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Neuroimaging in Neuropsychiatry

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Neuroimaging of neuropsychiatry

The neuroimaging of neuropsychiatric disorders continues to evolve as the field of neuroradiology progresses. New imaging techniques and modalities move from the research realm into the clinical world, increasing the imaging options for the clinician. Until quite recently, imaging of the psychiatric patient was characterized by and essentially limited to structural imaging techniques including CT and MRI, which provide anatomic images with excellent spatial and contrast resolution, and perfusion imaging techniques such as single-photon emission computed tomography (SPECT), which examines regional cerebral blood flow of an injected radiopharmaceutical agent [1]. With advances in neuroimaging techniques, radiographic evaluation of the psychiatric patient now encompasses additional, more sophisticated modalities, including functional MRI (fMRI), MR spectroscopy, and positron emission tomography (PET), which complement the structural and existing functional techniques [2]. These modalities allow noninvasive in vivo examination of the human brain, contributing significantly to the understanding of the pathophysiology of neuropsychiatric disorders.

This article reviews the basics of current neuroimaging techniques available to the practicing psychiatrist. These techniques include modalities clearly within the clinical realm as well as those that are primarily research tools. Structural and functional imaging techniques are addressed separately. Basic acquisition techniques of CT, MRI, fMRI, MR spectroscopy, and PET are provided. Although technical details are kept to a minimum, essential parameters are discussed, and the interested reader is directed to more detailed reviews as appropriate. Basic interpretations of each modality are also provided. Rather than providing a systematic review of research findings of neuropsychiatric disorders that have been investigated with

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neuroimaging, the discussion of imaging techniques is framed within the context of applications to neuropsychiatry.

It is hoped that this information will familiarize the nonimager with these sophisticated and powerful imaging techniques and will provide insight regarding the appropriate selection and application of these modalities to benefit the neuropsychiatric patient.

Structural neuroimaging

CT and MRI

CT and MRI are powerful techniques that provide exquisite anatomic images of the brain with excellent contrast and spatial resolution. Both can be used to evaluate for intracranial mass lesions, hemorrhage, and other pathologies and can demonstrate focal or regional brain atrophy. There are important differences between the two, including the generation of the images, specific advantages and disadvantages, and particular clinical indications of each technique.

To generate an image, CT uses ionizing radiation, a highly collimated X-ray beam that passes through the patient's head and then is recorded by CT detectors. The image produced depends on the degree of X-ray attenuation. Dense bone attenuates more of the X-ray beam than less dense tissue, such as air; the density of soft tissues lies between that of bone and air. Dense structures (like bone and acute blood) appear brighter or whiter on CT than less dense tissue (like air, cerebrospinal fluid, or fat), which appear darker or blacker (Fig. 1). Iodinated contrast material increases the attenuation of vessels and structures lacking an intact blood–brain barrier and appears white (Fig. 2). The degree of attenuation of a given tissue is measured in

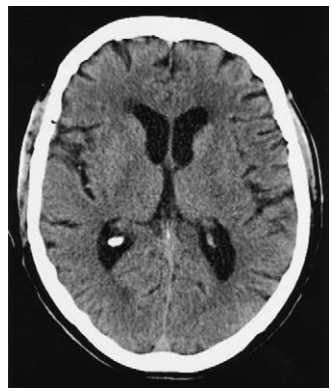

Fig. 1. Unenhanced axial CT image. The calvarium appears white, the cerebrospinal fluid appears black, and the gray matter is relatively "more white" (of greater attenuation) than the white matter.

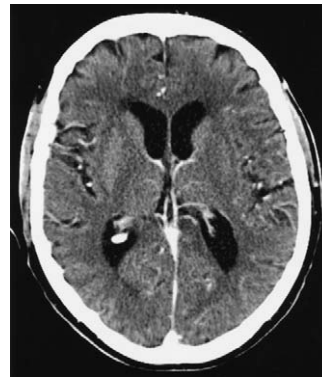

Fig. 2. Enhanced axial CT image demonstrating normal enhancement of cerebral arteries and veins.

