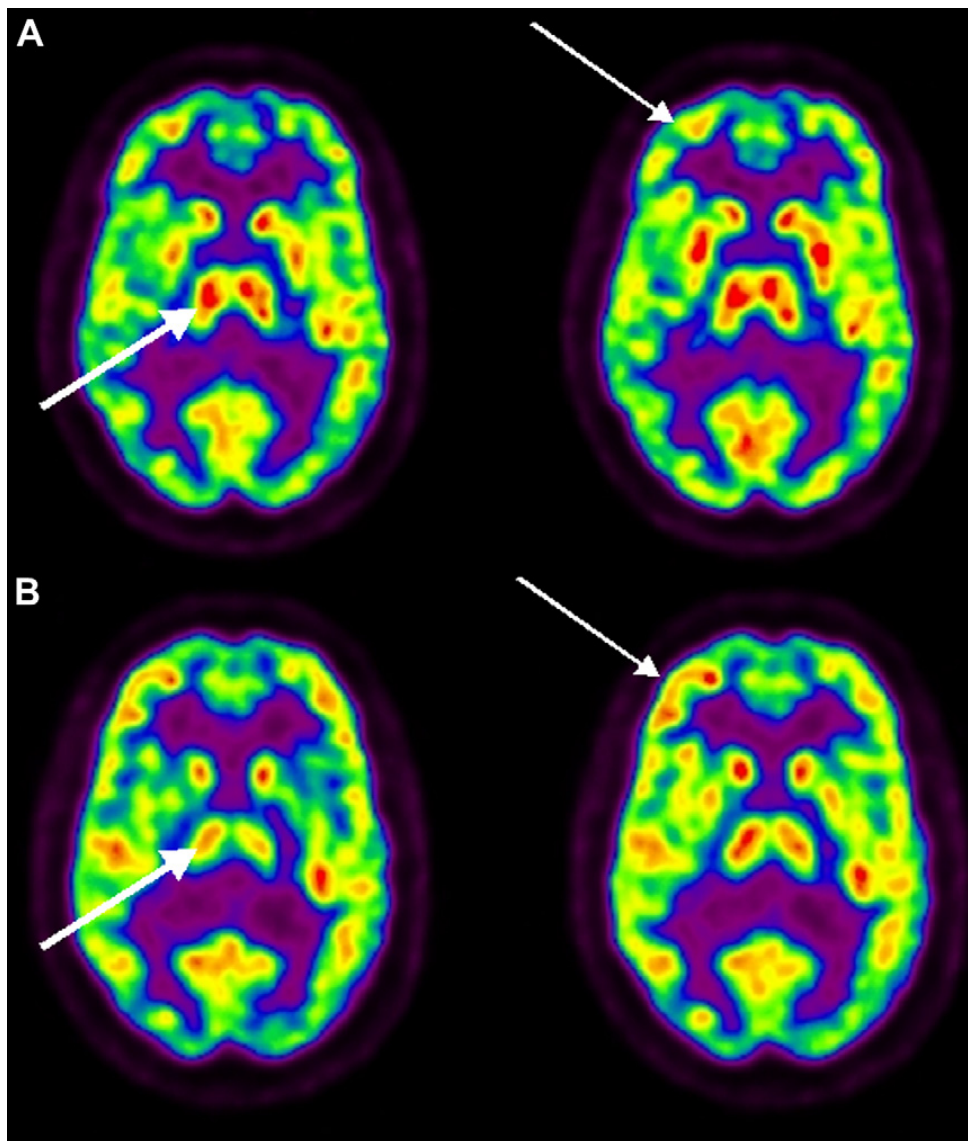


Fig. 3. FDG-PET scans of a subject at rest (A) and while performing a meditation task (B). During meditation, there is increased metabolism in the frontal lobes (*thin arrow*) and decreased metabolism in the thalami (*thick arrow*). These structures are involved in stress pathways and the observed effects in these scans are hypothesized to be associated reduced levels of stress and anxiety.

rCBF in the insula, prefrontal, and inferior frontal cortices.⁵⁸ 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.⁵⁹ 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.⁶⁰ 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.⁶¹ 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.⁶² 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.⁶³⁻⁶⁵ It has been suggested that schizophrenia is most commonly associated on PET scans (**Fig. 4**) with frontal lobe dysfunction,⁶⁶⁻⁶⁹ although other studies did not report such a finding.⁷⁰⁻⁷³ One study showed that the degree of frontal hypometabolism correlated with negative symptoms as opposed to positive symptoms,⁷⁴ although other studies have found an association between positive symptoms and decreased frontal activity.⁷⁵ 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.^{76,77} 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.^{78,79} It may also be that the frontal lobe activity changes during the course of the disorder and is more prominent in the acute setting⁸⁰ or that frontal lobe changes may vary with specific symptoms in individual patients.⁸¹ There are other areas that may also be affected in schizophrenia, including hypometabolism in the anterior cingulate cortex, striatum, and thalamus.⁸²⁻⁸⁵ Liddle and colleagues^{78,79} 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 thalamo-cortical-striatal circuit suggested as abnormal in some models of schizophrenia.^{86,87} The findings from this study also showed that schizophrenics

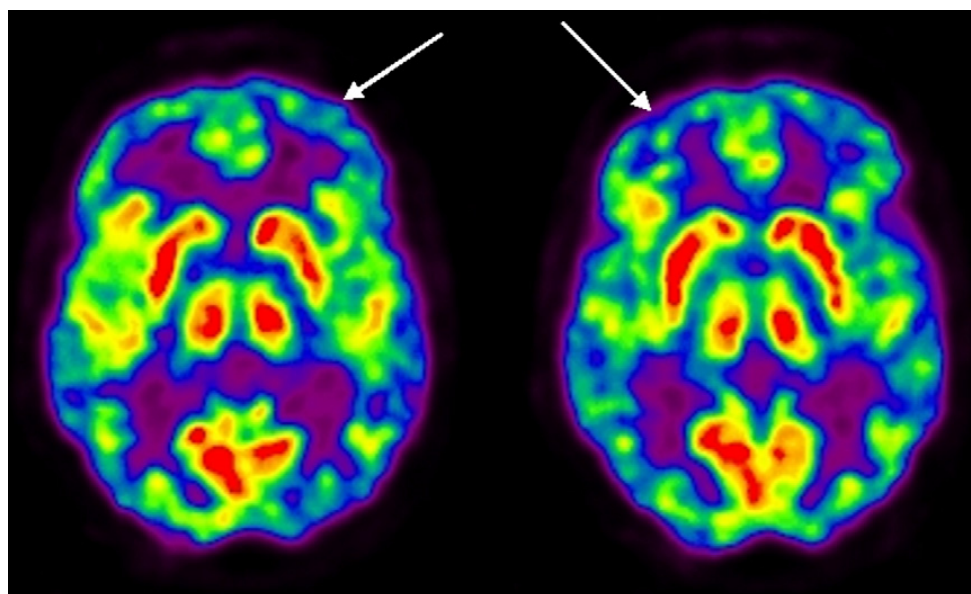


Fig. 4. FDG-PET scan of patient with schizophrenia showing a mild global decrease, particularly in the frontal regions (arrows), consistent with some of the reported findings in the literature.

