Brain SPECT in Neurology and Psychiatry*

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Structural and functional images of the brain play an important role as powerful adjuncts in the management of an increasing number of neurologic and psychiatric diseases. Brain SPECT, in particular, with perfusion agents or with neuroreceptor imaging radiopharmaceuticals, is rapidly becoming a clinical tool in many places. For many neurologic and psychiatric conditions, this imaging modality has been used in diagnosis, prognosis assessment, evaluation of response to therapy, risk stratification, detection of benign or malignant viable tissue, and choice of medical or surgical therapy. The importance of this technique in nuclear medicine today should not be overlooked, particularly in cerebrovascular diseases, dementias, epilepsy, head injury, malignant brain tumors, movement disorders, obsessive–compulsive disorder, Gilles de la Tourette's syndrome, schizophrenia, depression, panic disorder, and drug abuse.

Key Words: brain SPECT; ^{99m}Tc-hexamethylpropyleneamine oxime; ^{99m}Tc-L,L-ethyl cysteinate dimer; neurologic diseases; psychiatric disorders

J Nucl Med 2001; 42:611–623

The diagnostic process in neurology follows a logical sequence of steps (*1*): elicitation of clinical facts (history and neurologic examination), interpretation of anatomic and physiologic signs and symptoms, syndromic formulation and localization of the lesion (anatomic diagnosis), and anatomic diagnosis plus mode of onset and course plus other medical data plus appropriate laboratory tests (pathologic or etiologic diagnosis).

From the first of these steps to the last, the likelihood of diagnosis is continuously increasing for some diseases and decreasing for others. When interpreting a set of images, the nuclear physician follows a similar sequence of steps, with the probabilities of diseases continuously increasing and decreasing.

As one of the appropriate laboratory tests, nuclear medicine may contribute to the final diagnosis of neurologic and psychiatric diseases. The choice of the most convenient radiopharmaceutical in a given clinical condition is essential for optimal performance of brain SPECT as an effective diagnostic laboratory test.

Received Sep. 6, 2000; revision accepted Dec. 11, 2000.

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RADIOPHARMACEUTICALS

The ^{99m}Tc-labeled compounds hexamethylpropyleneamine oxime (HMPAO) and L,L-ethyl cysteinate dimer (ECD) have been the most successful and widely used for brain perfusion imaging, despite the fact that neither fulfils all the characteristics of an ideal radiopharmaceutical. The descriptions and discussion that follow on neurologic and psychiatric diseases are based largely on data obtained with these two agents, unless otherwise indicated. A detailed discussion on radiopharmaceuticals for brain perfusion and neuroreceptor imaging can be found in a previous continuing education article by Catafau (*2*).

PATIENT PREPARATION AND IMAGE ACQUISITION

Patient preparation, image acquisition, and related topics are described in the 1999 *Procedure Guidelines Manual* of the Society of Nuclear Medicine (*3*).

IMAGE INTERPRETATION

Images are interpreted visually using all the data in the sets of slices described in the *Procedure Guidelines Manual* (*3*). Semiquantitative analysis using the cortex-to-cerebellum ratio or circumferential profiles may be useful in subtle changes, provided that normal fluctuations, which may have coefficients of variation as high as 12% (*4*), are considered. A control group, with a minimum of 30 healthy volunteers, should be used to set the mean and SD of the semiquantitative analysis for each brain region. In patients with cerebellar disease, other regions (e.g., the pons) should be used as the reference.

The normal adult brain shows bilaterally symmetric tracer distribution, with higher activity in temporal, parietal, and occipital (primary visual) cortices, basal ganglia, thalami, and cingulate gyrus. Activity in the white matter and interhemispheric fissures is less (Fig. 1). Eyes open or closed may increase or decrease, respectively, the visual cortex activity by 30%. Motor and sensory stimuli have similar but asymmetric effects. Auditory stimuli effects are symmetric but less impressive. In the newborn, blood flow

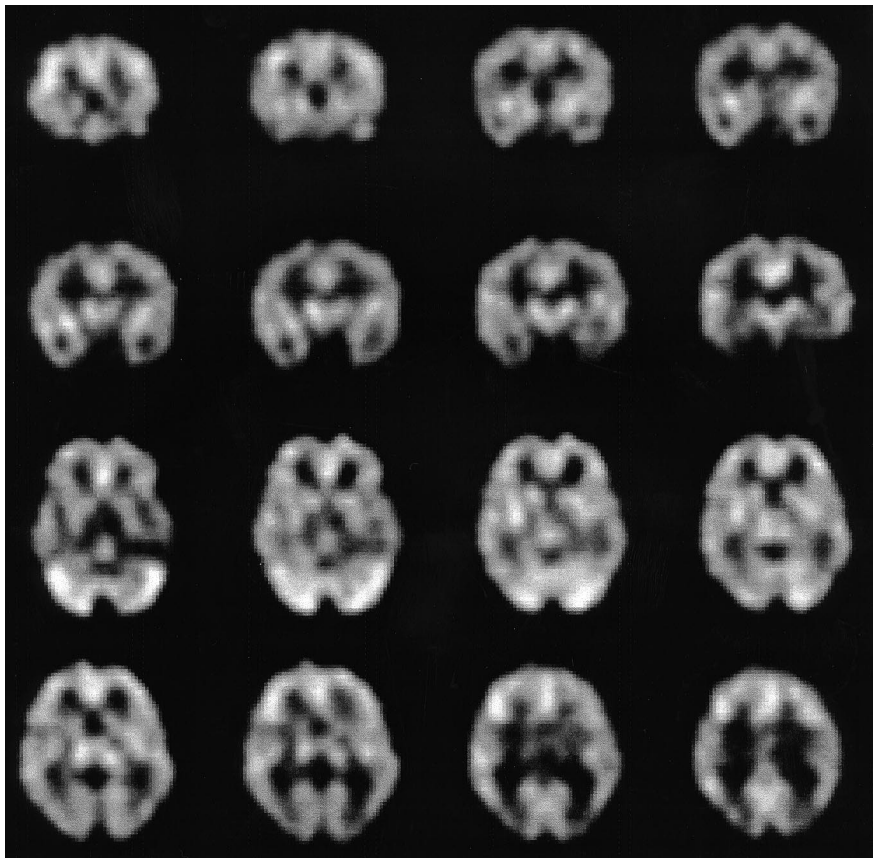

FIGURE 1. From top to bottom, two coronal and two transaxial slices with ^{99m}Tc-HMPAO using fanbeam collimator in healthy volunteer. Note symmetric tracer distribution in cerebral cortex. Areas with preferential perfusion include cingulate gyrus, primary visual cortex, basal ganglia, thalami, and cerebellar hemispheres.

to the frontal and temporoparietal regions is slightly decreased, and this pattern changes to the adult pattern by the age of 2 y. Abnormal findings include focal or regional areas of decreased or increased tracer uptake. Activation studies with brain SPECT have been performed and include visual stimulation, auditory stimulation, motor and sensory stimulation, memory tasks, pharmacologic challenges and interventions, and investigation of complex cognitive tasks (*5*,*6*).