Hounsfield units (HU), named after Sir Godfrey Hounsfield who developed CT for clinical use. The scale of attenuation ranges from +1000 HU for bone to −1000 HU for air. Similarly, the appearance of different tissues on CT ranges between white and black (Table 1). CT is relatively less expensive, quicker, and more available than MRI. CT is more sensitive than MRI in detecting acute hemorrhage and calcification and is superior in the depiction of bony architecture. CT remains the study of choice for evaluating the acute trauma patient, the uncooperative patient, suspected acute subarachnoid hemorrhage, and any acute neurologic emergency. There are essentially no contraindications for obtaining a CT scan. Although radiation exposure to the fetus from a head CT is low [3], a female patient should always inform the radiologist or technologist if there is a chance that she could be pregnant; alternative imaging tests, including MRI, may be chosen to reduce or eliminate radiation exposure to the fetus [4]. The risk of severe allergic reaction to iodinated contrast material is low. A relative disadvantage is that, practically, CT imaging is limited to the axial or transverse plane. Also, evaluation of the posterior fossa and brainstem may be degraded significantly by artifact from dense bone. Cwinn and Grahovac [5] provide an excellent discussion of basic CT physics and the use of CT head scans in the emergency patient.

The physical principles of MRI are much too complex to address in this article, but it is important to realize that MRI uses no ionizing radiation and uses a completely different mechanism to generate an image than CT. Rather than X-ray beam attenuation, MRI involves a complex interaction between external magnetic fields and tissues within the patient. One can think simplistically of MRI in terms of energy exchange between an external magnetic field and certain atomic nuclei. When a radiofrequency (RF) pulse is applied and then switched off, the tissue absorbs and then re-emits the energy. The energy is measured as an RF signal; translation of this information can

Table 1
CT attenuation values and appearance of central nervous system tissues

Tissue	Attenuation (HU)	Appearance
Bone	+1000	very white
Calcification	+140–200	white
Acute blood	+56–76	white
Gray matter	+32–41	White relative to white matter
White matter	+23–34	Gray relative to gray matter
Cerebrospinal fluid (water)	0	gray-black
Fat	−30–−100	black
Air	−1000	very black

produce an anatomic image. The appearance of the image depends on multiple factors, including specific intrinsic tissue properties (such as T1 and T2 relaxation times and proton density) and particular imaging techniques and parameters (including conventional spin-echo, fast spin-echo, or gradient-echo sequences, echo planar imaging, and different repetition times [TR], echo times [TE], and flip angles). Very simply, on a T1-weighted image (short TR, short TE) (Fig. 3), tissue with short T1 relaxation time (eg, fat) appears bright; long-T1 tissue (eg, water) is dark. On a T2-weighted image (long TR, long TE) (Fig. 4), tissue with short T2 relaxation time (fat) is dark; long-T2 tissue (water) is bright (Table 2). Balanced or proton density sequences essentially have been replaced by fluid attenuation inversion recovery (FLAIR) sequences, which provide T2-weighted contrast with dark cerebrospinal fluid (Fig. 5). Intravenous contrast material shortens the T1 relaxation time, resulting in increased T1 signal intensity of venous structures and those with

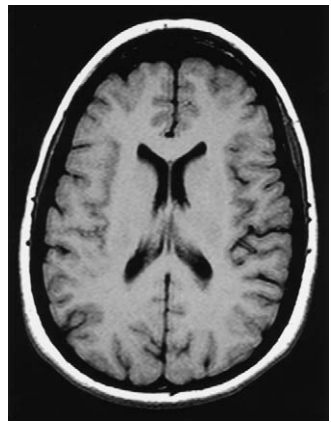

Fig. 3. Unenhanced axial T1-weighted MR image. The scalp fat appears bright or white, the cerebrospinal fluid appears dark or black, and the white matter appears white relative to the gray matter.

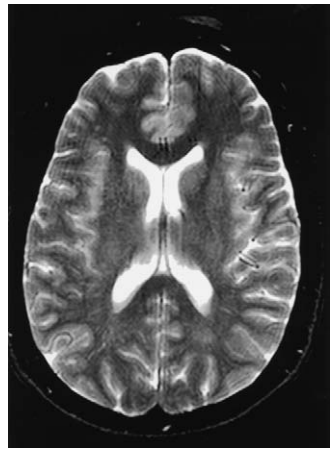

Fig. 4. Unenhanced axial T2-weighted MR image. The scalp fat appears dark, the cerebrospinal fluid appears white, and the white matter is dark relative to the gray matter.

an altered or absent blood–brain barrier (Fig. 6). Like contrast-enhanced CT, enhanced MRI complements the unenhanced examination and often increases the sensitivity and specificity of the examination in the detection of disease. MRI can be performed in any imaging plane (axial, sagittal, coronal, or oblique). It is relatively more expensive, takes longer to perform, and is less available than CT. Still, MRI is the initial study of choice in the evaluation of most intracranial processes because of its superior inherent tissue contrast and multiplanar imaging capabilities. MRI is more sensitive than CT in the evaluation of white matter disease, including multiple sclerosis, and in the screening of patients for suspected intracranial metastases. MRI is superior to CT in the differentiation of gray matter and in both cortical and subcortical regions. Contraindications for MRI include cardiac pacemakers, non–MRI-compatible aneurysm clips, neurostimulators, cochlear implants, and other

