

Clinical Problems in Psychiatric Treatment of the Medically Ill

Effective psychiatric intervention with the medically ill requires adapting the techniques of psychiatric diagnosis, psychotherapy, and psychopharmacology to each specific medical illness. This section, edited by **Barry S. Fogel**, M.D., and **Alan Stoudemire**, M.D., will address diagnostic technologies, special topics in clinical psychopharmacology, and special applications of psychotherapy appropriate to patients with concurrent medical and psychiatric disorders. Articles will review and examine the literature on these topics to derive guidelines for clinical practice.

The Role of SPECT Brain Imaging in Assessing Psychopathology in the Medically Ill

Ralph A. O'Connell, M.D., Steven N. Sireci, Jr., M.D.,
Melissa E. Fastov, Ph.D., Jeanette E. Cueva, M.D., Dana Luck, Ph.D.,
Mark R. Nathanson, M.D., and Ronald L. Van Heertum, M.D.

Abstract: *Cerebral single photon emission computed tomography (SPECT), a method of functional brain imaging, measures cerebral blood flow and metabolism. This paper describes the imaging procedure and several cases where cerebral SPECT was of use in the differential diagnosis of medically ill patients who also presented with psychopathology. SPECT patterns in cerebrovascular disease, dementia, focal epilepsy, and AIDS are at present the best described and seem to be the most specific. Often changes in regional cerebral blood flow are seen before structural changes become apparent on CT or MRI. Cerebral SPECT can add valuable diagnostic information in assessing psychopathology in the medically ill and can often lead to changes in treatment.*

Introduction

Karl Bonhoeffer, in an influential paper in 1909 on "exogenous psychoses," focused attention on "the psychotic disturbances which follow such physical conditions as acute infectious diseases, infectious chorea, acute exhaustion as in cachexia or anemia, auto intoxication as in dropsy, uraemia, jaundice, diabetes, and Basedow's disease" [1]. Although Bonhoeffer's differential diagnosis may be a little

out of date, the importance of recognizing any "organic" etiology of psychopathology is still universally agreed upon, because of the treatment and prognostic implications that follow. At the turn of the century, the terms "organic" and "functional" were used to distinguish neuropsychiatric disorders for which there was a known organic or metabolic cause from those in which only "functional" changes were observed. With recent advances in the neurosciences and molecular biology, this organic/functional dichotomy has become less meaningful, especially in the major psychiatric disorders. The principle, however, of ruling out an infectious process, a space-occupying lesion, or seizure focus as the cause of a psychosis or dementia is still valid. Because the brain is virtually impossible to access directly, psychiatrists always welcome advances in technology that might be of help in differential diagnosis.

In the past few years, new brain imaging techniques have become available and are of great interest to psychiatrists [2]. Computed tomography (CT) and magnetic resonance imaging (MRI) provide excellent structural information about the brain, far superior to skull x-rays, and are extremely valuable in diagnostic evaluation, especially if there is a probability that the presenting psychopathology may be due to a process with associated structural changes. The resolution and quality of CT and MRI head scans have rapidly

From the Departments of Psychiatry and Nuclear Medicine, St. Vincent's Hospital and Medical Center and New York Medical College.

Address requests for reprints to: Ralph A. O'Connell, M.D., 144 West 12th Street, New York, NY 10011.

improved, and the current images are truly remarkable. CT and MRI, however, primarily assess structure, not function, and may not detect early changes due to an infectious process, ischemia, or epilepsy.

Positron emission tomography (PET) represents a major technological advance for the neurosciences, and has already provided major insights into the pathogenesis of a number of neuropsychiatric disorders. PET measures cerebral metabolism and has been shown to be useful in distinguishing patterns among the dementias, evaluating stroke, and localizing seizure foci in patients with partial seizures [3]. PET can also be used to map neurotransmitter receptor systems, of major potential for psychiatric research. PET, however, is quite complicated and expensive and not within the reach of most clinical settings.