NEUROLOGIC DISEASES

Cerebrovascular Diseases

The brain perfusion imaging agents ^{99m}Tc-HMPAO and ^{99m}Tc-ECD are sensitive indicators of regional cerebral blood flow (rCBF) changes and can detect a reduction in blood flow immediately after an acute event. No other imaging modality currently has such a capability, despite considerable progress in the evaluation of cerebral blood flow with MRI over the past several years.

Brain SPECT has been used in acute ischemia, transient ischemic attacks (TIAs), stroke, assessment of late ischemic injuries, monitoring of medical or surgical therapy, assessment of cerebral blood flow reserve, estimation of prognosis, and assessment of interventional sequelae (e.g., in arterial occlusion). Therefore, this imaging modality can be useful for rapidly diagnosing ischemia to prevent irreversible brain damage, for identifying viable tissue at risk, and for screening patients who may benefit from medical and surgical interventions.

Focal or diffuse hypoperfusion or no perfusion is the most consistent finding in cerebrovascular disease, a direct consequence of local ischemia. Diaschisis, or decreased activity in a remote area, may be present, particularly in large strokes and usually as crossed cerebellar diaschisis. Hyperperfusion, or luxury perfusion, may be found in the evolution of strokes.

TIA. Typically, if the tracer is injected at the time of the attack, a focal or diffuse area of hypoperfusion will be found. After the event, however, study findings may be normal. On the other hand, should the perfusion defect persist in the first few days after TIA, the risk of early stroke is high (*7*).

The sensitivity of brain SPECT for detection of TIAs is approximately 60% in the first 24 h and declines to approximately 40% in the first week. The sensitivity can be improved significantly with substances that measure cerebrovascular reserve, such as CO_2, acetazolamide, and dipyridamole. The acetazolamide stress test has been used for evaluation of cerebrovascular reserve in TIA, stroke, and other diseases. Intravenous injection of 1 g acetazolamide produces vasodilation and increases rCBF by 30%–50% above baseline throughout the normally perfused brain within 20–30 min, returning to normal in 2–3 h. Areas at risk or with abnormal perfusion will show little or no

response to the challenge. Proper comparison with a baseline study and interpretation of this test may provide important information on the mechanism of ischemia (*8,9*).

With ^{123}I-iodoamphetamine [IMP], the acute perfusion changes and the response to intervention can be shown with a single injection by imaging the patient before 1 h (early image) and after 4–6 h (delayed image).

Acute Stroke. Brain SPECT with ^{123}I-IMP, ^{99m}Tc-HMPAO, or ^{99m}Tc-ECD is far superior to anatomic imaging modalities such as CT or MRI in the detection of acute stroke in the first few hours that follow the event. A focal or regional area of hypoperfusion or no perfusion will be shown immediately after the acute event. This area is larger than the lesion that will be later shown on CT or MRI. With either ^{99m}Tc-HMPAO or ^{99m}Tc-ECD, the perfusion defect will be fixed, whereas with ^{123}I-IMP, redistribution with partial reperfusion may occur. Crossed cerebellar diaschisis is frequent in cortical strokes and is caused by disconnection of the cerebellar–corticopontine fibers as a consequence of ischemia or stroke.

The sensitivity and specificity of brain SPECT for stroke localization are 85.5% and 97.6%, respectively (*10*). The sensitivity may decrease as the stroke evolves because of the luxury perfusion phenomenon, which starts between 1 and 5 d, leads to hyperemia (hyperperfusion) of the lesion, and may last as long as 20 d. By 30 d, the hypoperfused area should easily be detected again. Between the hyperemic and the delayed hypoperfusion phases, study findings may be normal. Luxury perfusion may be easier to detect with ^{99m}Tc-HMPAO than with ^{99m}Tc-ECD (*11*). False-negative brain SPECT findings in stroke are caused by lacunar or small cortical infarcts.

The investigation of subtypes of strokes is important for therapy. Brain SPECT may be helpful in screening different blood flow patterns after a stroke: some patients may have persistent ischemia and others may have spontaneous reperfusion. Therapy approaches and prognoses for these two situations are different.

The evaluation of response to therapy in patients with stroke is also important (*12*). A ^{99m}Tc-labeled tracer should be injected at admission and imaging performed when the patient is stable after medical or surgical treatment. This image represents the status of rCBF at the time of admission. A second image can be obtained later, with an additional injection, for comparison. A more elegant, theoretic approach would consist of simultaneously injecting ^{123}I-IMP and a ^{99m}Tc-labeled tracer at the time of admission and imaging the patient only once, later (4–6 h), with simultaneous acquisition of ^{123}I and ^{99m}Tc images. The ^{99m}Tc image would show the status of the rCBF at the time of admission, because ^{99m}Tc is a fixed tracer. The ^{123}I-IMP image could be similar to the ^{99m}Tc image (poor or no response to therapy) or show better perfusion (good response to therapy), because ^{123}I-IMP has redistribution. However, the fact that ^{123}I-IMP is not readily available poses a significant logistic problem to the development of such a protocol.

The image obtained before therapy is important for choosing the best candidates for therapy. Acute focal absence of rCBF suggests poor prognosis and unlikely benefit from therapy, decreased but not absent blood flow possibly indicates the best candidates for therapy, and normal or near-normal blood flow indicates patients who do not need therapy (*13*).

The prognostic implication of brain SPECT in stroke has been investigated. Early (<6 h) severe hypoperfusion was highly predictive of poor neurologic outcome in 92% of patients (*14*). The combination of brain SPECT and CT seems to improve prognostic accuracy in these patients; for example, the higher the ratio of the size of the SPECT lesion to the size of the CT lesion, the better the outcome of the patient. Redistribution of ^{123}I-IMP also seems to have prognostic implications, with higher counts in the affected area of the delayed image associated with better clinical outcome. Early imaging (within a few hours) of stroke patients correlates better with outcome than does imaging performed a few days or weeks later (*15,16*). In a study performed within 6 h of event onset (*17*), no infarction occurred in hyperperfused areas and infarction could be predicted if the lesion-to-contralateral count ratio was less than 0.6. Also, the perfusion patterns correlate with short-term outcome. In a group of 458 stroke patients (*18*), 97% of those with normal or increased perfusion recovered well, 52% of those with decreased perfusion had a moderate stroke, and 62% of those without perfusion had a poor outcome. Other tracers have also been proposed for investigation of strokes. ^{123}I-iomazenil, for example, may be useful for quantification of neuronal loss after an ischemic stroke (*19,20*).

Arterial Occlusion. Patients with aneurysm of the internal carotid artery may not be suited for surgical intervention. They may, instead, undergo balloon occlusion of the artery. Brain SPECT is important to show the effect of the procedure on rCBF. A baseline study is performed for assessment of the status of brain perfusion before intervention. A second study is then performed with tracer injection at the 15th minute of the 20-min balloon test occlusion procedure. Focal or diffuse hypoperfusion is usually shown, and its location, severity, and magnitude are important parameters to consider in deciding whether to perform a permanent occlusion or use a different approach (*21,22*). Brain SPECT is also useful in the evaluation of the status of cerebral blood flow and sequelae after vascular occlusion.