Table 2
MRI signal intensities of central nervous system tissues

Tissue	T1-weighted sequence	T2-weighted sequence
Bone	very dark	very dark
Calcification	very dark	very dark
Acute blood (oxyhemoglobin)	isointense	hyperintense
Subacute blood (intracellular methemoglobin)	very bright	dark
Chronic blood (hemosiderin)	very dark	very dark
Gray matter	isointense	bright
White matter	bright	isointense
Cerebrospinal fluid (water)	dark	bright
Fat	bright	intermediate
Air	very dark	very dark

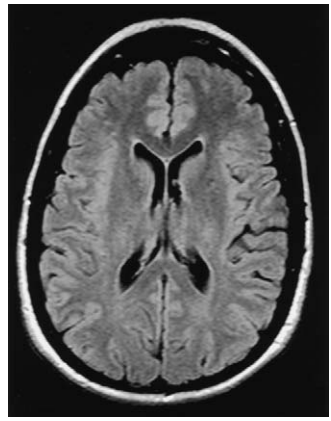

Fig. 5. Unenhanced axial FLAIR MR image. Note that the brain has a T2 appearance (white matter dark, relative to the gray matter), whereas the cerebrospinal fluid is dark.

metallic or electronic devices within the body [4]. Claustrophobia and acoustic noise are potential problems with MRI. For a more comprehensive discussion of MRI physics and techniques, the reader is directed to Sanders [6].

Structural images of the brain provided by CT and MRI can provide useful information in the evaluation of the psychiatric patient. MRI, with its superior depiction of cerebral white matter, has proved useful in investigating the possible role of oligodendroglial dysfunction in myelin maintenance and repair and the associated alteration in neuronal connectivity thought to be a central abnormality in schizophrenia. White matter hyperintensities have been seen in schizophrenic patients; white matter hyperintensities are

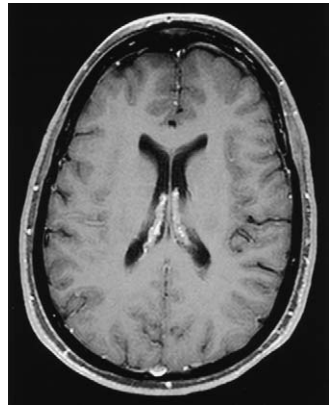

Fig. 6. Enhanced axial T1-weighted MR image demonstrating normal enhancement of the choroid plexus in the lateral ventricles, sagittal sinus, and cortical veins. The scalp fat appears dark because of the fat-saturation technique.

significantly more common in subjects who have late-life schizophrenia-like symptoms than in with age-matched controls. Also, decreases in both global and regional cerebral white matter have been seen; reductions in white matter volume in the prefrontal cortical region have been associated with negative symptoms [7].

Volumetric imaging of the brain can be performed with both CT and MRI and provides more quantitative assessment of regional atrophy in certain psychiatric disorders. A recent MRI study using high-resolution volumetric analysis comparing patients who had Huntington's disease with normal control subjects demonstrated extensive subcortical gray matter atrophy (particularly in the caudate nucleus and putamen), as well as significantly reduced cortical gray matter volume, consistent with previous findings. Novel findings from this study include significantly reduced volume of cerebellar gray and white matter, extensive reduction of cerebral white matter, and increased volume of abnormal cerebral white matter, suggesting that both the cerebellum and cerebral white matter integrity may be significant in the symptomatology of Huntington's disease [8]. An MRI study of patients who have Huntington's disease compared with age-matched healthy controls employing volumetric, diffusion-weighting, and magnetization transfer techniques has shown smaller caudate, putamen, and whole-brain volumes in patients who have Huntington's disease. An accompanying increase in the apparent diffusion coefficient values was seen on diffusion-weighted images in these regions as well as in the cerebral periventricular white matter, suggesting tissue damage at these sites. These imaging findings show correlation with disease severity [9]. The understanding of the pathophysiology of neurodegenerative central nervous system conditions such as Huntington's disease will continue to be advanced by such structural imaging techniques, allowing earlier diagnosis and serving as measures to monitor disease progression and treatment response.