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 hyperactivation 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 $^{15}\text{O}\text{-H}_2\text{O}$ PET. Also, Early and colleagues⁹² 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 colleagues⁹⁶ found that schizophrenic patients had higher left temporal lobe metabolic rates compared with controls when there was sensory stimulation of the right arm. Another study⁹⁷ 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 colleagues¹⁰⁵ 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 group¹¹⁸ 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 ^{18}F -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.¹¹⁹ In a review article by Howes and colleagues,¹²⁰ 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 with prodromal symptoms of schizophrenia as well as in those with frank schizophrenia.¹²¹ These findings suggest that striatal dopamine overactivity predates the onset of schizophrenia. Another study demonstrated that depressive symptoms in neuroleptic-naïve, first-admission schizophrenia patients have low presynaptic dopamine function.¹²² There has been no evidence of a change in serotonin receptors in patients with schizophrenia,^{123,124} although some investigators have reported a decrease in the frontal lobes in neuroleptic-naïve patients.¹²⁵

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.^{126,127} 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.¹²⁸ 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.¹²⁹ 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.^{130–132} Upregulation of dopamine D2 receptors has also been associated with a regional increase of blood flow and metabolism in the basal ganglia.¹³³ 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.^{134,135} In addition to D2 receptor blockade with antipsychotic drugs, Sedvall and colleagues¹³⁶ found that there is also blockade of the D1 receptors (D1 receptor activity was

measured with ¹¹C-SCH 23390). This is particularly true with the drug clozapine, which shows almost the same amount of D1 as D2 receptor occupancy.¹³⁷ 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.¹³⁸ 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.¹³⁹ 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.¹⁴⁰ 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.^{141,142} PET imaging has demonstrated gender differences related to the effects with antipsychotic medications with women having a reduction in cingulate gyrus metabolism compared with men with clozapine and fluphenazine.¹⁴³ 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.^{144–147} 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.¹⁴⁸ 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.¹⁴⁹

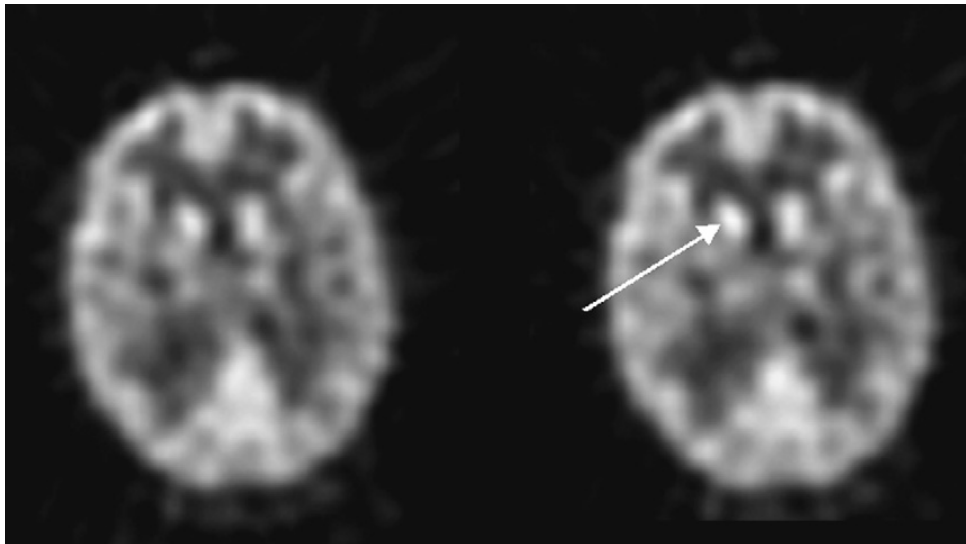


Fig. 5. FDG-PET of a patient with OCD showing increased glucose metabolism in the caudate nuclei bilaterally (arrow).

Behavior therapy responders also had significant bilateral decreases in caudate metabolism.¹⁵⁰ 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.¹⁵¹ 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.¹⁵⁰ This study, as well as others, also suggests that there is a prefrontal cortico-striato-thalamic network that mediates the symptoms of OCD.¹⁵² 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.¹⁵³ 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.¹⁵⁴ Another study showed that OCD was associated with decreased serotonin transporter binding in the insular cortex as measured by ¹¹C-DASB PET imaging.¹⁵⁵ 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.^{156,157} A study by Wik and colleagues¹⁵⁸ 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.¹⁵⁹ 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.¹⁶⁰ Patients with chronic alcoholism and cerebellar degeneration had significantly reduced glucose metabolism in the superior vermis compared with controls.¹⁶¹ Volkow and colleagues¹⁶² 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.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.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.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.^{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.^{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.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.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.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.¹⁷² PET studies have the potential of elucidating the mechanisms of the effects and the addictive properties of cocaine.¹⁷³ Initial studies with ¹¹C cocaine showed maximal uptake in the basal ganglia.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,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.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 colleagues¹⁷⁷ 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 study¹⁷⁸ 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.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,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

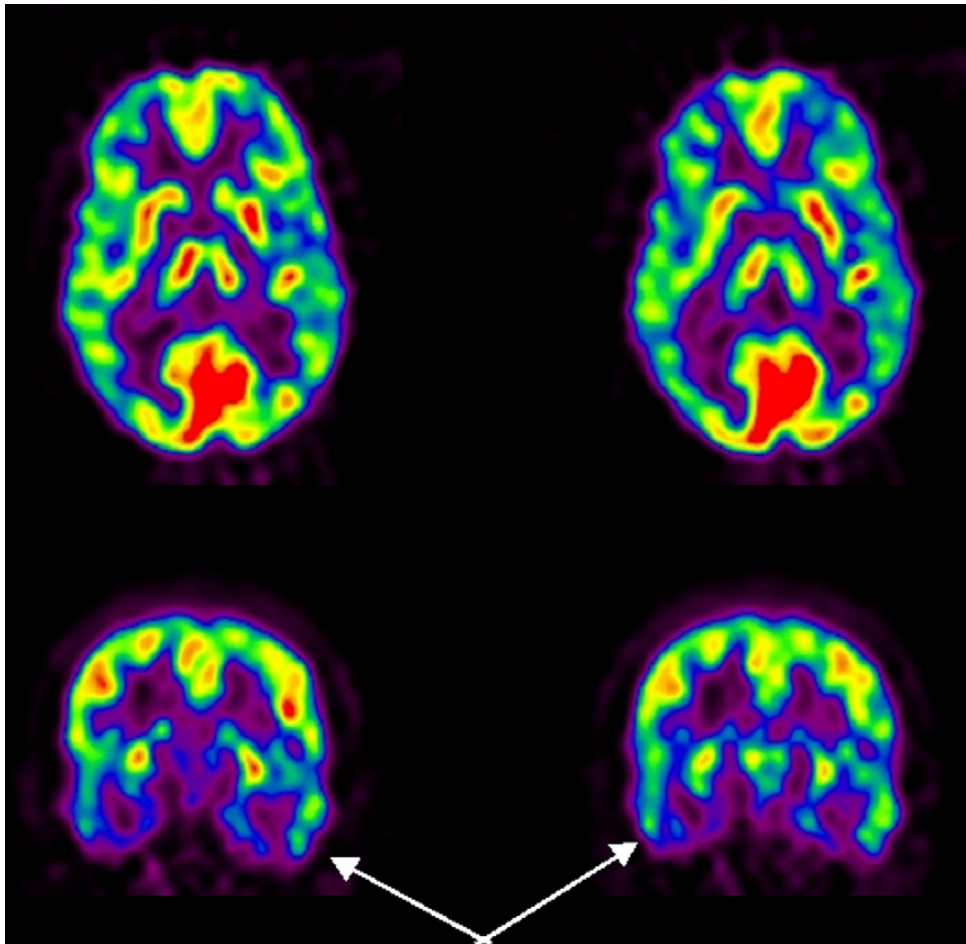


Fig. 6. FDG-PET scan of patient with chronic cocaine abuse showing global cortical decrease in glucose metabolism, particularly in the temporal lobes (*arrows*).

involved in cocaine abuse, however, are also involved in a circuit regulating repetitive behavior.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 craving¹⁸² 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.¹⁸³

PET receptor studies have attempted to determine the relationship between cocaine and dopamine receptors in the basal ganglia. For example, an ¹¹C-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.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.^{185,186} Another study suggests that the

thalamic dopamine pathways are also important in cocaine addiction.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.¹⁸⁸

Cocaine has been shown to significantly block dopamine transporters.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.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.