Subarachnoid Hemorrhage. Morbidity and mortality in patients with subarachnoid hemorrhage are caused by vasospasm. The consequences of vasospasm on rCBF are clearly shown on brain SPECT as absent perfusion; various degrees of focal or regional hypoperfusion, from mild to severe; and even hyperemia (*23*). These findings correlate well with the severity and magnitude of neurologic deficits in the evolution of the condition. Brain SPECT is also an important tool for decision making on the use of interventional therapy to reverse the hypoperfusion shown in the study. The post-

interventional study is essential for evaluating the response to therapy.

These images are also important in the evaluation of comatose patients. Preserved rCBF on brain SPECT despite significant vasospasm will reassure the clinician that the therapy has been successful and the prognosis is good; on the other hand, severe diffuse hypoperfusion has a poorer prognosis and points to a more aggressive therapeutic approach.

Dementias

Alzheimer's Disease. Alzheimer's disease (AD), the most important and common degenerative brain disease, has a prevalence of 0.3% in the 60- to 69-y-old population that increases dramatically to 10.8% in the 80- to 89-y-old group. Mental degeneration is insidious, and progressive memory loss is the most important symptom. Plaques, deposition of amyloid, and neurofibrillary tangles are found in postmortem specimens.

There is now agreement that AD is amenable to diagnosis and that the diagnosis should no longer be one of exclusion (*24*). Cerebral atrophy, a normal aging process not associated with dementia, cannot account for the perfusion abnormalities seen on brain SPECT scans of demented patients.

Brain SPECT of AD patients typically shows bilateral hypoperfusion of the parietal and posterior temporal lobes. The perfusion defects are frequently symmetric but not necessarily of the same magnitude and severity. Motor and sensory cortices are usually spared (Fig. 2). Hypoperfusion of the posterior association cortices is a finding that some authors consider specific for AD and positive evidence for its diagnosis (*25*), although other conditions may display a similar pattern. Temporoparietal hypoperfusion is more severe in early-onset AD than in late-onset AD (*26*).

In the early stages of the disease, MRI and CT images show normal findings. Nevertheless, MRI or CT should routinely be performed in patients suspected of having AD, because normal structural findings and abnormal brain SPECT findings, in the appropriate clinical setting, are additive and indicate an increased probability of the disease. As the disease progresses from mild to severe, the frontal cortex most affects cognitive decline; this fact supports the finding that deficit in functional imaging spreads from the posterior to the anterior temporal and frontal lobes with progression of the disease (*27–29*). The sensitivity and specificity of brain SPECT for the diagnosis of AD are 86% and 96%, respectively, with a diagnostic confidence of 98% (*30*).

Classification of perfusion defects into several perfusion patterns (*31*) is useful for interpreting studies. The perfusion patterns A–G and their respective probabilities of AD are as follows: A: normal, 19%; B: bilateral temporoparietal hypoperfusion, 82%; C: bilateral temporoparietal hypoperfusion with other defects, 77%; D: unilateral temporoparietal hypoperfusion, 57%; E: frontal hypoperfusion, 43%; F:

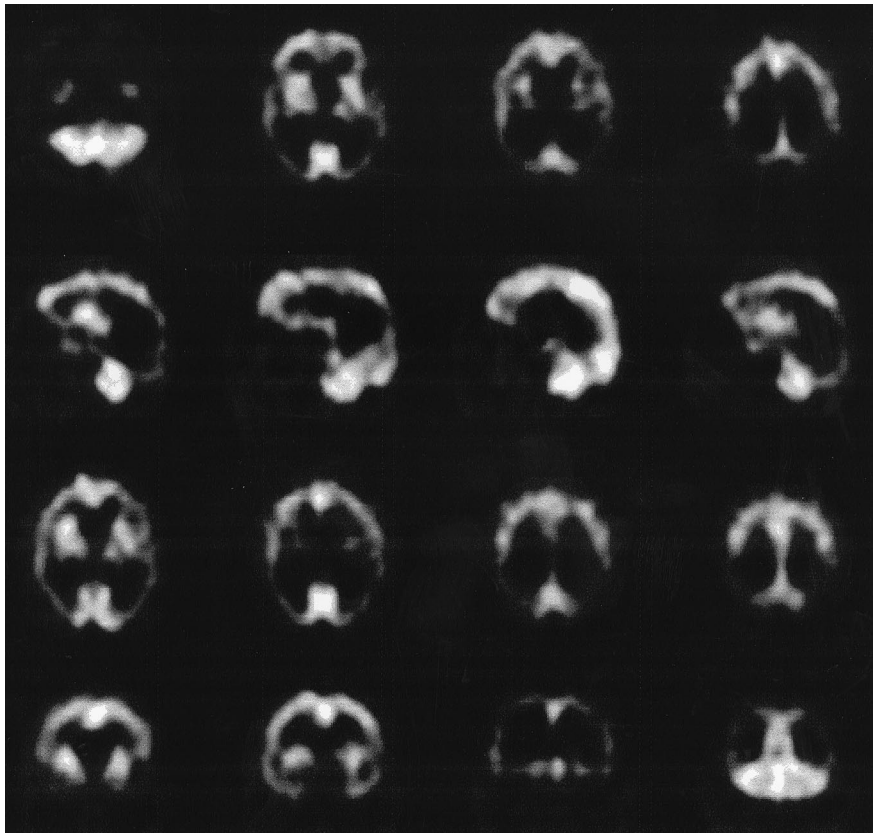

FIGURE 2. A 58-y-old right-handed man had 2-y history of progressive memory loss, which became worse over last 7 mo. His father and three cousins had dementia. Transaxial, sagittal, and coronal slices show marked bilateral, symmetric temporoparieto-occipital hypoperfusion, extending to frontal lobes. Basal ganglia, primary visual cortex, and cerebellum are spared.

other large defects, 18%; and G: multiple small defects, 0%. According to these findings, in the appropriate clinical setting, normal brain SPECT findings do not exclude AD; on the other hand, in the group studied, no AD was found in patients with images that are typical of vascular dementia (VD).

Labeling of the amyloid and plaques for a more specific diagnosis of AD has been attempted. With monoclonal antibody for Aβ protein 1-28 labeled with ^{99m}Tc (*32*), uptake of the tracer in AD patients could not be shown with brain SPECT. More recently, rhenium complexes, analogs of the potential imaging agent ^{99m}Tc, were shown to bind to Aβ amyloid fibrils in vitro and to stain amyloid plaques and vascular amyloid in postmortem brain sections of AD patients (*33*).

AD patients treated with lecithin and tetrahydroaminoacridine showed no significant clinical and perfusion changes from baseline studies. However, temporal, prefrontal, and occipital perfusion improved in patients treated with high-dose (75 mg) tetrahydroaminoacridine (*34*).