Volumetric MRI is also useful in the study of patients who have schizophrenia. A recent study of 39 schizophrenic patients studied with high-resolution whole-brain morphometry contradicted the supposition that the enlargement of the lateral cerebral ventricles seen in schizophrenia reflects diffuse brain atrophy. Rather, this study showed an association of larger ventricles with regionally specific decreases of brain parenchyma in both paraventricular and remote areas, including the thalamus, putamen, and superior temporal gyrus [10]. A similar study found reduction in volume of the mediodorsal and pulvinar nuclei of the thalamus in schizophrenia [11]. Results of both studies point to the possible role that the thalamus may have in schizophrenia.

Diffusion tensor imaging is a variation of MRI able to study brain tissue microstructure and examine white matter tracts. Although this tool is still in its infancy, it may improve the understanding of neural connectivity and how specific regions of the brain interconnect, with specific applications to neuropsychiatric disorders including dementia, schizophrenia, and

addictions [12]. For example, results of a recent study suggest abnormal patterns on diffusion tensor imaging linking declarative-episodic verbal memory deficits to the left uncinate fasciculus and deficits in executive function to the left cingulate bundle in patients who have schizophrenia [13].

Functional neuroimaging

Functional MRI

fMRI complements the excellent spatial and contrast resolution of the brain provided by structural MRI. Although fMRI identifies the regions of the brain that are active in response to a task, the technique does not actually identify the neuronal firing. Rather, by coupling changes in local cerebral blood flow with neural activation, fMRI allows noninvasive evaluation and localization of motor, sensory, and cognitive deficits or symptoms. Because fMRI can be performed at the same time as the structural MRI study, functional activity can be mapped onto high-resolution anatomic brain images.

Although it is possible to study cerebral blood volume with fMRI using the injection of contrast material, the fMRI technique most frequently employed in the evaluation of the neuropsychiatric patient takes advantage of the changes in signal intensity associated with variations in the level of cerebral blood oxygenation. Called blood oxygen level–dependent contrast, this technique is noninvasive and does not require the injection of exogenous contrast material. Neural activation is followed by increased cerebral blood flow to the activated region. An increased number of red blood cells carrying oxyhemoglobin flow into the particular activated region. The supply of oxyhemoglobin exceeds the neuronal demand, resulting in a net decrease in the local concentration of deoxyhemoglobin. Oxyhemoglobin is diamagnetic, and deoxyhemoglobin is paramagnetic. The significance for the imager is that the increased signal intensity seen on fMRI in the activated brain actually is caused by the loss of decreased signal intensity associated with the paramagnetic deoxyhemoglobin.

Regardless of the mechanism, fMRI allows the study of brain activity without use of either ionizing radiation or the injection of radiopharmaceuticals needed in SPECT and PET. FMRI can be performed on most clinical MR systems (1.5 T) with conventional hardware, although the increased signal/noise ratio (SNR) and the increased imaging speed of the higher-field-strength magnets (3 T) are distinct advantages of those systems. The advantage of increased SNR can be appreciated when one realizes that the changes in signal intensity associated with variations in the level of blood oxygenation are extremely small. Still, one can perform single-case fMRI studies on individual patients, rather than averaging data from several studies. Because of the rapid image acquisition possible with fMRI, repetitive studies also can be performed on the same patient at one sitting.

The temporal and spatial resolution of fMRI are better than those of PET or SPECT.

The fMRI technique is very sensitive to motion, and minor patient movement can make it difficult to identify neural activation. Limiting head motion is essential for obtaining high-quality images. Like other MR techniques, patient claustrophobia may be an issue.

A variety of task paradigms can be used with fMRI. Typically, baseline images are acquired with the patient at rest. Then the patient performs a specific task, and another set of images is acquired. Various motor, sensory, and cognitive paradigms can be employed, and visual and auditory stimuli can be presented. In each case, increased signal intensity associated with changes in blood oxygenation in the activated cortex can be visualized. For a more detailed explanation of the principles, techniques, and applications of fMRI, the reader is referred to Chong and colleagues [14].