Single photon emission tomography (SPECT) is another method of functional imaging used in heart, muscle, and skeletal studies, and more recently in brain [4]. SPECT provides an affordable means of studying regional cerebral blood flow (rCBF) and metabolism using the staff and nuclear medicine equipment available in most general hospitals. A number of radiopharmaceuticals are now available for SPECT, using nuclides such as iodine 123 and technetium 99. The radiopharmaceuticals used with SPECT emit a single photon, whereas PET nuclides emit a positron, which subsequently gives rise to two photons. The spatial resolution of the SPECT images is less than PET, but with the correct techniques and a knowledgeable staff, good spatial resolution is obtained and high-quality images result that contain important clinical information.

Our group has had extensive experience with SPECT in the setting of a university hospital. A pilot study of 94 psychiatric patients and 6 controls using I-123 N-isopropyl iodoamphetamine (IMP) to measure regional cerebral blood flow found that patients with dementias had distinct brain image patterns, consistent with the expected neuropathology [5]. We also reported decreased cortical and subcortical blood flow in depressed patients. This pattern was distinctly different from the pattern seen in Alzheimer's or multiinfarct dementia. Acutely psychotic patients frequently showed evidence of increased caudate nuclei activity with or without an associated temporal focus. The latter observation has to be approached with caution as no attempt was made to control for medications. We concluded that SPECT imaging can be of value

in the differential diagnosis of the dementias, as well as in distinguishing a true dementia from "functional" psychiatric disorders, especially in the early course before structural changes become apparent on CT or MRI. In the course of this work, we have had the opportunity to study a number of medically ill patients with associated psychopathology. This paper will report on our experiences with SPECT, present some representative cases, and discuss the role of functional brain imaging with SPECT in assessing psychopathology in the medically ill.

Method

Patients are seen on referral as part of an ongoing study of SPECT in neuropsychiatric disorders. After informed consent is obtained, the SPECT imaging procedure is done using a 400-mm field of view rotating scintillation detector, with a cut-off edge configuration clearing the shoulders. Imaging is done in a controlled environment with subdued lighting, eyes open, and low background noise. Imaging begins 20 minutes after the injection of 3 to 5 millicuries (mCi) (111–185 MBq) of IMP, or 12–22 mCi (444–814 MBq) of Tc-99m hexamethylpropyleneamineoxime (HMPAO). After the patient is positioned on an imaging couch, a total of 128 projection images are acquired at 20 seconds per view for IMP and 15 seconds per view for HMPAO, over a full 360-degree rotation orbit. The total acquisition time is approximately 35–45 minutes. The technical details of the SPECT method with IMP have been previously published [5]. If Tc-99m HMPAO is used, the only changes in the imaging and processing procedure involve the shorter time per view, the use of a high-resolution collimator, and the adjustment of the critical frequency of the preprocessing Butterworth filter to 0.48–0.52 cycles/cm.

We routinely gather data on multiple parameters of psychopathology on the supposition that although specific SPECT patterns may turn out to be associated with some diagnoses, patterns may be more generically related to psychopathologic symptoms or syndromes. Psychiatric diagnoses are made using the DSM-III-R criteria [6]. In addition, patients are rated on the Mini-Mental State [7], the Brief Psychiatric Rating Scale (BPRS) [8], the 21-item Hamilton Rating Scale for Depression (HAM-D) [9], and the mania rating scale of Young et al. [10]. CT head scans and EEGs are also obtained.

MRI was not routinely available. Whenever possible, patients' cognitive functioning is evaluated. The neuropsychological battery includes a combination of widely used measures of organic mental status, general intelligence, handedness, language, verbal and nonverbal memory, executive planning, motor coordination, attention and concentration, verbal and nonverbal conceptualization, and construction [11-13]. In the real world of the acute general hospital, it is often not possible to complete the whole battery of rating scales and neuropsychological tests.

Results

To date we have studied over 250 psychiatric patients using cerebral SPECT with IMP and HMPAO. Subjects tolerate the procedure well, and no adverse effects have been noted. In fact, patients seem to welcome the chance to participate. The normal cerebral SPECT study shows a homogeneous distribution of the radiopharmaceutical in cortical gray matter, with greatest uptake in the visual cortex of the occipital areas. Figure 1 shows a normal pattern with views of the (a) coronal, (b) sagittal and (c) transaxial planes. The following cases have been selected to illustrate the potential role of cerebral SPECT in assessing psychopathology in the medically ill.