With ^{123}I-iomazenil, a smaller volume of distribution throughout the cortex (except for the occipital lobe) and larger areas of decreased uptake were observed in comparison with ^{99m}Tc-HMPAO (*35*). In comparison with ^{99m}Tc-HMPAO images, ^{123}I-iomazenil images 3 h after injection showed clearer and more extensive regions of decreased activity in eight patients with probable AD (*36*).

VDs (Multiinfarct Dementias). VDs are the second cause of dementia in the elderly. In VD, impairment of intellectual function is caused by multiple infarcts that may occur unilaterally or bilaterally, are usually asymmetric, and may involve any part of the cerebral cortex. The history of one or more events can be disclosed, and the symptoms will have the characteristic temporal profile of such an event (*1*). The cause of multiple small emboli is atherosclerotic disease, usually in the carotid artery or in the middle cerebral artery distribution. VD frequently coexists with AD.

Brain SPECT in these patients shows multiple focal areas of hypoperfusion randomly distributed. Motor and sensory cortices may also be involved (Fig. 3). Again, correlation with anatomic images such as those from CT or MRI is important: cortical or subcortical infarcts are usually found on CT, and this finding increases the likelihood of the disease. Subcortical infarcts alone, without cortical lesions on CT, can explain nearby cortical perfusion defects by disconnection between cortical and subcortical neurons.

The Binswanger type of dementia, a rare variant of VD, is a gradually progressive syndrome caused by diffuse or patchy ischemic events to the deep white matter. The magnitude of cortical hypoperfusion correlated significantly with the severity of the disease (*37*).

Frontal Lobe Dementia. Lobar atrophy, or Pick's disease, is the most important type of frontal lobe dementia (FD), characterized by a special form of cerebral degeneration

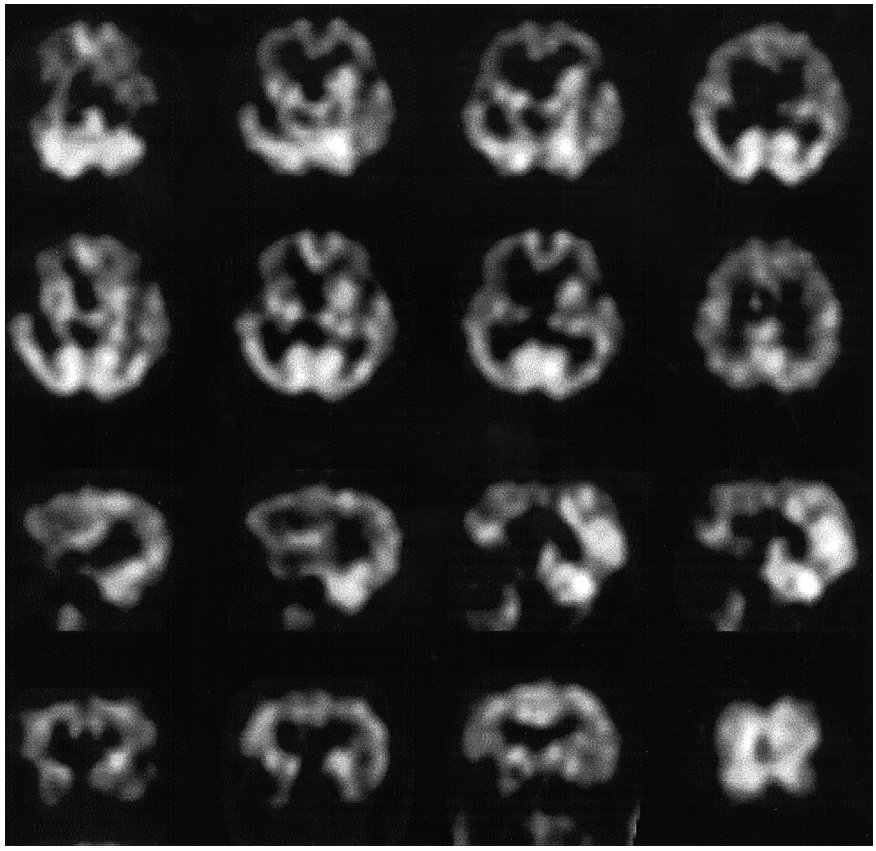

FIGURE 3. A 62-y-old right-handed, hypertensive man had stroke 2 y ago and now has severe memory impairment, dysarthria, and urinary incontinence. Radionuclide cisternography showed normal findings. Transaxial, sagittal, and coronal slices show multiple scattered focal areas of hypoperfusion involving entire cerebral cortex, a pattern frequently found in vascular dementia. Head CT scan showed white matter infarcts.

with atrophy circumscribed to frontal or temporal lobes involving both gray and white matter. Clinical diagnosis is difficult, and structural and functional imaging play an important role in differential diagnosis. Symptoms usually include gradual onset of confusion with respect to place and time, anomia, slowness of comprehension, inability to cope with unusual problems, loss of tact, and changes in personality and behavior (*1*).

Brain SPECT usually shows symmetric hypoperfusion of the frontal lobes extending to the cingulate gyrus (*38*). In the early phase of the disease, CT or MRI may show normal findings or only mild frontal cerebral atrophy, disproportionate to the degree of hypoperfusion (Fig. 4).

For interpretation of brain SPECT findings in the three types of dementia described above, a correlation between hypoperfusion pattern and type of dementia has been proposed (*39*) and has been useful. In cases of posterior bilateral hypoperfusion, AD is more likely than VD or FD; in cases of bilateral frontal hypoperfusion, FD is more likely than AD or VD; in cases of diffuse heterogeneous hypoperfusion, VD is more likely than AD or FD; and cases of unilateral anterior hypoperfusion with or without unilateral posterior and diffuse hypoperfusion do not contribute to the differential diagnosis of dementia.

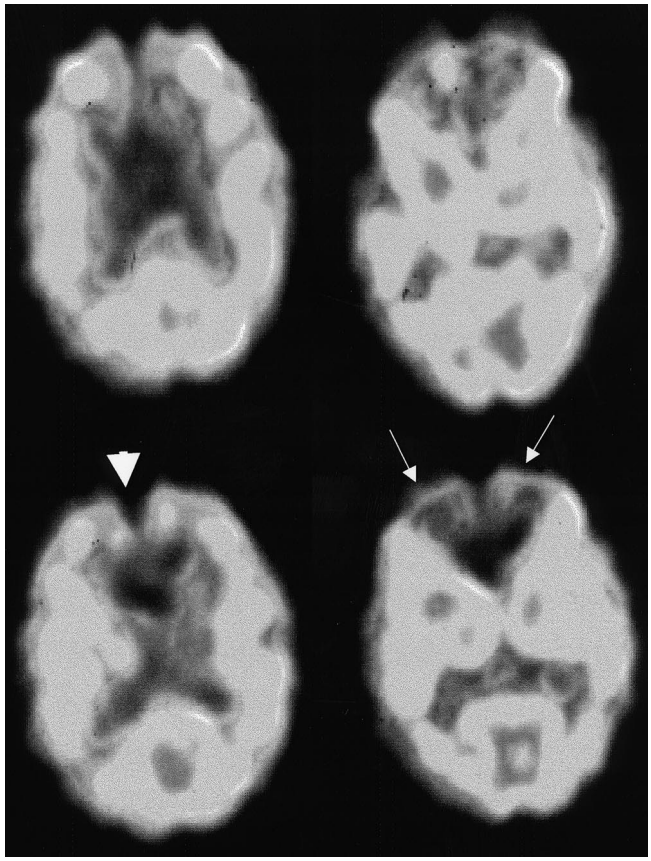

FIGURE 4. Transaxial slices of 73-y-old man with FD and 2-y history of progressive short-term memory loss show marked hypoperfusion of anterior cingulate gyrus (arrowhead) and mesial frontal lobes (arrows). MRI showed only mild frontal lobe atrophy, which could not explain brain SPECT findings.