A significant current use of fMRI is preoperative brain mapping, especially the mapping of the eloquent cortex in patients being considered for neurosurgery [15]. The technique also holds great promise in the evaluation of psychiatric and neurodegenerative conditions. Functional imaging can be of great help in testing hypotheses of disease etiology. For example, frontal lobe dysfunction is thought to be of fundamental importance in schizophrenia. The term hypofrontality describes a failure of task-induced frontal cerebral response [16]. Hypofrontality has been shown on fMRI studies of neuroleptic-naive schizophrenic patients during Wisconsin Card Sorting Test; specifically, reduced activation was seen in the right frontal lobe, left temporal lobe, and left cerebellum, findings consistent with prior PET and SPECT studies [17]. Enhanced prefrontal function on fMRI with verbal working memory experiments was demonstrated in schizophrenia patients after 6 weeks of treatment with an atypical antipsychotic agent [18]. Functional imaging may also provide useful information in the evaluation of patients who have dementia, providing a means for earlier diagnosis, for differentiation among various dementias, and for monitoring drug response. For example, fMRI was used to investigate the memory-associated activation of the medial temporal lobe in nondemented elderly patients who had mild cognitive impairment. The individuals who progressed to Alzheimer's disease within 2.5 years showed greater medial temporal lobe activation at initial fMRI, suggesting that this finding may serve as a marker for impending clinical decline [19]. Future fMRI research will certainly include investigation of other conditions in which abnormal brain function can be observed before visible structural alterations.

MR spectroscopy

MR spectroscopy is a noninvasive technique with broad applications in neuropsychiatry that relies on the same basic principles used by nuclear MR

but provides unique metabolic and biochemical information not available with MRI. MR spectroscopy allows noninvasive interrogation of the chemical environment of tissues, providing relative quantification of particular compounds and their constituents in certain regions of the brain. The complex physical principles behind MR spectroscopy cannot be addressed adequately in this article, but there are excellent more comprehensive reviews of basic MR spectroscopy techniques [20–22].

The nuclei studied with MR spectroscopy include proton [^{1}H], phosphorus [^{31}P], carbon [^{13}C], lithium [^{7}Li], fluorine [^{19}F], and sodium [^{23}Na]. The most current MR spectroscopy involves ^{1}H (proton MR spectroscopy), which can distinguish certain metabolites including *N*-acetyl aspartate (NAA), creatine and phosphocreatine, and choline-containing phospholipids. NAA is the largest peak seen on MR spectroscopy and is considered a marker on neuronal integrity. It is depleted in most conditions that replace or damage neurons. Creatine and phosphocreatine serve as useful internal references, because they are relatively constant metabolites in the brain, even in disease states. Choline reflects total choline brain stores and is associated with cell membrane synthesis and degradation; choline elevation suggests membrane turnover and often is seen with acute demyelination and cerebral neoplasms [23].

With MR spectroscopy, a spectrum associated with a particular region of interest is generated. A spectrum is simply a plot of peaks at different frequencies. Each peak is characterized by its resonant frequency and its height. Each metabolite in the spectrum is identified by its characteristic resonant frequency or location; the location is expressed in units of parts per million, plotted on the x-axis from right to left. The height of the peak (or area under the peak) yields the relative concentration of the metabolite.

Two main pulse sequences used in MR spectroscopy: stimulated echo acquisition method (STEAM) and point-resolved spectroscopy. Each has distinctive advantages and disadvantages. STEAM uses a shorter TE, has better water suppression, and is better able to identify more metabolites. These metabolites are often of interest to the psychiatrist and include myoinositol, glutamate, glutamine, and γ-aminobutyric acid (GABA). For example, myoinositol has been suggested as a marker for Alzheimer's disease, with increased myoinositol and decreased NAA seen in patients who have Alzheimer's disease [23]. Point-resolved spectroscopy uses a longer TE and has relatively greater SNR. The longer TE, however, results in loss of signal from most brain compounds, allowing the detection of only four metabolites: NAA, creatinine, choline-containing phospholipids, and lactate. Still, this technique may be adequate if one is interested in NAA and creatinine. For example, significantly lower NAA/creatine ratios were seen in ill Gulf War veterans than in healthy control subjects, confirming reduction of functioning neuronal mass in the basal ganglia and brainstem [24]. Appropriate selection of the particular pulse sequence is influenced by the metabolites of interest. If the referring clinician is especially interested in

a metabolite such as myoinositol or GABA, this information should be relayed to the radiologist so that the STEAM technique is used.

A unique application of MR spectroscopy in the psychiatric patient is the in vivo measurement of psychoactive drugs in the human brain, specifically the quantification of brain lithium and fluorinated drugs, which include most of the serotonin-specific reuptake inhibitors. Lithium is used for the treatment of bipolar disorders, with poor correlation between serum and brain lithium levels. A certain percentage of patients who have therapeutic serum lithium levels experience a relapse of symptoms, and serious toxicity can result from modest elevations of serum levels. ^{7}Li-MR spectroscopy can provide a noninvasive measurement of brain lithium in patients. Similarly, ^{19}F-MR spectroscopy may be useful in providing an in vivo means of measuring fluorinated drugs and their metabolites in the brain [25].