Case 1

The first case is an 84-year-old male admitted for the first time with decreased cognitive functioning, several recent falls, depression, and suicidal ideation. The differential diagnosis was between a dementia, depression with pseudodementia, or both. The patient had hypertension, peripheral vascular disease, and metastatic prostate cancer. His Mini-Mental State score was 26, BPRS 37, and HAM-D 26. An EEG was diffusely abnormal. CT scans of the head revealed bilateral frontal lobe and basal ganglia infarcts. SPECT scan (Figure 2) with IMP showed multiple areas of cerebral infarction and extensive white matter disease, most likely of vascular etiology, of the pattern seen in multiinfarct dementia, and also superimposed generalized decrease in frontal rCBF, a pattern often seen in depression. The final clinical diagnosis was multiinfarct dementia and depression. In this case the SPECT findings were consistent with both dementia and depression, and focused attention on the need to treat the depression.

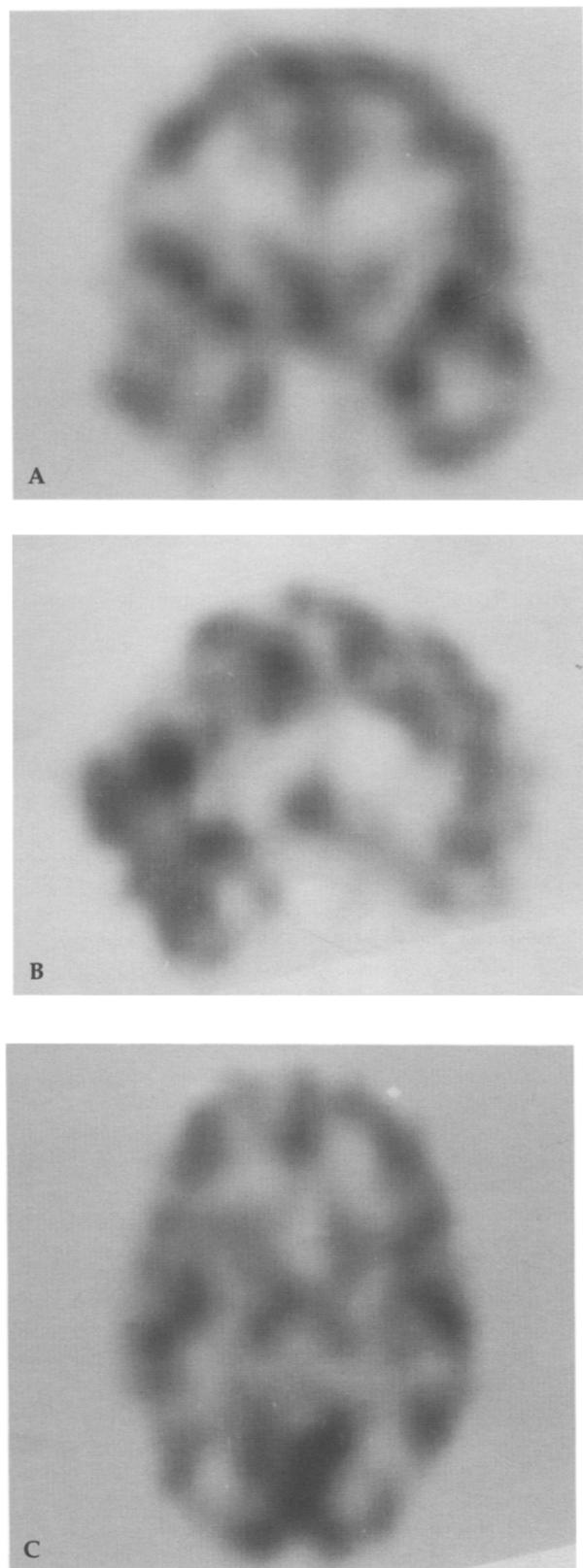


Figure 1. Normal SPECT brain images. **A.** Coronal. **B.** Sagittal. **C.** Transaxial.

