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centrotemporal spikes. J Child Neurol. 2013;28(4):435–445. 5.8 Neuroimaging Primary observation of structural and functional brain imaging in neuropsychiatric disorders such as dementia, movement disorders, demyelinating disorders, and epilepsy has contributed to a greater understanding of the pathophysiology of neurological and psychiatric illnesses and helps practicing clinicians in difficult diagnostic situations. Neuroimaging methodologies allow measurement of the structure, function, and chemistry of the living human brain. Over the past decade, studies using these methods have provided new information about the pathophysiology of psychiatric disorders that may prove to be useful for diagnosing illness and for developing new treatments. Computer tomographic (CT) scanners, the first widely used neuroimaging devices, allowed assessment of structural brain lesions such as tumors or strokes. Magnetic resonance imaging (MRI) scans, developed next, distinguish gray and white matter better than CT scans do and allow visualizations of smaller brain lesions as well as white matter abnormalities. In addition to structural neuroimaging with CT and MRI, a revolution in functional neuroimaging has enabled clinical scientists to obtain unprecedented insight into the diseased human brain. The foremost techniques for functional neuroimaging include positron emission tomography (PET) and single photon emission computed tomography (SPECT). USES OF NEUROIMAGING Indications for Ordering Neuroimaging in Clinical Practice Neurological Deficits. In a neurological examination, any change that can be localized to the brain or spinal cord requires neuroimaging. Neurological examination includes mental status, cranial nerves, motor system, coordination, sensory system, and reflex components. The mental status examination assesses arousal, attention, and motivation; memory; language; visuospatial function; complex cognition; and mood and affect. Consultant psychiatrists should consider a workup including neuroimaging for patients with new-onset psychosis and acute changes in mental status. The clinical examination always assumes priority, and neuroimaging is ordered on the basis of clinical suspicion of a central nervous system (CNS) disorder. Dementia. Loss of memory and cognitive abilities affects more than 10 million persons in the United States and will affect an increasing number as the population ages. Reduced mortality from cancer and heart disease has increased life expectancy and has allowed persons to survive to the age of onset of degenerative brain disorders, which have proved more difficult to treat. Depression, anxiety, and psychosis are common in patients with dementia. The most common cause of dementia is Alzheimer’s disease, which does not have a characteristic appearance on routine neuroimaging but,

rather, is associated with diffuse loss of brain volume. One treatable cause of dementia that requires neuroimaging for diagnosis is normal pressure hydrocephalus, a disorder of the drainage of cerebrospinal fluid (CSF). This condition does not progress to the point of acutely increased

intracranial pressure but stabilizes at a pressure at the upper end of the normal range. The dilated ventricles, which may be readily visualized with CT or MRI, exert pressure on the frontal lobes. A gait disorder is almost uniformly present; dementia, which may be indistinguishable from Alzheimer's disease, appears less consistently. Relief of the increased CSF pressure may completely restore gait and mental function. Infarction of the cortical or subcortical areas, or stroke, can produce focal neurological deficits, including cognitive and emotional changes. Strokes are easily seen on MRI scans. Depression is common among stroke patients, either because of direct damage to the emotional centers of the brain or because of the patient's reaction to the disability. Depression, in turn, can cause pseudodementia. In addition to major strokes, extensive atherosclerosis in brain capillaries can cause countless tiny infarctions of brain tissue; patients with this phenomenon may develop dementia as fewer and fewer neural pathways participate in cognition. This state, called vascular dementia, is characterized on MRI scans by patches of increased signal in the white matter. Certain degenerative disorders of basal ganglia structures, associated with dementia, may have a characteristic appearance on MRI scans. Huntington's disease typically produces atrophy of the caudate nucleus; thalamic degeneration can interrupt the neural links to the cortex (Fig. 5.8-1).

FIGURE 5.8-1 Brain slices. Top: Huntington disease. Atrophy of caudate nucleus and lentiform nuclei with dilatation of lateral ventricle. Bottom: Normal brain. (From Fahn S. Huntington disease. In: Rowland LP, ed. Merritt's Textbook of Neurology. 10th ed. Philadelphia: Lippincott Williams & Wilkins; 2000:659, with permission.) Space-occupying lesions can cause dementia. Chronic subdural hematomas and cerebral contusions, caused by head trauma, can produce focal neurological deficits or may only produce dementia. Brain tumors can affect cognition in several ways. Skullbased meningiomas can compress the underlying cortex and impair its processing. Infiltrative glial cell tumors, such as astrocytoma or glioblastoma multiforme, can cut off communication between brain centers by interrupting white matter tracts. Tumors located near the ventricular system can obstruct the flow of CSF and gradually increase the intracranial pressure. Chronic infections, including neurosyphilis, cryptococcosis, tuberculosis, and Lyme disease, can cause symptoms of dementia and may produce a characteristic enhancement of the meninges, especially at the base of the brain. Serological studies are needed to complete the diagnosis. Human immunodeficiency virus (HIV) infection can