Another neuropsychiatric application of MR spectroscopy is the in vivo measurement of brain GABA levels. Abnormal GABA levels have been measured in several neuropsychiatric conditions, including epilepsy, anxiety disorders, major depression, and drug addiction. In disorders with abnormally low GABA levels, treatment may include medications that block the reuptake or degradation of GABA [26].

Results of an MR spectroscopy study of nine autistic children found lower NAA levels in the cerebellum, consistent with neuropathic reports of decreased numbers of Purkinje cells and granule cells in the cerebellar cortex of autistic patients. Also, lactate was detected in the frontal cortex of one autistic child; lactate is not detectable in normal brain on MR spectroscopy. Plasma lactate levels were also significantly higher in the autistic group. These findings are consistent with altered energy metabolism in some children, which may have therapeutic implications [27]. Although the study was small, the results suggest further evaluation of autistic individuals may be warranted.

^{1}H-MR spectroscopy of patients who had parkinsonism showed significant correlation between the severity of various diseases causing parkinsonism and the NAA/creatinine ratios in the both the putamen and the frontal lobe. Significant correlation was also seen between the impairment of executive function and frontal lobe NAA/creatinine ratio. These findings suggest that MR spectroscopy may be helpful in the diagnosis and monitoring of patients who have parkinsonism syndromes [28].

Future directions include MR spectroscopy with higher-field-strength magnets. Performing MR spectroscopy with 3T magnets will provide increased sensitivity, better SNR, and improved spatial resolution. Metabolite peaks can be detected and measured more precisely. The study of GABA with ^{1}H-MR spectroscopy would certainly benefit from higher magnetic field [27]. Detection of GABA will also be improved with ^{13}C-MR spectroscopy, in which injected ^{13}C-labeled glucose is incorporated into glutamate and then into GABA [27]. The increased SNR available with higher-field-strength systems would facilitate ^{31}P-MR spectroscopy, which

may be of benefit in the study of membrane phospholipid metabolism in patients who have schizophrenia [29] and the study of high-energy phosphate metabolism in the frontal lobes of patients who have panic disorder [30].

Positron emission tomography

Emission tomography includes PET and SPECT. Both nuclear imaging techniques involve the injection of certain short-lived radiopharmaceuticals and the detection of particular emitted radiation by gamma scintillation cameras. In SPECT, gamma rays are detected as the primary decay product. In PET, emitted positrons collide with electrons, annihilating both particles. Two 511-kEv gamma rays are produced 180° apart. For the event to be recorded, nearly simultaneous detection on opposite sides of the patient is required. The information originating in different regions of the brain is processed to create a three-dimensional image. SPECT tracers are more limited than PET tracers in the types of brain activity that can be studied. SPECT tracers have longer half-lives than PET agents and do not require an onsite cyclotron for production. With the greater temporal and spatial resolution of PET compared with SPECT, the development of newer PET tracers, and the increasingly greater availability and affordability of PET, PET will probably be the imaging study of choice for emission tomography studies of the brain. This article therefore focuses solely on PET and its applications in neuropsychiatry. The reader is directed to Hartshorne [31] for a more comprehensive discussion of the performance of PET in the central nervous system.

PET has wide applications in the study of brain disorders, cardiac disease, and oncology [32]. Radionuclides used in PET include Carbon 11 [^{11}C], Nitrogen 13 [^{13}N], Oxygen 15 [^{15}O] and Fluorine 18 [^{18}F]. Clinically, the most widely used PET radionuclide is ^{18}F, which has a longer half-life than ^{11}C, ^{13}N, or ^{15}O and is a label for the glucose analogue fluoro-2-deoxy-D-glucose (FDG). [^{18}F]-FDG-PET is especially valuable in the study of brain function because the rate of glucose metabolism increases in regions of brain activity. Regional cerebral metabolism has been studied in various neurodegenerative and psychiatric conditions, stroke, and trauma with [^{18}F]-FDG-PET [33]. PET also allows noninvasive study of cerebral blood flow and volume, oxygen metabolism, and drug concentrations in particular brain regions. For example, PET studies with ^{11}C tracers can provide valuable information in the study of neuroreceptor mapping and for psychotropic drug development [34].