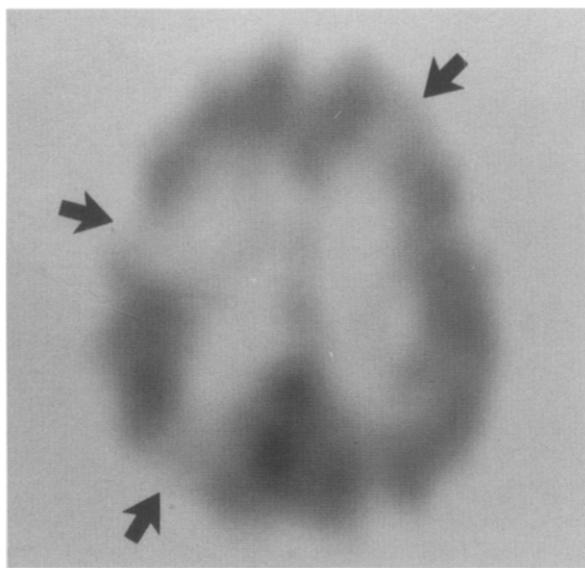


Figure 2. SPECT scan showing multiple areas of infarction.

Case 2

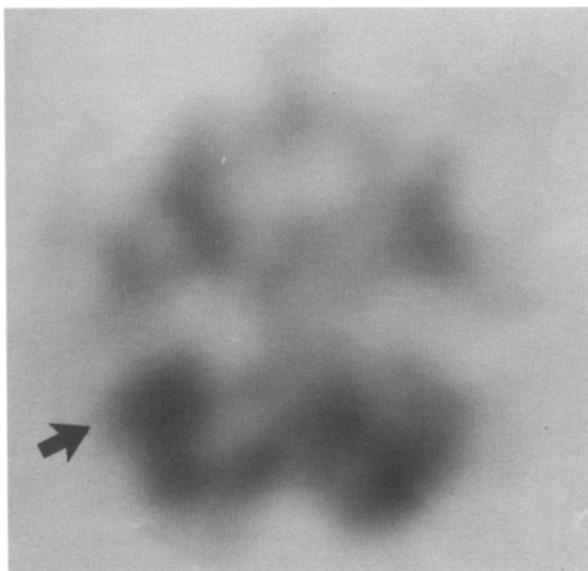
The second case is a 43-year-old male who had sustained a gunshot wound to the right frontoparietal region at age 21 while in Vietnam with resultant craniotomy. Beginning at age 25 he started hearing voices and was hospitalized with a diagnosis of schizophrenia. He has since had several psychiatric hospitalizations and regularly takes antipsychotic medications. There is no history of alcohol abuse, but occasional use of marijuana was reported. Upon admission, the patient reported symptoms of depression, sleeping difficulty, decreased energy, suicidal ideation, and auditory hallucinations. The differential diagnoses included an organic hallucinosis, schizophrenia, or psychotic depression. Neuropsychological evaluation revealed IQ scores in the Average range with significant variability among subtests. Cognitive screening on the Mattis Dementia Rating Scale was adequate, although scattered errors suggested attention difficulties. On a verbal selective reminding task, problems with organization of short-term memory suggested frontal system involvement. An EEG was moderately abnormal, with changes involving the right frontal and central regions consistent with the presence of a skull defect and an underlying structural abnormality. CT scans of the head with contrast showed slight atrophy, a right frontal craniotomy defect, and no evidence of mass lesions or other significant abnormality. Cerebral SPECT scanning with IMP showed asymmetry in caudate activity, although the rCBF in both caudates was within normal limits. Mildly decreased frontal cortex activity was seen bi-

laterally. His SPECT findings were consistent with an organic mental disorder secondary to trauma. In this case, the SPECT findings did not suggest any changes in treatment.

Case 3

The third case is that of a 16-year-old right-handed male who had undergone several psychiatric hospitalizations since age 9, variously diagnosed as having a reading disability, major depression, and conduct disorder. He complained of headaches with blurred vision, and admitted to alcohol and other nonintravenous drug abuse. The patient had episodes of impulsive, disruptive, aggressive, and self-destructive behavior of which he often had little recall. Neuropsychological assessment revealed a WAIS-R IQ in the Superior range with intertest scatter ranging from Average to Very Superior. Performance on the Mattis Dementia Rating Scale was satisfactory. Further testing confirmed signs of early learning dysfunction. Specific tests of visual-spatial perception and reasoning, language, verbal and nonverbal memory, and executive motor control suggested generally intact cognitive functioning. An EEG showed generalized spike and wave activity. CT head scans without contrast were negative. An MRI scan also failed to show any abnormality. In contrast, SPECT scanning with HMPAO demonstrated a focal area of increased uptake in the right posterior temporal lobe (Figure 3), suggestive of an active seizure focus. A repeat cerebral SPECT study with HMPAO, after the patient had been on carbamazepine 800 mg per day for 2 weeks

Figure 3. SPECT scan showing increased uptake in the right temporal lobe.