cause dementia directly, in which case is seen a diffuse loss of brain volume, or it can allow proliferation of Creutzfeldt-Jakob virus to yield progressive multifocal leukoencephalopathy, which affects white matter tracts and appears as increased white matter signal on MRI scans. Chronic demyelinating diseases, such as multiple sclerosis, can affect cognition because of white matter disruption. Multiple sclerosis plaques are easily seen on MRI scans as periventricular patches of increased signal intensity. Any evaluation of dementia should consider medication effects, metabolic derangements, infections, and nutritional causes that may not produce abnormalities on neuroimaging. Indications for Neuroimaging in Clinical Research Analysis of Clinically Defined Groups of Patients. Psychiatric research aims to categorize patients with psychiatric disorders to facilitate the discovery of neuroanatomical and neurochemical bases of mental illness. Researchers have used functional neuroimaging to study groups of patients with such psychiatric conditions as schizophrenia, affective disorders, and anxiety disorders, among others. In schizophrenia, for example, neuropathological volumetric analyses have suggested a loss of brain weight, specifically of gray matter. A paucity of axons and dendrites appears present in the cortex, and CT and MRI

may show compensatory enlargement of the lateral and third ventricles. Specifically, the temporal lobes of persons with schizophrenia appear to lose the most volume relative to healthy persons. Recent studies have found that the left temporal lobe is generally more affected than the right. The frontal lobe may also have abnormalities, not in the volume of the lobe, but in the level of activity detected by functional neuroimaging. Persons with schizophrenia consistently exhibit decreased metabolic activity in the frontal lobes, especially during tasks that require the prefrontal cortex. As a group, patients with schizophrenia are also more likely to have an increase in ventricular size than are healthy controls. Disorders of mood and affect can also be associated with loss of brain volume and decreased metabolic activity in the frontal lobes. Inactivation of the left prefrontal cortex appears to depress mood; inactivation of the right prefrontal cortex elevates it. Among anxiety disorders, studies of obsessive-compulsive disorder with conventional CT and MRI have shown either no specific abnormalities or a smaller caudate nucleus. Functional PET and SPECT studies suggest abnormalities in the corticolimbic, basal ganglial, and thalamic structures in the disorder. When patients are experiencing obsessivecompulsive disorder symptoms, the orbital prefrontal cortex shows abnormal activity. A partial normalization of caudate glucose metabolism appears in patients taking medications such as fluoxetine (Prozac) or clomipramine (Anafranil) or undergoing behavior modification. Functional neuroimaging studies of persons with attention-deficit/hyperactivity disorder (ADHD) either have shown no abnormalities or have shown decreased volume of the right prefrontal cortex and the right globus pallidus. In addition, whereas normally the right caudate nucleus is larger than the left caudate nucleus, persons with

ADHD may have caudate nuclei of equal size. These findings suggest dysfunction of the right prefrontal-striatal pathway for control of attention. Analysis of Brain Activity during Performance of Specific Tasks. Many original conceptions of different brain region functions emerged from observing deficits caused by local injuries, tumors, or strokes. Functional neuroimaging allows researchers to review and reassess classic teachings in the intact brain. Most work, to date, has been aimed at language and vision. Although many technical peculiarities and limitations of SPECT, PET, and functional MRI (fMRI) have been overcome, none of these techniques has demonstrated clear superiority. Studies require carefully controlled conditions, which subjects may find arduous. Nonetheless, functional neuroimaging has contributed major conceptual advances, and the methods are now limited mainly by the creativity of the investigative protocols. Studies have been designed to reveal the functional neuroanatomy of all sensory modalities, gross and fine motor skills, language, memory, calculations, learning, and disorders of thought, mood, and anxiety. Unconscious sensations transmitted by the autonomic nervous system have been localized to specific brain regions. These analyses provide a basis for comparison with results of studies of clinically defined patient groups and may lead to improved therapies for mental illnesses. SPECIFIC TECHNIQUES CT Scans In 1972, CT scanning revolutionized diagnostic neuroradiology by allowing imaging of the brain tissue in live patients. CT scanners are currently the most widely available and convenient imaging tools available in clinical practice; practically every hospital emergency room has immediate access to a CT scanner at all times. CT scanners effectively take a series of head X-ray pictures from all vantage points, 360 degrees around a patient’s head. The amount of radiation that passes through, or is not absorbed from, each angle is digitized and entered into a computer. The computer uses matrix algebra calculations to assign a specific density to each point within the head and displays these data as a set of two-dimensional images. When viewed in sequence, the images allow mental reconstruction of the shape of the brain. The CT image is determined only by the degree to which tissues absorb X-irradiation. The bony structures absorb high amounts of