PET/CT fusion is a relatively new technique that allows the nearly synchronous acquisition of images and precise coregistration of the functional (PET) and anatomic (CT) data sets. Potential advantages of the combined technique also include better-quality PET images because of

more accurate attenuation correction and shorter imaging times [32,35]. Studies comparing standard PET with PET/CT in patients who have head and neck cancer demonstrated that the combined technique provided improved anatomic localization of abnormalities identified on PET, resulting in improved diagnostic accuracy and a reduced number of equivocal PET findings. These findings led to a change in patient care in 12 of the 68 patients studied [36]. It is reasonable to assume that the improved anatomic localization PET/CT findings will have similar positive applications for the neuropsychiatric patient.

Coregistration of PET images with MRI images has also proved useful. A recent [^{18}F]-FDG-PET study of glucose metabolism within specific thalamic subdivisions of schizophrenic patients co-registered the PET and axial T1-weighted MRI images of 41 unmedicated schizophrenic patients compared with 60 matched control subjects. In the schizophrenic patients, glucose metabolism in the mediodorsal nucleus and the centromedian nucleus was significantly lower and glucose metabolism in the pulvinar was significantly higher than in controls. Lower glucose metabolism in the mediodorsal nucleus was associated with more negative symptoms, whereas lower glucose metabolism in the pulvinar was associated with more hallucinations and more positive symptoms. The demonstration of abnormal glucose metabolism in distinct thalamic regions with specific cortical connections and the association of these abnormalities with clinical symptoms furthers the understanding of schizophrenia [37].

PET has proved to be important in the evaluation of patients who have neurodegenerative disorders, especially in aiding with the difficult diagnosis of Alzheimer's disease. [^{18}F]-FDG-PET demonstrates bilateral temporoparietal hypometabolism in patients who have probable and definite Alzheimer's disease [38]. Frontotemporal deficits are seen on PET scans of patients who have frontotemporal dementia (Fig. 7) [39]. [^{18}F]-FDG-PET studies may allow earlier and more definite diagnosis of Alzheimer's disease, aiding in the differentiation of patients who have various types of dementia. [40]. Recently developed molecular imaging agents include [^{18}F]-FDDNP, a PET ligand that can determine the localization and load of neurofibrillary tangles and beta-amyloid plaques in the brains of living patients who have Alzheimer's disease; specifically, greater accumulation of the ligand was seen in the temporal lobes of nine patients who had Alzheimer's compared with seven controls [41]. Another agent that targets beta-amyloid deposits, [^{11}C]PIB, which is a thioflavin-T analogue, localized in the frontal and temporoparietal regions of nine patients who had "mild" Alzheimer's disease compared with five healthy controls. [^{11}C]PIB is now in clinical trials in Sweden [42]. These agents certainly hold promise in the development of effective drug therapy, in aiding early diagnosis, and in monitoring a patient's progress.

The study of the central serotonin system in mood disorders has been greatly advanced with PET imaging and the development of particular

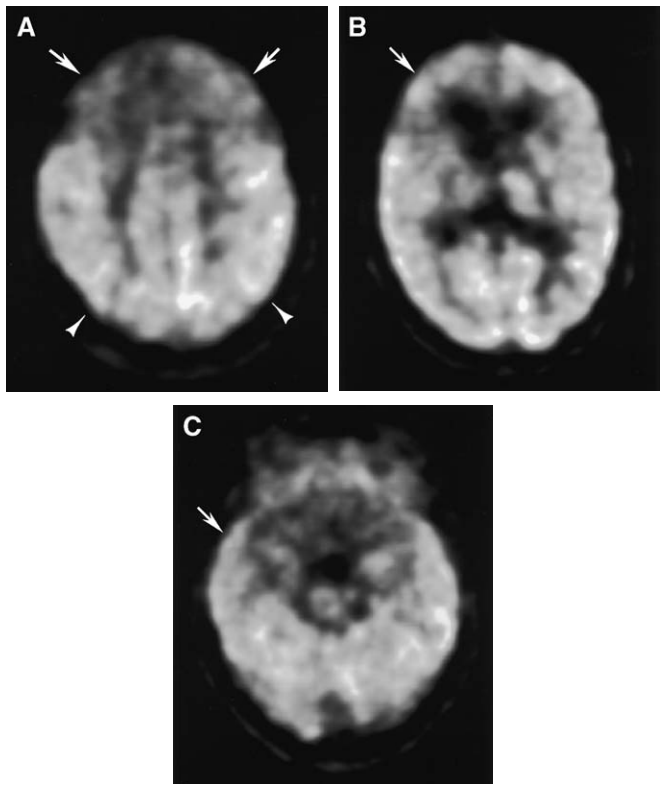

Fig. 7. [^{18} F]-FDG-PET image in a 70-year-old woman with frontotemporal dementia. (*A*) Normal metabolic activity is seen within both parietal lobes (*arrowheads*). (*A*, *B*) FDG-PET shows prominent diminished FDG uptake in both frontal lobes, more marked on the right (*arrows*). (*C*) Diminished FDG uptake is seen to a lesser degree within the temporal lobes and is more marked on the right (*arrow*).