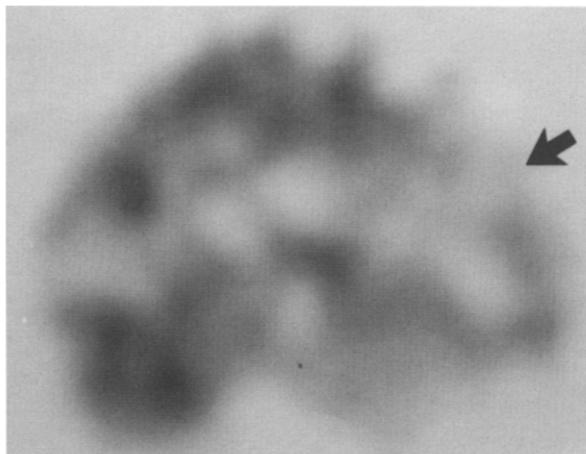


at therapeutic drug levels, showed significant resolution of the focus in the right temporal lobe, but with a small area of increased uptake still present. The patient's behavior improved significantly. The final diagnosis included a variant of temporal lobe epilepsy. In this case SPECT added diagnostic information not available from EEG or MRI.

Case 4

Case number 4 is a 62-year-old male with a 40-year history of alcohol abuse, with blackouts and withdrawal symptoms, but no hallucinosis or seizures. Following 4 months of inpatient alcohol rehabilitation, the patient returned to work. Over the course of the next week, he exhibited increasing signs of depressive symptoms, including decreased concentration and memory difficulties leading to rehospitalization. Medical history included hepatitis, ulcer disease, and kidney stones. Results of a limited neuropsychological screening revealed WAIS-R IQ scores in the Low Average range with relatively little variability among subtests. Signs of higher premorbid potential were noted. His overall performance on the Mattis Dementia Rating Scale revealed significant cognitive dysfunction with specific deficits on tasks of word fluency and short-term memory. CT scans of the head, without contrast, showed mild diffuse atrophy. An MRI was not done. Cerebral SPECT scanning with IMP demonstrated heterogeneous cortical distribution of radiopharmaceutical with decreased cortical activity, most prominently in the frontal lobes bilaterally (Figure 4). Moderate asymmetry was noted in thalamic uptake and a small focal defect was noted in the left prefrontal cortex (arrow) thought to be due to old trauma or a cerebrovascular accident in this

Figure 4. SPECT scan with decreased uptake in frontal lobe. Note focal defect in the left prefrontal cortex (arrow).



location. The pattern of decreased cortical uptake in the frontal lobes is seen in depression and dementias involving the frontal lobes. In this case, the SPECT findings indicated more extensive organic pathology, including a focal deficit, than previously suspected and helped develop more realistic expectations in discharge planning.

Case 5

The fifth case is a 31-year-old male with a long history of alcohol and cocaine abuse. This was his first psychiatric hospitalization for symptoms including homicidal and suicidal ideation, paranoia, and disorganization. A urine drug screen at the time of admission was positive for cocaine and THC. Liver function tests, including GGT, were all significantly elevated, and chronic active hepatitis B was diagnosed. HIV status was negative. Cognitive testing revealed a WAIS-R IQ in the Borderline range with variability among subtests ranging from Defective to Low Average. The pattern of findings suggests a decline from a higher premorbid level of cognitive functioning. An EEG was normal. CT head scans without contrast showed bilateral lenticular nuclei calcifications. Cerebral SPECT scanning with IMP demonstrated mildly heterogeneous cortical uptake with focal areas of increased uptake and photopenia, mild prominence of the central white matter photopenic area, and an area of intense focal increased uptake in the thalamus. This pattern of pathological findings involving the cortex, white matter, and deep gray matter in our experience is commonly seen in patients with histories of drug abuse, especially cocaine. The SPECT findings in these patients often suggest more extensive CNS pathology than is evident clinically or from other diagnostic techniques.