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-naïve patients and found global cerebral glucose hypometabolism, particularly in the premotor cortex and in the superior PFC.¹⁹¹ Two follow-up studies by the same group, however, did not find the same global or regional deficits.^{192,193} Two other PET studies did suggest that there are frontostriatal abnormalities associated with ADHD.^{194,195}

PET studies have shown that brain dopamine neurotransmission is disrupted in ADHD and that these deficits may underlie core symptoms of inattention and impulsivity.¹⁹⁶ One PET study showed lower L-¹¹C-DOPA use in adolescents with ADHD compared with control subjects, especially in subcortical regions.¹⁹⁷ 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.^{198–200} Other studies, however, have reported increased dopamine transporter binding in the striatum of ADHD patients.²⁰¹ A PET study of 53 ADHD patients showed that specific binding of D2 receptors and dopamine transporters was lower in ADHD than in controls, particularly in regions of the dopamine reward pathway in the left side of the brain.²⁰² Ratings of attention correlated with D2/D3 receptor binding in the nucleus accumbens, midbrain, caudate, and hypothalamus and with dopamine transporter binding in the midbrain.

AUTISM

Autism is a neurodevelopmental disorder characterized by repetitive or obsessive interests and behavior as well as deficits in sociability and communication. An FDG-PET study showed that patients with autism spectrum disorders had greater metabolism in the right caudate nucleus and lower glucose metabolic rates bilaterally in the ventral caudate, putamen, and thalamus.²⁰³ These results suggest that there is a deficit in the anterior cingulate–ventral striatum–anterior thalamic pathway in autistic patients with autism spectrum disorders. A PET study with ¹⁵O-H₂O demonstrated decreased CBF in the superior temporal lobe in autistic patients that also correlated with the severity of disease.²⁰⁴ This

corroborated previous studies that also demonstrated hypoperfusion in the bilateral temporal lobes.^{205,206} Another study on the effects of SSRI treatment in autism showed that metabolic rates were significantly higher in the right anterior cingulate gyrus and the OFC after fluoxetine treatment.²⁰⁷ In addition, patients with higher metabolic rates in the medial frontal region and anterior cingulate pretreatment were more likely to respond to fluoxetine.

The pathophysiology of autism is also postulated to be related to abnormalities of the serotonergic and dopaminergic systems. The actual pathophysiology of autism, however, remains to be fully elucidated. A recent study showed that serotonin transporter binding is significantly lower in the brain of autistic individuals compared with controls.²⁰⁸ The decrease in the cingulate cortex was correlated with impairment of social cognition. There also was a significant correlation between repetitive or obsessive behaviors and the reduction of serotonin transporter binding in the thalamus. In the same group of autistic patients, dopamine transporter binding was significantly higher in the OFC and binding was inversely correlated with serotonin transporter binding.

SUMMARY

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.

REFERENCES

1. Fu CHY, McGuire PK. Functional neuroimaging in psychiatry. *Philos Trans R Soc Lond, B, Biol Sci* 1999;354:1359–70.
2. Kung HF. Overview of radiopharmaceuticals for diagnosis of central nervous disorders. *Crit Rev Clin Lab Sci* 1991;28:269–86.
3. Maziere B, Maziere M. Positron emission tomography studies of brain receptors. *Fundam Clin Pharmacol* 1991;5:61–91.
4. Gatley SJ, DeGrado TR, Kornguth ML, et al. Radiopharmaceuticals for positron emission tomography: development of new, innovative tracers for

- measuring the rates of physiologic and biochemical processes. *Acta Radiol Suppl (Stockh)* 1990; 374:7–11.
5. Kopin TJ. In-vivo quantitative imaging of catecholaminergic nerve terminals in brain and peripheral organs using positron emission tomography (PET). *J Neural Transm Suppl* 1990; 32:19–27.
 6. Sadzot B, Mayberg HS, Frost JJ. Detection and quantification of opiate receptors in man by positron emission tomography. Potential applications to the study of pain. *Neurophysiol Clin* 1990;20:323–34.
 7. Frost JJ. Receptor imaging by positron emission tomography and single-photon emission computed tomography. *Invest Radiol* 1992;27(Suppl 2):S54–8.
 8. Abadie P, Baron JC, Bisslerbe JG, et al. Central benzodiazepine receptors in human brain: estimation of regional Bmax and KD values with positron emission tomography. *Eur J Pharmacol* 1992;213: 107–15.
 9. Varastet M, Brouillet E, Chavoix C, et al. In vivo visualization of central muscarinic receptors using [¹¹C] quinuclidinyl benzilate and positron emission tomography in baboons. *Eur J Pharmacol* 1992; 213:275–84.
 10. O'Connell RA, Van Heertum RL, Holt AR, et al. Single photon emission computed tomography in psychiatry. *Clin Nucl Med* 1987;12(Suppl 9):13.
 11. Phelps ME, Mazziotta JC, Baxter L, et al. Positron emission tomographic study of affective disorders. Problems and strategies. *Ann Neurol* 1984; 15(Suppl):S149–56.
 12. Bench CJ, Friston KJ, Brown RG, et al. The anatomy of melancholia—focal abnormalities of cerebral blood flow in major depression. *Psychiatry Med* 1992;22:607–15.
 13. Dolan RJ, Bench CJ, Brown RG, et al. Regional cerebral blood flow abnormalities in depressed patients with cognitive impairment. *J Neurol Neurosurg Psychiatr* 1992;55:768–73.
 14. Drevets WC, Price JL, Simpson JR Jr, et al. Subgenual prefrontal cortex abnormalities in mood disorders. *Nature* 1997;386(6627):824–7.
 15. Ho AP, Gillin JC, Buchsbaum MS, et al. Brain glucose metabolism during non-rapid eye movement sleep in major depression. A positron emission tomography study. *Arch Gen Psychiatry* 1996;53(7):645–52.
 16. Kumar A, Newberg A, Alavi A, et al. Regional cerebral glucose metabolism in late life depression and Alzheimer's disease: a preliminary positron emission tomography study. *Proc Natl Acad Sci U S A* 1993;90:7019–23.
 17. Osuch EA, Ketter TA, Kimbrell TA, et al. Regional cerebral metabolism associated with anxiety symptoms in affective disorder patients. *Biol Psychiatry* 2000;48(10):1020–3.
 18. Brody AL, Saxena S, Silverman DH, et al. Brain metabolic changes in major depressive disorder from pre- to post-treatment with paroxetine. *Psychiatry Res* 1999;91(3):127–39.
 19. Milak MS, Parsey RV, Lee L, et al. Pretreatment regional brain glucose uptake in the midbrain on PET may predict remission from a major depressive episode after three months of treatment. *Psychiatry Res* 2009;173(1):63–70.
 20. Konarski JZ, Kennedy SH, Segal ZV, et al. Predictors of nonresponse to cognitive behavioural therapy or venlafaxine using glucose metabolism in major depressive disorder. *J Psychiatry Neurosci* 2009;34(3):175–80.
 21. Mayberg HS, Brannan SK, Tekell JL, et al. Regional metabolic effects of fluoxetine in major depression: serial changes and relationship to clinical response. *Biol Psychiatry* 2000;48(8):830–43.
 22. Wu J, Buchsbaum MS, Gillin JC, et al. Prediction of antidepressant effects of sleep deprivation by metabolic rates in the ventral anterior cingulate and medial prefrontal cortex. *Am J Psychiatry* 1999;156(8):1149–58.
 23. Smith GS, Reynolds CF 3rd, Pollock B, et al. Cerebral glucose metabolic response to combined total sleep deprivation and antidepressant treatment in geriatric depression. *Am J Psychiatry* 1999; 156(5):683–9.
 24. Bewernick BH, Hurlmann R, Matusch A, et al. Nucleus accumbens deep brain stimulation decreases ratings of depression and anxiety in treatment-resistant depression. *Biol Psychiatry* 2010;67(2):110–6.
 25. Baxter LR, Phelps ME, Mazziotta JC, et al. Cerebral metabolic rates for glucose in mood disorders. *Arch Gen Psychiatry* 1985;42:441–7.
 26. Schwartz JM, Baxter LR, Mazziotta JC, et al. The differential diagnosis of depression. Relevance of positron emission tomography studies of cerebral glucose metabolism to the bipolar-unipolar dichotomy. *JAMA* 1987;258:1368–74.
 27. Buchsbaum M, Wu J, Haier R, et al. Positron emission tomography assessment of effects of benzodiazepines on regional glucose metabolic rate in patients with anxiety disorder. *Life Sci* 1986;40: 2393–400.
 28. Morris P, Rapoport GI. Neuroimaging and affective disorder in late life: a review. *Can J Psychiatry* 1990;35:347–54.
 29. Meltzer CC, Price JC, Mathis CA, et al. PET imaging of serotonin type 2A receptors in late-life neuropsychiatric disorders. *Am J Psychiatry* 1999;156(12):1871–8.
 30. Yatham LN, Liddle PF, Shiah IS, et al. Brain serotonin receptors in major depression: a positron emission tomography study. *Arch Gen Psychiatry* 2000;57(9):850–8.