Other Dementias. In frontotemporal dementia, brain SPECT shows hypoperfusion of the orbitofrontal area and the temporal lobe in 25% of patients. When the right temporal lobe is involved, behavioral disturbances are found; aphasia is more frequent when the left temporal lobe is involved.

Creutzfeldt-Jakob encephalopathy leads to a rapidly deteriorating dementia, possibly associated with a prion agent. Brain SPECT images show various degrees of focal or diffuse hypoperfusion, which correlate with the severity of the disease.

In AIDS dementia, brain SPECT shows randomly distributed focal or regional areas of hypoperfusion. These perfusion abnormalities may be present before the symptoms of dementia and correlate better with cognitive improvement after therapy than do structural images (*40*). Brain SPECT should be used in early diagnosis and follow-up of AIDS patients, especially when CT and MRI still show normal findings (*41*).

Parkinson's disease is a degenerative condition characterized by tremor, hypokinesis, and rigidity. Approximately 10% of Parkinson's disease patients develop dementia, with parietal, temporal, and occipital lobe hypoperfusion seen on brain SPECT studies. Demented Parkinson's disease patients and AD patients share a common pattern of marked posterior hypoperfusion. However, the defects are more prominent and extensive in AD (*42*).

Recent studies with neuroreceptor imaging have found that ^{123}I-β-2β-carbomethoxy-3β-(4-iodophenyl)tropane (CIT) and ^{123}I-fluoropropyl-CIT may be useful markers of the severity of Parkinson's disease: as the severity increases, the uptake in the striatum decreases (*43*,*44*).

Huntington's disease (HD), an autosomal dominant, degenerative neurologic movement disorder, is characterized by chorea, dementia, and psychiatric symptoms. Brain SPECT of symptomatic patients shows decreased or absent tracer uptake in the caudate nucleus or basal ganglia (*45*). A recent study has shown that basal ganglia damage in symptomatic HD patients may not be permanent and tracer uptake may return to normal after therapy with olanzapine (*46*).

Hypothyroid dementia has been described in patients with hypothyroidism. Brain SPECT of these patients shows global cortical hypoperfusion that normalizes with effective therapy (*47*).

Epilepsy

Epilepsy is one of the most prevalent neurologic disorders and affects approximately 1% of the general population. Most complex seizures arise from the temporal lobes, and the condition of 10%–20% of these patients is refractory to medication. Many can be rendered seizure free with surgery. Only 40%–50% of extratemporal lobe seizures can be treated by surgery.

Seizures can be classified, in a simplified manner, as either partial (focal) or generalized. Partial seizures originate in a given area of the brain and can be further divided into simple (with no impairment of consciousness) and complex (with impairment of consciousness). Both simple and complex partial seizures may be preceded by sensations such as buzzing, tingling, smells, and gastrointestinal sensations.

Temporal lobe seizures are usually accompanied by head deviation, aphasia, swallowing, tooth grinding, a chewing motion, and staring spells. Frontal lobe seizures are rapid and may include sexual automatisms and vocalizations. Occipital lobe seizures include symptoms such as visual hallucinations, blinking, and eyelid fluttering. Parietal lobe seizures do not seem to have a characteristic set of symptoms.

The role of brain SPECT in epilepsy is not the diagnosis of the disease but the localization of the seizure focus for surgical therapy, especially in temporal lobe epilepsy. Ideally, the patient should be imaged twice: in the interictal or seizure-free condition and in the ictal condition, with the tracer injected at the very beginning of a seizure episode. Alternatively, the ictal study can be replaced by a postictal study, with the tracer injected after a seizure episode.

In the interictal or seizure-free study, brain SPECT shows focal or diffuse hypoperfusion that is usually of the anteromedial temporal lobe and may extend to the ipsilateral frontal lobe. However, in approximately 50% of the patients the study may show normal findings, and in 10% the study may show hyperperfusion, which may change to hypoperfusion in subsequent studies. Whenever possible, tracer injection should be performed under electroencephalography (EEG) monitoring to ensure that a subtle seizure does not go undetected.

The ictal study consists of a tracer injection at the very beginning of a seizure episode. The patient is placed in a special room, with continuous video and EEG monitoring, and the medication is tapered off or discontinued to increase the likelihood of a seizure episode. The injection time will be best defined by EEG and careful observation criteria, in close collaboration with the neurology team, before the seizure becomes generalized. With injections performed during generalized seizures, image interpretation and definition of the seizure focus may be impossible, because the abnormal perfusion may extend to other areas. Typically, effective tracer injections are performed within 5–10 s of seizure onset. Such timing is possible only with a tracer already labeled and maintained at the patient's bedside at all times.

The images show hyperperfusion of the temporal lobe, usually extending to the ipsilateral basal ganglia and thalamus and possibly also extending to the ipsilateral motor cortex and contralateral cerebellar cortex. Presently, brain SPECT is the only imaging modality able to capture the rCBF changes associated with seizures.

The postictal study is defined as a tracer injection between 1 and 10 min after a seizure. The images usually show hypoperfusion that may extend to the ipsilateral hemisphere and contralateral temporal lobe. Hyperperfusion, if present, will be seen in the anteromedial temporal lobe for up to 5 min after the seizure ends.