Case 6

Case number 6 is a 31-year-old bisexual male found to be HIV-positive 5 years prior to this first psychiatric admission but the diagnosis of ARC or AIDS had not been made. Psychiatric symptoms included paranoid delusions, auditory hallucinations, decreased sleep, weight loss, suicidal ideation, and mild cognitive slowing. A neuropsychological evaluation revealed WAIS-R IQ scores in the Low Average range with variability among subtests ranging from Low to High Average, suggesting higher premorbid capacity than his IQ scores reflected. Low scores were noted on tasks requiring sustained attention and concentration. Screening with the Mattis Dementia Rating Scale was adequate. Further testing revealed difficulties with verbal and visual short-term memory. While higher cortical executive motor functions were intact, signs of motor dysfunction suggested frontal-subcortical

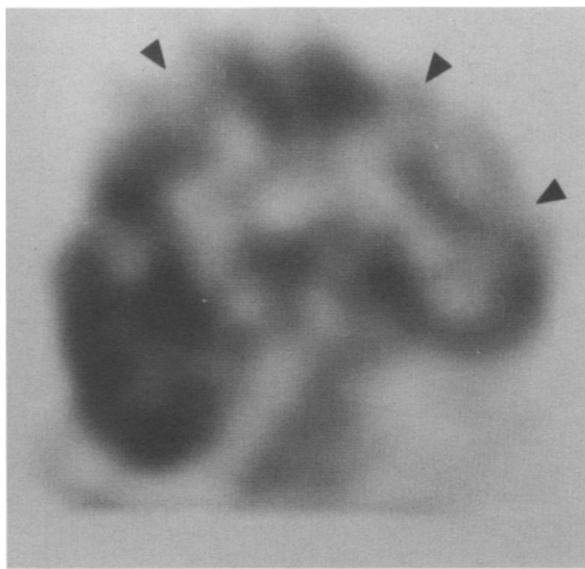


Figure 5. SPECT scan with decreased cortical and thalamic uptake. Note focal areas of photopenia (arrows).

involvement (right hemisphere greater than left). Visual-spatial perception and reasoning, conceptualization, and language skills were generally intact. An EEG was normal. CT scans of the head, with and without contrast, showed slight atrophy and a small hypodensity in the deep white matter in the right frontoparietal region. Incidentally noted were cavum septum pellucidum et vergae. An MRI was not available. Cerebral SPECT scanning with HMPAO (Figure 5) showed decreased and heterogeneous cortical uptake diffusely with focal areas of photopenia (arrows), prominence of the central white matter photopenic region, and focal decreased uptake in the right thalamus. This trinity of pathological findings in the cortex, white matter, and deep gray matter is consistent with AIDS encephalopathy, although drug-induced dementia is also a consideration in a patient with a history of substance abuse. Upon completion of his diagnostic work-up, treatment with AZT was started.

Discussion

These cases are typical of patients seen in a general hospital with coexistent medical and psychiatric symptoms; they present diagnostic challenges of assessing multiple systems and attempting to understand the etiology and interactions of the presenting symptoms. Our experience indicates that cerebral SPECT imaging has a role in the differential diagnosis of psychopathology. The information contributed by SPECT adds to that of other diagnostic techniques and may suggest changes in

treatment. Sometimes the SPECT data help confirm a diagnosis; at other times they open up a new consideration. Cerebral SPECT images must always be interpreted in the context of all the other relevant clinical data.

At this point the SPECT patterns seen in cerebral infarct, focal epilepsy, and dementia, either of the Alzheimer's type or multiinfarct, are the best described and appear to be the most specific [4,14]. SPECT can demonstrate changes in bilateral posterior parietal and temporal rCBF in Alzheimer's disease before structural changes are evident and can be helpful in evaluating a patient in the early phase of the disease. Johnson et al. [15], in a study of 58 Alzheimer patients using IMP SPECT, reported an overall diagnostic sensitivity and specificity of 88% and 87%, respectively. They concluded that IMP SPECT may be a useful adjunct in clinical diagnosis in early and mild disease. Cerebral SPECT has been shown to differentiate Alzheimer's disease from multiinfarct dementia [16-18], as well as from Korsakoff's psychosis [19]. Decreased IMP uptake in the caudate nucleus has been found in patients with Huntington's chorea [20]. While it is unclear at present whether this finding precedes structural changes, cerebral SPECT may provide diagnostic information in a disorder that often presents with functional psychiatric symptoms.