31. Drevets WC, Frank E, Price JC, et al. Serotonin type-1A receptor imaging in depression. *Nucl Med Biol* 2000;27(5):499–507.
32. Drevets WC, Thase ME, Moses-Kolko EL, et al. Serotonin-1A receptor imaging in recurrent depression: replication and literature review. *Nucl Med Biol* 2007;34(7):865–77.
33. Biver F, Wikler D, Lotstra F, et al. Serotonin 5-HT₂ receptor imaging in major depression: focal changes in orbito-insular cortex. *Br J Psychiatry* 1997;171:444–8.
34. Meyer JH. Imaging the serotonin transporter during major depressive disorder and antidepressant treatment. *J Psychiatry Neurosci* 2007;32: 86–102.
35. Zanardi R, Artigas F, Moresco R, et al. Increased 5-hydroxytryptamine-2 receptor binding in the frontal cortex of depressed patients responding to paroxetine treatment: a positron emission tomography scan study. *J Clin Psychopharmacol* 2001;21(1): 53–8.
36. Meyer JH, Kapur S, Eisefeld B, et al. The effect of paroxetine on 5-HT_{2A} receptors in depression: an [(18)F]setoperone PET imaging study. *Am J Psychiatry* 2001;158(1):78–85.
37. Sargent PA, Kjaer KH, Bench CJ, et al. Brain serotonin_{1A} receptor binding measured by positron emission tomography with [11C]WAY-100635: effects of depression and antidepressant treatment. *Arch Gen Psychiatry* 2000;57(2):174–80.
38. Saijo T, Takano A, Suhara T, et al. Effect of electroconvulsive therapy on 5-HT_{1A} receptor binding in patients with depression: a PET study with [11C]WAY 100635. *Int J Neuropsychopharmacol* 2010;1–7. [Epub ahead of print].
39. Yatham LN, Liddle PF, Dennie J, et al. Decrease in brain serotonin 2 receptor binding in patients with major depression following desipramine treatment: a positron emission tomography study with fluorine-18-labeled setoperone. *Arch Gen Psychiatry* 1999;56(8):705–11.
40. Selvaraj S, Venkatesha Murthy N, Bhagwagar Z, et al. Diminished brain 5-HT transporter binding in major depression: a positron emission tomography study with [(11)C]DASB. *Psychopharmacology (Berl)* 2009. [Epub ahead of print].
41. Martinot M, Bragulat V, Artiges E, et al. Decreased presynaptic dopamine function in the left caudate of depressed patients with affective flattening and psychomotor retardation. *Am J Psychiatry* 2001; 158(2):314–6.
42. Saijo T, Takano A, Suhara T, et al. Electroconvulsive therapy decreases dopamine D₂ receptor binding in the anterior cingulate in patients with depression: a controlled study using positron emission tomography with radioligand [(11)C]FLB 457. *J Clin Psychiatry* 2009. [Epub ahead of print].
43. Pearlson GD, Wong DF, Tune LE, et al. In vivo D₂ dopamine receptor density in psychotic and nonpsychotic patients with bipolar disorder. *Arch Gen Psychiatry* 1995;52(6):471–7.
44. Klumpers UM, Veltman DJ, Drent ML, et al. Reduced parahippocampal and lateral temporal GABA-[11C]flumazenil binding in major depression: preliminary results. *J Nucl Med Mol Imaging* 2010;37(3):565–74.
45. Reiman E, Rachle M, Butler F, et al. A focal brain abnormality in panic disorder: a severe form of anxiety. *Nature* 1984;310:683–5.
46. Reiman E, Rachle M, Robbins E, et al. Neuroanatomical correlates of a lactate-induced anxiety attack. *Arch Gen Psychiatry* 1989;46:493–500.
47. Reiman E, Rachle M, Robbins E, et al. The application of positron emission tomography to the study of panic disorder. *Am J Psychiatry* 1986; 143:469–77.
48. Wu JC, Buchsbaum MS, Hershey TG, et al. PET in generalized anxiety disorder. *Biol Psychiatry* 1991; 29(12):1181–99.
49. Kern S, Oakes TR, Stone CK, et al. Glucose metabolic changes in the prefrontal cortex are associated with HPA axis response to a psychosocial stressor. *Psychoneuroendocrinology* 2008;33(4): 517–29.
50. Mountz J, Modell J, Wilson M, et al. PET evaluation of cerebral blood flow during anxiety state in simple phobia. *Arch Gen Psychiatry* 1989;46:501–4.
51. Pardo JV, Fox PT, Raichle ME. Localization of a human system for sustained attention by positron emission tomography. *Nature* 1991;349:61–4.
52. Herzog H, Lele VR, Kuwert T, et al. Changed pattern of regional glucose metabolism during Yoga meditative relaxation. *Neuropsychobiology* 1990-1991;23:182–7.
53. Lou HC, Kjaer TW, Friberg L, et al. A ¹⁵O-H₂O PET study of meditation and the resting state of normal consciousness. *Hum Brain Mapp* 1999;7:98–105.
54. Newberg AB, Iversen J. The neural basis of the complex mental task of meditation: neurotransmitter and neurochemical considerations. *Med Hypotheses* 2003;61(2):282–91.
55. Akimova E, Lanzenberger R, Kasper S. The serotonin-1A receptor in anxiety disorders. *Biol Psychiatry* 2009;66(7):627–35.
56. Kjaer TW, Bertelsen C, Piccini P, et al. Increased dopamine tone during meditation-induced change of consciousness. *Brain Res Cogn Brain Res* 2002; 13(2):255–9.
57. Pruessner JC, Dedovic K, Pruessner M, et al. Stress regulation in the central nervous system: evidence from structural and functional neuroimaging studies in human populations—2008 Curt Richter Award Winner. *Psychoneuroendocrinology* 2010;35(1):179–91.