The sensitivity of brain SPECT, in comparison with EEG and surgery, in temporal lobe epilepsy is 44% and 43%, respectively, for interictal studies; 97% and 100%, respectively, for ictal studies; and 75% and 77%, respectively, for postictal studies (*48*). The combination of hypoperfusion in the interictal study followed by hyperperfusion in the ictal study in the same area has absolute specificity, because no

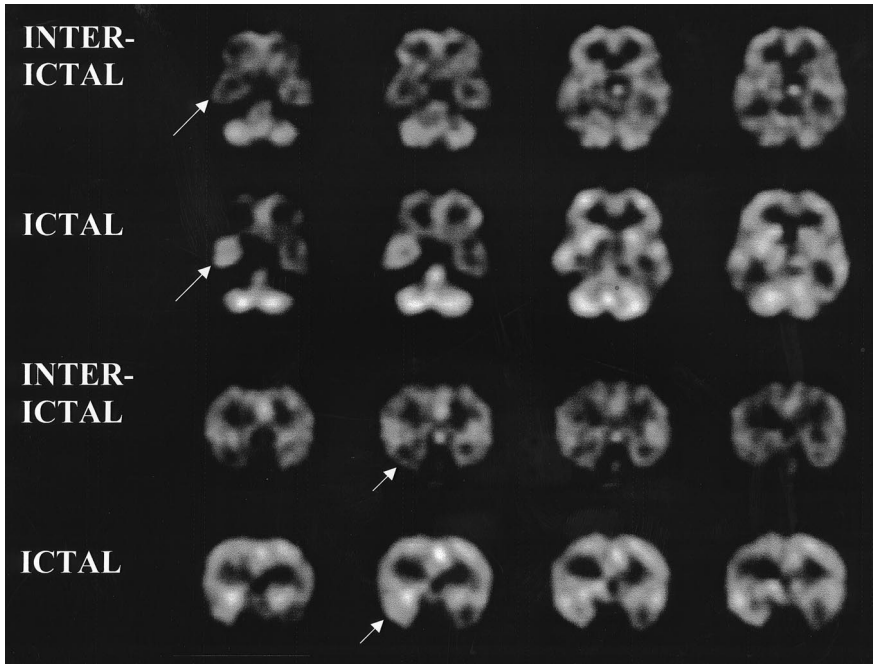

FIGURE 5. A 21-y-old left-handed man had history of tonic–clonic seizures since age 8. Head CT findings were normal. MRI showed T2-weighted hyperintense signal and slightly decreased size of right hippocampus. EEG showed acute waves in right frontal and temporal lobes. Interictal and ictal transaxial and coronal slices show hypoperfusion and hyperperfusion, respectively, of right temporal lobe (arrows).

other neurologic condition can cause this phenomenon (Fig. 5). However, correlation with structural imaging, especially MRI, is important for a better understanding of the pathologic process and for excluding or confirming other causes of seizures such as a primary brain tumor.

Comparisons of the ^{99m}Tc-labeled agents ECD and HMPAO have found them equivalent for localization of the seizure focus in critical studies, with a significant difference in utilization time after labeling (*49*,*50*).

Hypoperfusion of the ipsilateral thalamus in 26% of interictal studies (*51*) and crossed cerebellar hyperperfusion in 75% of ictal studies (*52*) are interesting additional findings in temporal lobe epilepsy and should be used to facilitate image interpretation. With ^{123}I-IMP for interictal studies, hypoperfusion in the early image may have any of three aspects in the delayed image: be the same, become normal, or show hyperperfusion (*53*). Surgical outcome was better when the findings became normal.

A most peculiar finding has been described (*54*) in what was called a preictal brain SPECT study: a significant increase in rCBF in the epileptic temporal lobe was observed in two patients, without EEG changes, 11 and 12 min before seizure. According to the authors, a change in neuronal activity precipitated the transition from the interictal to the ictal state.

Landau-Kleffner syndrome is a rare disturbance of childhood characterized by acquired aphasia and epilepsy, sometimes associated with behavioral disturbances and psychotic manifestations. In all the members of a small group of children with this condition, hypoperfusion of the left temporal lobe, interictally, was found (*55*), and this finding returned to normal after corticosteroid therapy.

Conflicting results on the role of neuroreceptor imaging for localization of the seizure focus have been described. ^{123}I-iomazenil has been found to be less precise than ^{18}F-FDG and ^{11}C-flumazenil for seizure focus localization (*56*); in contrast, another study (*57*) claimed that the same tracer is better than FDG and perfusion agents for seizure focus localization.

The Wada test has been used for speech and memory lateralization before surgery. The classical Wada test consists of slowly injecting approximately 2 mL amobarbital sodium (Amytal; Eli Lilly and Co., Indianapolis, IN) in the internal carotid artery to anesthetize the ipsilateral cerebral hemisphere. This test has two major problems. The first is that in 89% of the population, perfusion of the mesial temporal lobe (important for memory lateralization) is supplied by the posterior cerebral artery, not the internal carotid artery. The second is that high-volume, high-pressure radiographic contrast is used to map the distribution of amobarbital sodium, and contrast and amobarbital sodium distributions are assumed to be the same despite the different flow regimens. A more physiologic approach to this test that has been proposed (*58*) uses a mixture of amobarbital sodium and ^{99m}Tc-HMPAO for intracarotid injection and subsequent imaging. In a group of 22 patients, brain SPECT found amobarbital sodium in only 7 posterior cerebral artery territories; conventional angiography found it in 15 (8 in error), and digital angiography, in 11 (4 in error).

In extratemporal lobe epilepsy, brain SPECT may be helpful despite its low sensitivity in the interictal state. The ictal study has sensitivity ranging from 85% to 91%. In frontal lobe seizures, the difficulty in detecting the epileptogenic focus is caused by the short duration of the seizure and the magnitude of hyperperfusion, frequently less than that of temporal lobe epilepsy.

Head Trauma

Brain SPECT is more sensitive than CT or MRI for revealing lesions caused by head injury, especially in the acute (<24 h) phase. In the subacute (2 d to <6 mo) and chronic (>6 mo) phases, the performance of brain SPECT is less well documented.

Regardless of the type of injury (subdural hematoma, cerebral contusion, or subarachnoid hemorrhage), the images show focal, multifocal, or regional areas of hypoperfusion that correlate better with the clinical status of the patient than do structural images. In addition, these images are capable of revealing both the acute and the chronic effects of head trauma (*59*,*60*).

Focal cerebral hyperemia after head injury was associated with a lower mortality rate and better outcome than was lack of hyperemia after head injury (*61*). In patients with mild traumatic brain injury and normal CT findings, brain SPECT was useful and sensitive enough to show perfusion changes, even when the patient did not lose consciousness; these changes correlated better with neurologic findings in the absence of anatomic abnormalities. Also, normal brain SPECT findings were found to be a reliable tool in the exclusion of the clinical sequelae of mild head injury (*62*,*63*).

Cerebral Neoplasms

Brain SPECT perfusion agents such as ^{123}I-IMP, ^{99m}Tc-HMPAO, and ^{99m}Tc-ECD have not been useful for imaging primary brain tumors. Primary tumors usually display decreased uptake of ^{123}I-IMP and an increased concentration of ^{99m}Tc-HMPAO proportional to the degree of malignancy. However, conflicting results have been obtained with perfusion tracers: in one study (*64*), 77% of patients with brain tumor showed an increased concentration of ^{99m}Tc-HMPAO and normal uptake of ^{99m}Tc-ECD. Metastatic lesions show decreased uptake of brain perfusion tracers.