Like PET, SPECT has been helpful in localizing seizure foci in patients with intractable complex partial seizures [21,22]. We have studied several patients who showed focal increases in temporal lobe rCBF. Clinically, these patients did not have typical temporal lobe epilepsy; rather, they had periodic psychoses, often with marked affective and behavioral symptoms. They appear to be similar to those described as temporal lobe syndromes, which respond to carbamazepine [23]. Cerebral SPECT may prove very helpful in understanding the relationship of periodic psychoses and seizure disorders.

We have found cerebral SPECT useful in the early diagnosis of AIDS dementia. The pattern of rCBF changes in AIDS is heterogeneous, involves cortical and subcortical regions, and can occur before structural changes are evident on CT or MRI. Similar findings have been reported in PET and SPECT studies [24,25]. The early diagnosis of AIDS encephalopathy is a consideration that will become more important as new treatments become available.

Our group is studying SPECT in psychiatric dis-

orders [5]. A consistent finding has been a pattern of decreased cortical, especially frontal, and basal ganglia rCBF in patients with major depressive disorders. The pattern returns toward normal with improvement of the depression. This finding may be of importance in distinguishing the pseudodementia of depression from other dementias. A pattern of increased caudate rCBF has been seen in schizophrenia and other psychoses, but it is unclear whether this is related to the psychosis or exposure to antipsychotic medications.

To produce scans of diagnostic quality, a SPECT-capable gamma camera is required with the appropriate software for brain imaging, a trained technologist, and a nuclear medicine physician experienced in interpreting brain images. The quality of the images can vary greatly between different institutions. Our experience has been primarily with IMP and HMPAO. The cost of either agent is about the same, approximately \$150-\$175 a dose. IMP has been well studied. It is provided ready to use by the manufacturer and must be used on the day received. HMPAO has a higher resolution and shorter acquisition time but must be prepared on-site by a nuclear pharmacy. The relative advantages for these compounds and others in development and the indications for different conditions need further study. The details of the methodology of SPECT brain imaging are beyond the scope of this paper.

Table 1 shows those disorders in which cerebral SPECT has been found to have a potential in differential diagnosis and recent references. As SPECT brain imaging becomes increasingly available, undoubtedly more patients with psychopathologic symptoms will be imaged as part of the diagnostic workup. CT and MRI are superior in delineating brain structure, whereas PET and SPECT provide information about regional blood flow and metabolism. These findings are often seen before structural changes are evident. Our experience is that a combination of a structural and a functional brain imaging method is helpful in the diagnostic process. SPECT has the advantages of availability and lower cost over PET. However, as with any new technology, it will take time and experience to determine the diagnostic specificity of SPECT brain image patterns for specific neuropsychiatric disorders.

Perhaps the more exciting possibility for psychiatry is the potential for functional brain imaging to help delineate subtypes of the major functional disorders, schizophrenia and the affective disor-

Table 1. Cerebral SPECT in differential diagnosis

Diagnosis	References
Stroke	4, 14
Multiinfarct dementia	16, 17, 18
Alzheimer's disease	15
AIDS encephalopathy	25
Complex partial seizures	4, 21, 22
Major depression	5
Korsakoff's psychosis	19
Huntington's disease	20

ders. Radiopharmaceuticals that bind to specific neurotransmitter receptors are under development. We began with a quote from Bonhoeffer on the exogenous psychoses and will end with one from Eugen Bleuler who wrote in 1911: "By the term 'dementia praecox' or 'schizophrenia' we designate a group of psychoses whose course is at times chronic, at times marked by intermittent attacks, and which can stop or retrograde at any stage, but does not permit a full *restitutio ad integrum*" [26]. The key word is "group." Many clinicians and researchers have concluded that schizophrenia and the affective disorders are heterogeneous, i.e., composed of several different related conditions. Hopefully, brain imaging techniques like cerebral SPECT will help separate out the subtypes and provide information leading to more specific treatment selection.

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