58. Fernandez M, Pissioti A, Frans O, et al. Brain function in a patient with torture related post-traumatic stress disorder before and after fluoxetine treatment: a positron emission tomography provocation study. *Neurosci Lett* 2001;297(2):101–14.
59. Molina ME, Isoardi R, Prado MN, et al. Basal cerebral glucose distribution in long-term post-traumatic stress disorder. *World J Biol Psychiatry* 2007(Sep 13);1–9.
60. Shin LM, McNally RJ, Kosslyn SM, et al. Regional cerebral blood flow during script-driven imagery in childhood sexual abuse-related PTSD: a PET investigation. *Am J Psychiatry* 1999;156(4):575–84.
61. Shin LM, Orr SP, Carson MA, et al. Regional cerebral blood flow in the amygdala and medial prefrontal cortex during traumatic imagery in male and female Vietnam veterans with PTSD. *Arch Gen Psychiatry* 2004;61(2):168–76.
62. Semple WE, Goyer PF, McCormick R, et al. Higher brain blood flow at amygdala and lower frontal cortex blood flow in PTSD patients with comorbid cocaine and alcohol abuse compared with normals. *Psychiatr* 2000;63(1):65–74.
63. Liddle PF. PET scanning and schizophrenia—what progress? *Psychiatry Med* 1992;22:557–60.
64. Sedvall G. The current status of PET scanning with respect to schizophrenia. *Neuropsychopharmacology* 1992;7:41–54.
65. Cleghorn JM, Zipursky RB, List SJ. Structural and functional brain imaging in schizophrenia. *J Psychiatry Neurosci* 1991;16:53–74.
66. Kim JJ, Mohamed S, Andreasen NC, et al. Regional neural dysfunctions in chronic schizophrenia studied with positron emission tomography. *Am J Psychiatry* 2000;157(4):542–8.
67. Ingvar DH, Franzen G. Abnormalities of cerebral blood flow distribution in patients with chronic schizophrenia. *Acta Psychiatr Scand* 1974;50:425–62.
68. Andreasen NC, O'Leary DS, Flaum M, et al. Hypofrontality in schizophrenia: distributed dysfunctional circuits in neuroleptic-naïve patients. *Lancet* 1997;349(9067):1730–4.
69. Lehrer DS, Christian BT, Mantil J, et al. Thalamic and prefrontal FDG uptake in never medicated patients with schizophrenia. *Am J Psychiatry* 2005;162(5):931–8.
70. Gur RE, Resnick SM, Alavi A, et al. Regional brain function in schizophrenia I. A positron emission tomography study. *Arch Gen Psychiatry* 1987;44:119–25.
71. Wiesel FA, Wik G, Sjogren I, et al. Altered relationships between metabolic rates of glucose in brain regions of schizophrenic patients. *Acta Psychiatr Scand* 1987;76:642–7.
72. Wiesel FA, Wik G, Sjogren I, et al. Regional brain glucose metabolism in drug-free schizophrenic patients and clinical correlates. *Acta Psychiatr Scand* 1987;76:628–41.
73. Soyka M, Koch W, Möller HJ, et al. Hypermetabolic pattern in frontal cortex and other brain regions in unmedicated schizophrenia patients. Results from a FDG-PET study. *Eur Arch Psychiatry Clin Neurosci* 2005;255(5):308–12.
74. Volkow ND, Wolf AP, Van Gelder P, et al. Phenomenological correlates of metabolic activity in 18 patients with chronic schizophrenia. *Am J Psychiatry* 1987;144:151–8.
75. McGuire PK, Quested DJ, Spence SA, et al. Pathophysiology of 'positive' thought disorder in schizophrenia. *Br J Psychiatry* 1998;173:231–5.
76. Buchanan RW, Breier A, Kirkpatrick B, et al. The deficit syndrome. Functional and structural characteristics. *Schizophrenia Res* 1991;4:400–1.
77. Schroder J, Buchsbaum MS, Siegel BV, et al. Cerebral metabolic activity correlates of subsyndromes in chronic schizophrenia. *Schizophr Res* 1996;19(1):41–53.
78. Liddle PF, Friston KJ, Frith CD, et al. Cerebral blood flow and mental processes in schizophrenia. *J R Soc Med* 1992;85:224–7.
79. Liddle PF, Friston KJ, Frith CD, et al. Patterns of cerebral blood flow in schizophrenia. *Br J Psychol* 1992;160:179–86.
80. Spence SA, Hirsch SR, Brooks DJ, et al. Prefrontal cortex activity in people with schizophrenia and control subjects. Evidence from positron emission tomography for remission of 'hypofrontality' with recovery from acute schizophrenia. *Br J Psychiatry* 1998;172:316–23.
81. Sabri O, Erkwow R, Schreckenberger M, et al. Correlation of positive symptoms exclusively to hyperperfusion or hypoperfusion of cerebral cortex in never-treated schizophrenics. *Lancet* 1997;349(9067):1735–9.
82. Haznedar MM, Buchsbaum MS, Luu C, et al. Decreased anterior cingulate gyrus metabolic rate in schizophrenia. *Am J Psychiatry* 1997;154(5):682–4.
83. Fujimoto T, Takeuch K, Matsumoto T, et al. Abnormal glucose metabolism in the anterior cingulate cortex in patients with schizophrenia. *Psychiatry Res* 2007;154(1):49–58.
84. Hazlett EA, Buchsbaum MS, Byne W, et al. Three-dimensional analysis with MRI and PET of the size, shape, and function of the thalamus in the schizophrenia spectrum. *Am J Psychiatry* 1999;156(8):1190–9.
85. Buchsbaum MS, Someya T, Teng CY, et al. PET and MRI of the thalamus in never-medicated patients with schizophrenia. *Am J Psychiatry* 1996;153(2):191–9.
86. Katz M, Buchsbaum MS, Siegel BV Jr, et al. Correlational patterns of cerebral glucose metabolism in