In contrast, brain SPECT with ^{201}Tl-thallous chloride and ^{99m}Tc-sestamibi have been useful in distinguishing radiation effects from residual or recurrent tumor, a distinction not possible with CT or MRI. ^{201}Tl uptake in high-grade gliomas has been found to be increased in comparison with that in low-grade gliomas. Using doses of 148 MBq (4 mCi) ^{201}Tl and an uptake index (average counts per pixel in the tumor divided by the average counts per pixel in the homologous region) in the immediate (5-min) image, an abil-

ity to distinguish low-grade lesions (1.21 ± 0.34) from high-grade tumors (2.28 ± 0.49) has been found (*65*).

^{201}Tl in combination with ^{99m}Tc-HMPAO images has also been used to distinguish tumor from radiation necrosis and to assess survival in patients with glioblastoma multiforme. Patients with a ^{201}Tl ratio less than 2 had an 83.3% 1-y survival rate; for a ^{201}Tl ratio of 2–3.5, the 1-y survival rate was 29.2%; and for a ratio greater than 3.5, the 1-y survival rate was only 6.7% (*66*).

In routine evaluation of patients suspected of having residual or recurrent tumor after therapy, early ^{201}Tl imaging (10–30 min after injection), followed by delayed (1- to 2-h) imaging with or without quantification and with simultaneous acquisition of ^{99m}Tc-HMPAO or ^{99m}Tc-ECD images, is helpful. Typically, tumors (especially of high grade) have either a constant uptake or an increase in ^{201}Tl uptake over time, in contrast to nontumoral lesions that display poor or no uptake with washout over time. This approach has been useful for distinguishing cerebral lymphoma from infection in AIDS patients (*67–69*).

^{123}I-α-methyl tyrosine has also been used for diagnosis of recurrent glioma and seems to be a promising new tracer. Patients with recurrent tumor had a significantly higher lesion-to-background ratio than did patients without recurrence (*70*).

Multidrug resistance of tumors has been investigated with ^{99m}Tc-sestamibi, with encouraging results for evaluation of the presence of MDR-1 gene expression in gliomas (*71*).

Movement Disorders

Parkinson's Disease. Akinesia, bradykinesia, tremor, rigidity, and disturbance of postural reflexes are characteristic of Parkinson's disease. The symptoms are caused by loss of the dopamine-containing pigmented neurons of the substantia nigra and locus caeruleus, leading to reduced dopamine in the striatum. Parkinson's disease may also be defined as a dopamine deficiency state in which the excitatory cholinergic activity in the striatum can no longer be counterbalanced. However, this mechanism does not explain all symptoms of Parkinson's disease.

Using brain perfusion agents, finding a specific perfusion pattern in the cerebral cortex and basal ganglia in Parkinson's disease has been difficult. An absence of cortical perfusion defects, various degrees of cortical hypoperfusion and cerebellar hypoperfusion, and normal findings all have been described. Striatal perfusion is usually normal in Parkinson's disease.

Neuroreceptor imaging in Parkinson's disease has shown potential for further investigation. With ^{123}I-iodolisuride, a dopamine D_2 agent, and semiquantitative analysis of basal ganglia–to–cerebellum ratios at 120 min, no difference was found in D_2 receptors between healthy volunteers and Parkinson's disease patients (*72*). With ^{123}I-epidepride, another D_2 agent, similar results were obtained: tracer uptake measured 3 h after intravenous injection of 185 MBq (5 mCi) was normal in the basal ganglia of Parkinson's disease patients but was decreased in patients with multiple-system atrophy, progressive supranuclear palsy, and HD. Therefore, these agents have the potential for distinguishing Parkinson's disease from other movement disorders (*73*).

However, with ^{123}I-β-CIT, a reduction in striatal dopamine transporter binding, with two different components, has been shown. Decreased striatal binding contralateral to the clinically affected side is more prominent, and reduction is greater in the putamen than in the caudate nucleus (*74*). That this tracer may be sensitive enough to detect subclinical involvement of dopamine receptors in Parkinson's disease is conceivable (*75*).

HD. HD is characterized by rapid, jerky, involuntary movements of the face, arms, and legs. Dementia and psychiatric symptoms may also occur. Histologically, basal ganglia neuronal dysfunction with premature neuronal cell death and gliosis is present, especially in the heads of both caudate nuclei. Less extensive changes may also occur in the putamen.

Brain SPECT studies with perfusion agents, similar to PET studies, show decreased or absent tracer uptake in the caudate or basal ganglia of symptomatic patients. Perfusion defects in the basal ganglia are usually bilateral but are not necessarily symmetric (*76*). The sensitivity of brain SPECT with perfusion agents in these patients has been high, even in those with normal CT or MRI findings (*77*). Decreased caudate nuclei uptake has also been reported for several individuals at risk of HD who have undergone brain SPECT with perfusion tracers (*78*).

An unusual finding of hyperperfusion in the caudate nuclei in five of seven patients with HD, all with various degrees of cortical hypoperfusion, has been reported (*45*). This finding is somewhat similar to the recent report (*46*) that basal ganglia uptake in an HD patient returned to normal after therapy with olanzapine.

Neuroreceptor imaging with ^{123}I-iodobenzamide (IBZM) has shown that striatal dopamine D_2 receptor binding is reduced in HD (*78*).

PSYCHIATRIC DISORDERS

Brain SPECT in psychiatric disorders is still investigational. Despite considerable research interest in this area, specific perfusion patterns of the various diseases have not been definitely recognized. However, perfusional and receptor imaging findings may be used as an additional diagnostic tool to guide clinicians searching for a definite diagnosis.

Obsessive–Compulsive Disorder

Obsessive–compulsive disorder is rare (<5% of psychiatric patients), with a usually gradual onset in adolescence or early adult life and a slightly greater prevalence in females. Family history shows a high incidence in other members. Obsessions are imperative, distressing thoughts that persist despite the desire to resist them and may take various forms: intellectual (phrases, rhymes, ideas, images), impulsive (killing, stabbing, performing abject acts), or

inhibiting. Compulsions are acts that result from obsessions, such as checking rituals, repeated hand washing, and wiping objects (*1*). The existence of various types of obsessive–compulsive disorder with different clinical manifestations is now conceivable and may explain the conflicting imaging findings.

Brain SPECT findings in patients with obsessive–compulsive disorder have been investigated by several authors. Hyperperfusion of the anterior portion of the cingulate gyrus; bilateral orbitofrontal regions; and, in some patients, basal ganglia before therapy has been described (*79–81*). These changes returned to normal after treatment with fluoxetine (*80,81*). In contrast, hypoperfusion of the frontal lobes, right caudate nucleus, and right thalamus has also been found (*82*). Patients with poor insight on their condition or with schizo-obsessive behavior probably will display hypoperfusion of the frontal lobes, whereas patients with adequate insight tend to display hyperperfusion of frontal lobes and cingulate gyrus (Fig. 6).

Gilles de la Tourette's Syndrome

Gilles de la Tourette's syndrome is the rarest and most severe tic syndrome. Multiple tics are present, associated with snorting, sniffing, loud and irritating vocalization, aggressive impulses, jumping, squatting, and explosive utterance of obscenities. This disorder is closely related to obsessive–compulsive disorder, and often the two conditions coexist, probably as parts of the same continuum (*1*).