ligands. Alterations of brain serotonin (5-HT) transmission, especially changes in availability of the presynaptically located serotonin transporter (SERT), have been implicated in the pathophysiology of depression [43]. [^{11}C](+)McN5652 is a selective PET radioligand for imaging the human 5-HT transporter site, which allows the in vivo detection of cerebral SERT availability. Serotonin transporter binding is a marker of the level of intrasynaptic serotonin. Decreased transporter binding indicates fewer serotonin nerve terminals or less intrasynaptic serotonin; either condition results in reduced serotonin function [34]. Thirteen antidepressant-naive or -free patients who had either major depressive disorder or bipolar disorder and 21 healthy controls were recently studied with [^{11}C](+)McN5652 PET. Thalamic SERT availability was significantly increased in the patient group, especially in those who had major mood disorder, compared with controls; no difference between the two groups was found in midbrain

SERT availability [44] This finding suggests an altered integration of the serotonergic neurons in patients who have mood disorders and possibly a thalamic role in mood disorder pathophysiology. Another recent [^{11}C](+)McN5652 PET study reported significantly greater ligand binding to the 5-HT transporter sites in the left frontal region and right cingulate region of four drug-free depressed patients compared with healthy controls [45]. These findings suggest increased 5-HT transporter sites in the frontal and cingulated cortex of depressed patients and support the hypothesis that alterations in 5-HT transporter sites may be significant in the pathophysiology and treatment of depression and mood disorders. PET and SPECT studies using SERT tracers have also investigated other psychiatric disorders, including obsessive-compulsive disorder, schizophrenia, and drug abuse, and neurologic diseases such as Parkinson's and Wilson's disease [43]. Further PET studies will continue to expand the understanding of the role of the serotonergic and other neurotransmitter systems in the pathophysiology of neuropsychiatric disorders.

PET also has an important role in epilepsy. [^{18}F]-FDG-PET has been useful in the localization of the epileptic focus, because seizure foci are seen as areas of hypermetabolism ictally and hypometabolism interictally [33]. Imaging has been especially helpful in evaluating patients who have refractory temporal lobe epilepsy being considered for surgery. Single hypometabolic foci can be seen on interictal PET studies in 55% to 80% of patients who have focal electroencephalographic abnormalities [33]. In seizures caused by foci in the medial and inferior aspects of the frontal lobes, PET has been shown to be superior to electroencephalography in the accurate localization of the seizure focus [33]. Foci of hypometabolism on [^{18}F]-FDG-PET studies have been seen in patients who have temporal lobe epilepsy and no evidence of hippocampal sclerosis on MRI [46]. PET may also be a useful tool in the general epilepsy population, in the exclusion of pathology in patients who have nonepileptic seizures, in primary generalized epilepsies, and in the identification of patients previously thought not to be surgical candidates [47]. Finally, SPECT may still be useful in the evaluation of the seizure patient. SPECT with [^{123}I]-iododexetimide (IDEX) can depict tracer uptake by muscarinic acetylcholine receptors, which are thought to play an important role in the generation of seizures. A recent study showed that IDEX SPECT was superior to the interictal PET in localizing seizures in patients who have temporal lobe epilepsy and suggested that the 6-hour IDEX SPECT scan is a viable alternative to [^{18}F]-FDG-PET imaging in localizing seizure foci in these patients [48].

Future applications of PET imaging in neuropsychiatry seem almost limitless in areas of scientific interest and of clinical importance. The use of coregistered or fused anatomic images with PET data will continue to bridge the gap between structural and functional imaging. The continued development of additional PET ligands will allow further in vivo molecular imaging of the brain.

Summary

Once limited to structural imaging modalities such as CT and MRI, radiographic evaluation of the psychiatric patient now includes more sophisticated functional techniques such as fMRI, MR spectroscopy, and PET. With the increased sensitivity that these new tools bring comes greater complexity. As new imaging techniques continue to transition from research to clinical application, the imaging options and associated complexity will increase. Consultation with neuroradiology colleagues will allow the practicing psychiatrist to evaluate their patients optimally. These techniques will continue to provide insight into the pathophysiology, etiology, diagnosis, treatment, and prognosis of these patients.

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