- never-medicated schizophrenics. *Neuropsychobiology* 1996;33(1):1–11.
87. Siegel BV Jr, Buchsbaum MS, Bunney WE Jr, et al. Cortical-striatal-thalamic circuits and brain glucose metabolic activity in 70 unmedicated male schizophrenic patients. *Am J Psychiatry* 1993;150(9):1325–36.
 88. Gur RE, Chin S. Laterality in functional brain imaging studies of schizophrenia. *Schizophr Bull* 1999;25(1):141–56.
 89. Gur RE, Resnick SM, Gur RC, et al. Regional brain function in schizophrenia. II. Repeated evaluation with positron emission tomography. *Arch Gen Psychiatry* 1987;44:126–9.
 90. Gur RE, Resnick SM, Gur RC. Laterality and frontality of cerebral blood flow and metabolism in schizophrenia. Relationship to symptom specificity. *Psychiatry Res* 1989;27:325–34.
 91. Sheppard G, Gruzelier J, Manchanda R, et al. Positron emission tomographic scanning in predominantly never-treated acute schizophrenic patients. *Lancet* 1983;2:1448–52.
 92. Early TS, Reiman EM, Raichle ME, et al. Left globus pallidus abnormality in never-medicated patients with schizophrenia. *Proc Natl Acad Sci U S A* 1987;84:561–3.
 93. Laakso A, Vilkmann H, Alakare B, et al. Striatal dopamine transporter binding in neuroleptic-naive patients with schizophrenia studied with positron emission tomography. *Am J Psychiatry* 2000;157(2):269–71.
 94. Cohen RM, Semple WE, Gross M, et al. From syndrome to illness. Delineating the pathophysiology of schizophrenia with PET. *Schizophr Bull* 1988;14:169–76.
 95. Cohen RM, Semple WE, Gross M, et al. Dysfunction in a prefrontal substrate of sustained attention in schizophrenia. *Life Sci* 1987;43:2031–9.
 96. DeLisi LE, Buchsbaum MS, Holcomb HH, et al. Increased temporal lobe glucose use in chronic schizophrenic patients. *Biol Psychiatry* 1989;25:835–51.
 97. Gunther W. MRI-SPECT and PET-EEG findings on brain dysfunction in schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry* 1992;16:445–62.
 98. Siegel BV Jr, Nuechterlein KH, Abel L, et al. Glucose metabolic correlates of continuous performance test performance in adults with a history of infantile autism, schizophrenics, and controls. *Schizophr Res* 1995;17(1):85–94.
 99. Carter CS, Mintun M, Nichols T, et al. Anterior cingulate gyrus dysfunction and selective attention deficits in schizophrenia: [¹⁵O]H₂O PET study during single-trial Stroop task performance. *Am J Psychiatry* 1997;154(12):1670–5.
 100. Artiges E, Martinot JL, Verdys M, et al. Altered hemispheric functional dominance during word generation in negative schizophrenia. *Schizophr Bull* 2000;26(3):709–21.
 101. Heckers S, Curran T, Goff D, et al. Abnormalities in the thalamus and prefrontal cortex during episodic object recognition in schizophrenia. *Biol Psychiatry* 2000;48(7):651–7.
 102. Crespo-Facorro B, Paradiso S, Andreasen NC, et al. Recalling word lists reveals “cognitive dysmetria” in schizophrenia: a positron emission tomography study. *Am J Psychiatry* 1999;156(3):386–92.
 103. Heckers S, Goff D, Schacter DL, et al. Functional imaging of memory retrieval in deficit vs nondéficit schizophrenia. *Arch Gen Psychiatry* 1999;56(12):1117–23.
 104. Carter CS, Perlstein W, Ganguli R, et al. Functional hypofrontality and working memory dysfunction in schizophrenia. *Am J Psychiatry* 1998;155(9):1285–7.
 105. Volkow ND, Wolf AP, Brodie JD, et al. Brain interactions in chronic schizophrenics under resting and activation conditions. *Schizophr Res* 1988;1:47–53.
 106. Andreasen NC, O’Leary DS, Cizadlo T, et al. Schizophrenia and cognitive dysmetria: a positron-emission tomography study of dysfunctional prefrontal-thalamic-cerebellar circuitry. *PNAS* 1996;93(18):9985–90.
 107. Artiges E, Salame P, Recasens C, et al. Working memory control in patients with schizophrenia: a PET study during a random number generation task. *Am J Psychiatry* 2000;157(9):1517–9.
 108. Heckers S, Rauch SL, Goff D, et al. Impaired recruitment of the hippocampus during inconspicuous recollection in schizophrenia. *Nat Neurosci* 1998;1(4):318–23.
 109. Fletcher PC, McKenna PJ, Frith CD, et al. Brain activations in schizophrenia during a graded memory task studied with functional neuroimaging. *Arch Gen Psychiatry* 1998;55(11):1001–8.
 110. Ragland JD, Gur RC, Glahn DC, et al. Frontotemporal cerebral blood flow change during executive and declarative memory tasks in schizophrenia: a positron emission tomography study. *Neuropsychology* 1998;12(3):399–413.
 111. Hyde TM, Weinberger DR. The brain in schizophrenia. *Semin Neurol* 1990;10:275–85.
 112. Sedvall G. Monoamines and schizophrenia. *Acta Psychiatr Scand Suppl* 1990;358:7–13.
 113. Okubo Y, Suhara T, Suzuki K, et al. Decreased prefrontal dopamine D1 receptors in schizophrenia revealed by PET. *Nature* 1997;385(6617):634–6.
 114. Sedvall G, Farde L, Hall H, et al. PET scanning—a new tool in clinical psychopharmacology. *Psychiatr Serv* 1988;5:27–33.
 115. Farde L, Nordstrom AL, Eriksson L, et al. Comparison of methods used with (¹¹C)NMSP for the PET-determination of central D2 dopamine receptors. *Clin Neuropharmacol* 1990;13:87–8.

116. Wong DF, Wagner HN Jr, Tune LE, et al. Positron emission tomography reveals elevated D2 dopamine receptors in drug-naive schizophrenics. *Science* 1986;234:1558–63.
117. Tune L, Barta P, Wong D, et al. Striatal dopamine D2 receptor quantification and superior temporal gyrus: volume determination in 14 chronic schizophrenic subjects. *Psychiatry Res* 1996;67(2):155–8.
118. Seeman P, Guan HC, Niznik HB. Endogenous dopamine lowers the dopamine D2 receptor density as measured by (3H)raclopride: implications for positron emission tomography of the human brain. *Synapse* 1989;3:96–7.
119. Kessler RM, Woodward ND, Riccardi P, et al. Dopamine D2 receptor levels in striatum, thalamus, substantia nigra, limbic regions, and cortex in schizophrenic subjects. *Biol Psychiatry* 2009;65(12):1024–31.
120. Howes OD, Montgomery AJ, Asselin MC, et al. Molecular imaging studies of the striatal dopaminergic system in psychosis and predictions for the prodromal phase of psychosis. *Br J Psychiatry Suppl* 2007;51:s13–8.
121. Howes OD, Montgomery AJ, Asselin MC, et al. Elevated striatal dopamine function linked to prodromal signs of schizophrenia. *Arch Gen Psychiatry* 2009;66(1):13–20.
122. Hietala J, Syvalahti E, Vilkkumä H, et al. Depressive symptoms and presynaptic dopamine function in neuroleptic-naive schizophrenia. *Schizophr Res* 1999;35(1):41–50.
123. Verhoeff NP, Meyer JH, Kecojevic A, et al. A voxel-by-voxel analysis of [18F]setoperone PET data shows no substantial serotonin 5-HT_{2A} receptor changes in schizophrenia. *Psychiatry Res* 2000;99(3):123–35.
124. Okubo Y, Suhara T, Suzuki K, et al. Serotonin 5-HT₂ receptors in schizophrenic patients studied by positron emission tomography. *Life Sci* 2000;66(25):2455–64.
125. Ngan ET, Yatham LN, Ruth TJ, et al. Decreased serotonin 2A receptor densities in neuroleptic-naive patients with schizophrenia: a PET study using [(18)F]setoperone. *Am J Psychiatry* 2000;157(6):1016–8.
126. Volkow ND, Brodie JD, Wolf AP, et al. Brain metabolism in patients with schizophrenia before and after acute neuroleptic administration. *J Neurol Neurosurg Psychiatr* 1986;49:1199–202.
127. Resnick SM, Gur RE, Alavi A, et al. Positron emission tomography and subcortical glucose metabolism in schizophrenia. *Psychiatry Res* 1988;24:1–11.
128. Buchsbaum MS, Potkin SG, Siegel BV Jr, et al. Striatal metabolic rate and clinical response to neuroleptics in schizophrenia. *Arch Gen Psychiatry* 1992;49(12):966–74.
129. Bartlett EJ, Brodie JD, Simkowitz P, et al. Effect of a haloperidol challenge on regional brain metabolism in neuroleptic-responsive and nonresponsive schizophrenic patients. *Am J Psychiatry* 1998;155(3):337–43.
130. Kapur S, Zipursky R, Jones C, et al. Relationship between dopamine D(2) occupancy, clinical response, and side effects: a double-blind PET study of first-episode schizophrenia. *Am J Psychiatry* 2000;157(4):514–20.
131. Farde L, Wiesel FA, Halldin C, et al. Central D2-dopamine receptor occupancy in schizophrenic patients treated with antipsychotic drugs. *Arch Gen Psychiatry* 1988;45:71–6.
132. Kapur S, Remington G, Jones C, et al. High levels of dopamine D2 receptor occupancy with low-dose haloperidol treatment: a PET study. *Am J Psychiatry* 1996;153(7):948–50.
133. Miller DD, Andreasen NC, O'Leary DS, et al. Effect of antipsychotics on regional cerebral blood flow measured with positron emission tomography. *Neuropsychopharmacology* 1997;17(4):230–40.
134. Wolkin A, Barouche F, Wolf AP, et al. Dopamine blockade and clinical response. Evidence for two biological subgroups of schizophrenia. *Am J Psychiatry* 1989;146:905–8.
135. Martinot JL, Pailliere-Martinot ML, Loc HC, et al. Central D2 receptor blockade and antipsychotic effects of neuroleptics. Preliminary study with positron emission tomography. *Psychiatr Psychiatrobiol* 1990;5:231–40.
136. Sedvall G, Farde L, Stone-Lander S, et al. Dopamine D1-receptor binding in the living human brain. In: Breese GR, Creese I, editors. *Neurobiology of central D1-dopamine receptors*. New York: Plenum; 1986.
137. Farde L, Wiesel F-A, Nordstrom A-L, et al. D1 and D2-dopamine receptor occupancy during treatment with conventional and atypical neuroleptics. *Psychiatropharmacol* 1989;99:S28–31.
138. Kapur S, Zipursky R, Jones C, et al. A positron emission tomography study of quetiapine in schizophrenia: a preliminary finding of an antipsychotic effect with only transiently high dopamine D2 receptor occupancy. *Arch Gen Psychiatry* 2000;57(6):553–9.
139. Kessler RM, Ansari MS, Riccardi P, et al. Occupancy of striatal and extrastriatal dopamine D2 receptors by clozapine and quetiapine. *Neuropsychopharmacology* 2006;31(9):1991–2001 [Epub 2006 May 31].
140. Agid O, Mamo D, Ginovart N, et al. Striatal vs extrastriatal dopamine D2 receptors in antipsychotic response—a double-blind PET study in schizophrenia. *Neuropsychopharmacology* 2007;32(6):1209–15.
141. Kapur S, Cho R, Jones C, et al. Is amoxapine an atypical antipsychotic? Positron-emission