Hyperperfusion of the frontal lobes, cingulate gyrus, basal ganglia, and thalami may be found all together in the same patient or in different combinations. With ^{123}I-IBZM, patients free of medication showed decreased striatal binding of this agent (*83*).

Schizophrenia

Schizophrenia comprises a group of closely related disorders characterized by a particular type of disordered affect, behavior, and thinking (*1*). Symptoms are usually categorized as positive (auditory, tactile, visual, or olfactory hallucinations; persecutory, grandiose, or religious delusions; aggressiveness; bizarre appearance; abnormal sexual behavior; disordered thoughts) or negative (poor eye contact, speech, or hygiene; inappropriate affect; blocking; apathy; social inattentiveness).

Brain SPECT most frequently shows hypofrontality, especially during a specific task; perfusional changes in the basal ganglia, possibly related to the use of neuroleptic drugs; and temporal lobe hypoperfusion, usually on the left side and frequently associated with ipsilateral frontal lobe hypoperfusion (*84*). However, patients who are not receiv-

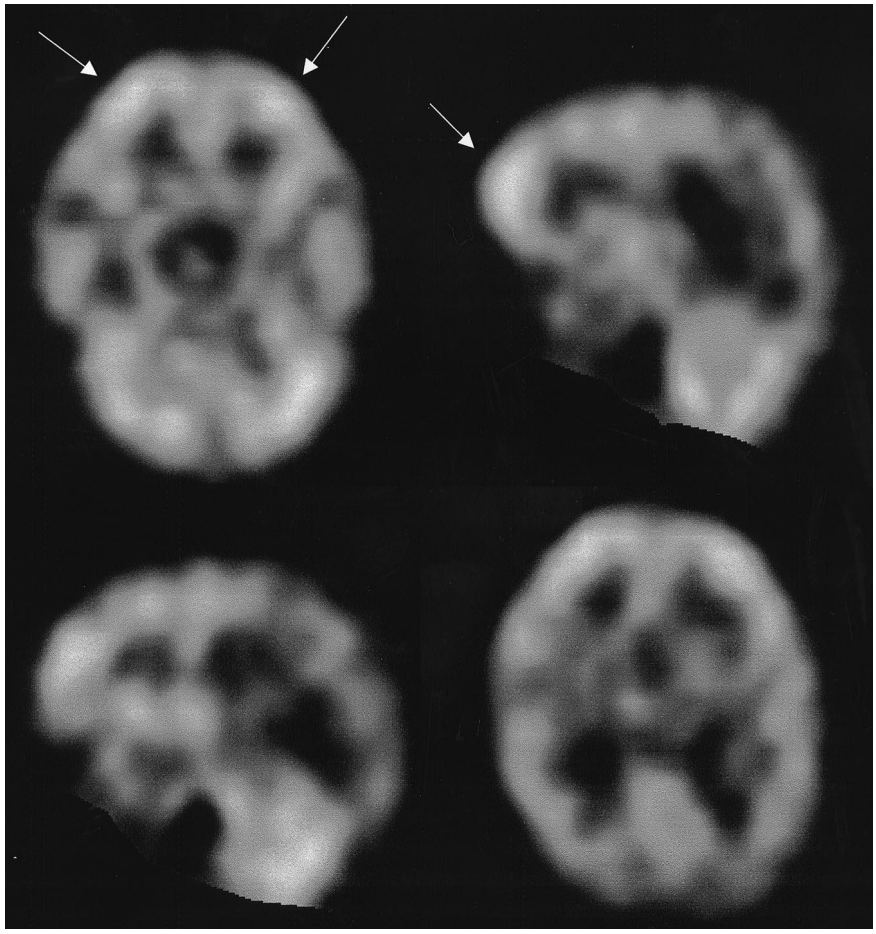

FIGURE 6. A 13-y-old boy complained of severe anxiety and compulsions (washing hands) over last 4 y. His insight was intact. Transaxial and sagittal slices show hyperperfusion of orbitofrontal area, bilaterally (arrows).

ing medication and have either positive or negative symptoms may show conflicting findings (hypo- and hyperperfusion) with the perfusion tracers (*85*). Injection of perfusion agents at the time of visual or auditory hallucinations shows hyperperfusion of the primary visual or auditory cortex, respectively (*86*).

Several investigators have used ^{123}I-IBZM in schizophrenic patients, sometimes with contradictory results. Striatal D_2 or D_3 receptor blockade by neuroleptic drugs was found to simulate negative symptoms (*87*). In contrast, some investigators (*88*) have proposed that worsening of negative symptoms may be related to increased availability of D_2 receptors, perhaps because of decreased endogenous dopamine. Studies performed before and after challenge with intravenous amphetamine showed that D_2 receptor density was normal in the baseline study but decreased after an amphetamine challenge, and this finding was associated with positive symptoms (*89*). Semiquantitative analysis of these images may help predict treatment outcome: the ratio of the basal ganglia to the frontal cortex decreased with therapy in good responders and increased in poor responders (*90*).

Unipolar Depression

Loss of interest or pleasure is the key symptom of unipolar depression. Other symptoms include feelings of hopelessness, worthlessness, and emotional pain; reduced energy and motivation; trouble sleeping; decreased appetite; and weight loss (*91*).

Brain SPECT with perfusion agents in patients free of medication has shown hypoperfusion of the following areas: the prefrontal area and temporal lobes, cingulate gyrus, and left caudate nucleus (*92–94*); the prefrontal, limbic, and paralimbic areas in both unipolar and bipolar depression (*95*); and the lateral frontal area in acute depression in the elderly (*96*). Hypofrontality was shown to be associated with severe negative symptoms (*97*).

Panic Disorder

Patients with panic disorder may display shortness of breath, dizziness, tachycardia, sweating, nausea or abdominal distress, chest pain or discomfort, and fear of dying. Caffeine, alcohol, and nicotine are some of the drugs that may trigger a panic attack.

Brain SPECT has shown hypoperfusion in the frontal lobes of patients with panic disorder with yohimbine challenge; however, the same drug did not cause any changes in healthy volunteers (*92*). With ^{123}I-iomazenil, a significant decrease in activity occurred 2 h after injection in the lateral inferior temporal lobes, left medial inferior temporal lobe, and inferior frontal lobes (*98*).

Psychoactive Substance Abuse and Dependence

Psychoactive substance abuse and dependence are disorders defined by patterns of maladaptive behavior related to the procurement and ingestion of substances of abuse (marijuana, hallucinogens, inhalants, cocaine, crack, heroin, stimulants, alcohol, and others) (*91*).

Brain SPECT, similar to PET, has shown disseminated cerebral blood flow defects in abusers of cocaine, crack, and alcohol (*92,99*). Disappearance or improvement of the lesions after a period of abstinence has been described, suggesting that arterial spasms may cause the defects (*100,101*). Patients with a history of inhalation of industrial solvents, such as glue, paint, and gasoline, have similar perfusion abnormalities.

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