- tomography investigation of its dopamine₂ and serotonin₂ occupancy. *Biol Psychiatry* 1999;45(9):1217–20.
142. Kapur S, Zipursky RB, Remington G, et al. 5-HT₂ and D₂ receptor occupancy of olanzapine in schizophrenia: a PET investigation. *Am J Psychiatry* 1998;155(7):921–8.
 143. Cohen RM, Nordahl TE, Semple WE, et al. The brain metabolic patterns of clozapine- and fluphenazine-treated female patients with schizophrenia: evidence of a sex effect. *Neuropsychopharmacology* 1999;21(5):632–40.
 144. Baxter L, Schwartz J, Mazziotto J, et al. Cerebral glucose metabolic rates in nondepressed patients with obsessive-compulsive disorder. *Am J Psychiatry* 1988;145:1560–3.
 145. Nordahl TE, Benkelfat C, Semple W, et al. Cerebral glucose metabolic rates in obsessive compulsive disorder. *Neuropsychopharmacology* 1989;2:23–8.
 146. Sawle GV, Hymas NF, Lees AJ, et al. Obsessional slowness. Functional studies with positron emission tomography. *Brain* 1991;114:2191–202.
 147. Insel TR, Winslow JT. Neurobiology of obsessive-compulsive disorder. *Psychiatr Clin North Am* 1992;15:813–24.
 148. Swedo SE, Schapiro MB, Grady CL, et al. Cerebral glucose metabolism in childhood-onset obsessive-compulsive disorder. *Arch Gen Psychiatry* 1989;46:518–23.
 149. Brody AL, Saxena S, Schwartz JM, et al. FDG-PET predictors of response to behavioral therapy and pharmacotherapy in obsessive compulsive disorder. *Psychiatry Res* 1998;84(1):1–6.
 150. Schwartz JM, Stoessel PW, Baxter LR, et al. Systematic changes in cerebral glucose metabolic rate after successful behavior modification treatment of obsessive-compulsive disorder. *Arch Gen Psychiatry* 1996;53(2):109–13.
 151. Saxena S, Brody AL, Maidment KM, et al. Localized orbitofrontal and subcortical metabolic changes and predictors of response to paroxetine treatment in obsessive-compulsive disorder. *Neuropsychopharmacology* 1999;21(6):683–93.
 152. Rauch SL, Jenike MA, Alpert NM, et al. Regional cerebral blood flow measured during symptom provocation in obsessive-compulsive disorder using oxygen 15-labeled carbon dioxide and positron emission tomography. *Arch Gen Psychiatry* 1994;51(1):62–70.
 153. Perani D, Garibotto V, Gorini A, et al. In vivo PET study of 5HT_{2A} serotonin and D₂ dopamine dysfunction in drug-naïve obsessive-compulsive disorder. *Neuroimage* 2008;42(1):306–14.
 154. Moresco RM, Pietra L, Henin M, et al. Fluvoxamine treatment and D₂ receptors: a pet study on OCD drug-naïve patients. *Neuropsychopharmacology* 2007;32(1):197–205.
 155. Matsumoto R, Ichise M, Ito H, et al. Reduced serotonin transporter binding in the insular cortex in patients with obsessive-compulsive disorder: a [¹¹C]DASB PET study. *Neuroimage* 2010;49(1):121–6.
 156. Samson Y, Baron JC, Feline A, et al. Local cerebral glucose utilization in chronic alcoholics, a positron tomography study. *J Neurol Neurosurg Psychiatr* 1986;49:1165–70.
 157. Sach H, Russel JAG, Christman DR, et al. Alterations in regional cerebral glucose metabolic rate in non-Korsakoff chronic alcoholism. *Arch Neurol* 1987;44:1242–51.
 158. Wik G, Borg S, Sjogren I, et al. Positron emission tomography determination of regional cerebral glucose metabolism in alcohol-dependent men and healthy controls using 11C-glucose. *Acta Psychiatr Scand* 1988;78:234–41.
 159. Volkow ND, Fowler JS. Neuropsychiatric disorders. Investigation of schizophrenia and substance abuse. *Semin Nucl Med* 1992;22:254–67.
 160. Wang GJ, Volkow ND, Fowler JS, et al. Regional cerebral metabolism in female alcoholics of moderate severity does not differ from that of controls. *Alcohol Clin Exp Res* 1998;22(8):1850–4.
 161. Gilman S, Adams K, Koeppe RA, et al. Cerebellar hypometabolism in alcoholic cerebellar degeneration studied with FDG and PET. *Neurol* 1988;38:365.
 162. Volkow ND, Wang G-J, Hitzemann R, et al. Decreased cerebral response to inhibitory neurotransmission in alcoholics. *Am J Psychiatry* 1993;150:417–22.
 163. Johnson-Greene D, Adams KM, Gilman S, et al. Effects of abstinence and relapse upon neuropsychological function and cerebral glucose metabolism in severe chronic alcoholism. *J Clin Exp Neuropsychol* 1997;19(3):378–85.
 164. Volkow ND, Wang GJ, Hitzemann R, et al. Recovery of brain glucose metabolism in detoxified alcoholics. *Am J Psychiatry* 1994;151(2):178–83.
 165. Volkow ND, Hitzemann R, Wolf AP, et al. Acute effects of ethanol on regional brain glucose metabolism and transport. *Psychiatry Res* 1990;35:39–48.
 166. Volkow ND, Wang GJ, Begleiter H, et al. Regional brain metabolic response to lorazepam in subjects at risk for alcoholism. *Alcohol Clin Exp Res* 1995;19(2):510–6.
 167. Volkow ND, Wang GJ, Fowler JS, et al. Decreases in dopamine receptors but not in dopamine transporters in alcoholics. *Alcohol Clin Exp Res* 1996;20(9):1594–8.
 168. Tiihonen J, Vilkmann H, Rasanen P, et al. Striatal presynaptic dopamine function in type 1 alcoholics measured with positron emission tomography. *Mol Psychiatry* 1998;3(2):156–61.

169. Gilman S, Koeppe RA, Adams KM, et al. Decreased striatal monoaminergic terminals in severe chronic alcoholism demonstrated with (+)[11C]dihydrotrabenazine and positron emission tomography. *Ann Neurol* 1998;44(3):326–33.
170. Hommer D, Andreasen P, Rio D, et al. Effects of m-chlorophenylpiperazine on regional brain glucose utilization: a positron emission tomographic comparison of alcoholic and control subjects. *J Neurosci* 1997;17(8):2796–806, 1997.
171. Gilman S, Adams KM, Johnson-Greene D, et al. Effects of disulfiram on positron emission tomography and neuropsychological studies in severe chronic alcoholism. *Alcohol Clin Exp Res* 1996;20(8):1456–61.
172. Johanson CE, Fishman MW. The pharmacology of cocaine related to its abuse. *Pharmacol Rev* 1989;41:3–52.
173. Strickland TL, Miller BL, Kowell A, et al. Neurobiology of cocaine-induced organic brain impairment: contributions from functional neuroimaging. *Neuropsychol Rev* 1998;8(1):1–9.
174. Fowler JS, Volkow ND, Wolf AP, et al. Mapping cocaine binding sites in human and baboon brain in vivo. *Synapse* 1989;4:371–7.
175. Cook CE, Jeffcoat AR, Perez-Reys M. Pharmacokinetic studies of cocaine and phencyclidine in man. In: Barnett G, Chiang CN, editors. *Pharmacokinetics and pharmacodynamics of psychoactive drugs*. Foster City (CA): Biomedical Publications; 1985. p. 48–74.
176. London ED, Cascella NG, Wong DF, et al. Cocaine-induced reduction of glucose utilization in human brain. A study using positron emission tomography and (Fluorine-18)-fluorodeoxyglucose. *Arch Gen Psychiatry* 1990;47:567–74.
177. Volkow ND, Hitzemann R, Wang GJ, et al. Long-term frontal brain metabolic changes in cocaine abusers. *Synapse* 1992;11:184–90.
178. Volkow ND, Fowler JS, Wolf AP, et al. Changes in brain glucose metabolism in cocaine dependence and withdrawal. *Am J Psychiatry* 1991;148:621–6.
179. Volkow ND, Wang GJ, Fowler JS, et al. Association of methylphenidate-induced craving with changes in right striato-orbitofrontal metabolism in cocaine abusers: implications in addiction. *Am J Psychiatry* 1999;156(1):19–26.
180. Baxter L, Phelps M, Mazziotta J, et al. Local cerebral glucose metabolic rates in obsessive-compulsive disorder. A comparison with rates in unipolar depression and normal controls. *Arch Gen Psychiatry* 1987;44:211–8.
181. Modell JG, Mountz JM, Curtis G, et al. Neurophysiologic dysfunctions in basal ganglia limbic striatal and thalamocortical circuit as a pathogenetic mechanism of obsessive compulsive disorder. *J Neuropsychiatry* 1989;1:27–36.
182. Childress AR, Mozley PD, McElgin W, et al. Limbic activation during cue-induced cocaine craving. *Am J Psychiatry* 1999;156(1):11–8.
183. Wang GJ, Volkow ND, Fowler JS, et al. Regional brain metabolic activation during craving elicited by recall of previous drug experiences. *Life Sci* 1999;64(9):775–84.
184. Martinez D, Broft A, Foltin RW, et al. Cocaine dependence and d2 receptor availability in the functional subdivisions of the striatum: relationship with cocaine-seeking behavior. *Neuropsychopharmacol* 2004;29(6):1190–202.
185. Schlaepfer TE, Pearlson GD, Wong DF, et al. PET study of competition between intravenous cocaine and [11C]raclopride at dopamine receptors in human subjects. *Am J Psychiatry* 1997;154(9):1209–13.
186. Wu JC, Bell K, Najafi A, et al. Decreasing striatal 6-FDOPA uptake with increasing duration of cocaine withdrawal. *Neuropsychopharmacology* 1997;17(6):402–9.
187. Volkow ND, Wang GJ, Fowler JS, et al. Decreased striatal dopaminergic responsiveness in detoxified cocaine-dependent subjects. *Nature* 1997;386(6627):830–3.
188. Martinez D, Slifstein M, Narendran R, et al. Dopamine D1 receptors in cocaine dependence measured with PET and the choice to self-administer cocaine. *Neuropsychopharmacol* 2009;34(7):1774–82.
189. Volkow ND, Wang GJ, Fischman MW, et al. Effects of route of administration on cocaine induced dopamine transporter blockade in the human brain. *Life Sci* 2000;67(12):1507–15.
190. Volkow ND, Wang GJ, Fowler JS, et al. Enhanced sensitivity to benzodiazepines in active cocaine-abusing subjects: a PET study. *Am J Psychiatry* 1998;155(2):200–6.
191. Zametkin AJ, Nordahl TE, Gross M, et al. Cerebral glucose metabolism in adults with hyperactivity of childhood onset. *N Engl J Med* 1990;323:1361–6.
192. Ernst M, Libenauer LL, King AC, et al. Reduced brain metabolism in hyperactive girls. *J Am Acad Child Adolesc Psychiatry* 1994;33:858–68.
193. Zametkin AJ, Liebenauer LL, Fitzgerald GA, et al. Brain metabolism in teenagers with attention-deficit hyperactivity disorder. *Arch Gen Psychiatry* 1993;50:333–40.
194. Ernst M, Grant SJ, London ED, et al. Decision making in adolescents with behavior disorders and adults with substance abuse. *Am J Psychiatry* 2003;160:33–40.
195. Schweitzer JB, Faber TL, Grafton ST, et al. Alterations in the functional anatomy of working memory in adult attention deficit hyperactivity disorder. *Am J Psychiatry* 2000;157:278–80.

196. Rosa Neto P, Lou H, Cumming P, et al. Methylphenidate-evoked potentiation of extracellular dopamine in the brain of adolescents with premature birth. *Ann N Y Acad Sci* 2002;965:434–9.
197. Forsberg H, Fernell E, Waters S, et al. Altered pattern of brain dopamine synthesis in male adolescents with attention deficit hyperactivity disorder. *Behav Brain Funct* 2006;2:40.
198. Volkow ND, Wang GJ, Newcorn J, et al. Depressed dopamine activity in caudate and preliminary evidence of limbic involvement in adults with attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry* 2007;64(8):932–40.
199. Volkow ND, Wang GJ, Newcorn J, et al. Brain dopamine transporter levels in treatment and drug naïve adults with ADHD. *Neuroimage* 2007;34(3):1182–90.
200. Jucaite A, Fernell E, Halldin C, et al. Reduced midbrain dopamine transporter binding in male adolescents with attention-deficit/hyperactivity disorder: association between striatal dopamine markers and motor hyperactivity. *Biol Psychiatry* 2005;57(3):229–38.
201. Spencer TJ, Biederman J, Madras BK, et al. Further evidence of dopamine transporter dysregulation in ADHD: a controlled PET imaging study using altropane. *Biol Psychiatry* 2007;62(9):1059–61.
202. Volkow ND, Wang GJ, Kollins SH, et al. Evaluating dopamine reward pathway in ADHD: clinical implications. *JAMA* 2009;302(10):1084–91.
203. Haznedar MM, Buchsbaum MS, Hazlett EA, et al. Volumetric analysis and three-dimensional glucose metabolic mapping of the striatum and thalamus in patients with autism spectrum disorders. *Am J Psychiatry* 2006;163(7):1252–63.
204. Gendry Meresse I, Zilbovicius M, Boddaert N, et al. Autism severity and temporal lobe functional abnormalities. *Ann Neurol* 2005;58(3):466–9.
205. Ohnishi T, Matsuda H, Hashimoto T, et al. Abnormal regional cerebral blood flow in childhood autism. *Brain* 2000;123:1838–44.
206. Zilbovicius M, Boddaert N, Belin P, et al. Temporal lobe dysfunction in childhood autism: a PET study. *Am J Psychiatry* 2000;157:1988–93.
207. Buchsbaum MS, Hollander E, Haznedar MM, et al. Effect of fluoxetine on regional cerebral metabolism in autistic spectrum disorders: a pilot study. *Int J Neuropsychopharmacol* 2001;4(2):119–25.
208. Nakamura K, Sekine Y, Ouchi Y, et al. Brain serotonin and dopamine transporter bindings in adults with high-functioning autism. *Arch Gen Psychiatry* 2010;67(1):59–68.