irradiation and tend to obscure details of neighboring structures, an especially troublesome problem in the brainstem, which is surrounded by a thick skull base. Within the brain itself, there is relatively little difference in the attenuation between gray matter and white matter in X-ray images. Although the gray–white border is usually distinguishable, details of the gyral pattern may be difficult to appreciate in CT scans. Certain tumors may be invisible on CT because they absorb as much irradiation as the surrounding normal brain. Appreciation of tumors and areas of inflammation, which can cause changes in behavior, can be increased by intravenous infusion of iodine-containing contrast agents.

Iodinated compounds, which absorb much more irradiation than the brain, appear white. The intact brain is separated from the bloodstream by the blood–brain barrier, which normally prevents the passage of the highly charged contrast agents. The blood– brain barrier, however, breaks down in the presence of inflammation or fails to form within tumors and thus allows accumulation of contrast agents. These sites appear whiter than the surrounding brain. Iodinated contrast agents must be used with caution in patients who are allergic to these agents or to shellfish. With the introduction of MRI scanning, CT scans have been supplanted as the nonemergency neuroimaging study of choice (Fig. 5.8-2). The increased resolution and delineation of detail afforded by MRI scanning is often required for diagnosis in psychiatry. In addition, performing the most detailed study available inspires the most confidence in the analysis. The only component of the brain better seen on CT scanning is calcification, which may be invisible on MRI. FIGURE 5.8-2 Comparison of computed tomography (CT) and magnetic resonance imaging (MRI). A. CT scan in the axial plane at the level of the third ventricle. The cerebrospinal fluid (CSF) within the ventricles appears black, the brain tissue appears gray, and the skull appears white. There is very poor discrimination between the gray and white matter of the brain. The arrow indicates a small calcified lesion in a tumor of the pineal gland. Detection of calcification is one role in which CT is superior to MRI. B. T2-weighted image of the same patient at roughly the same level. With T2, the CSF appears white, the gray matter appears gray, the white matter is clearly distinguished from the gray matter; the skull and indicated calcification appear black. Much more detail of the brain is visible than with CT. C. T1-weighted image of the same patient at roughly the same level. With T1, the CSF appears dark, the brain appears more uniformly gray, and the skull and indicated calcification appear black. T1 MRI images are the most similar to CT images. (Reprinted from Grossman CB. Magnetic Resonance Imaging and Computed Tomography of the Head and Spine. 2nd ed. Baltimore: Williams & Wilkins; 1996:101, with permission.)

MRI Scans MRI scanning entered clinical practice in 1982 and soon became the test of choice for clinical psychiatrists and neurologists. The technique does not rely on the absorption of X-rays but is based on nuclear magnetic resonance (NMR). The principle of NMR is that the nuclei of all atoms are thought to spin about an axis, which is randomly oriented in space. When atoms are placed in a magnetic field, the axes of all odd-numbered nuclei align with the magnetic field. The axis of a nucleus deviates away from the magnetic field when exposed to a pulse of radiofrequency electromagnetic radiation oriented at 90 or 180 degrees to the magnetic field. When the pulse terminates, the axis of the spinning nucleus realigns itself with the magnetic field, and during this realignment, it emits its own radiofrequency signal. MRI scanners collect the emissions of individual, realigning nuclei and use computer analysis to generate a series of two-dimensional images that represent the brain. The images can be in the axial, coronal, or sagittal planes. By far the most abundant odd-numbered nucleus in the brain belongs to hydrogen. The rate of

realignment of the hydrogen axis is determined by its immediate environment, a combination of both the nature of the molecule of which it is a part and the degree to which it is surrounded by water. Hydrogen nuclei within fat realign rapidly, and hydrogen nuclei within water realign slowly. Hydrogen nuclei in proteins and carbohydrates realign at intermediate rates. Routine MRI studies use three different radiofrequency pulse sequences. The two parameters that are varied are the duration of the radiofrequency excitation pulse and the length of the time that data are collected from the realigning nuclei. Because T1 pulses are brief and data collection is brief, hydrogen nuclei in hydrophobic environments are emphasized. Thus, fat is bright on T1, and CSF is dark. The T1 image most closely resembles that of CT scans and is most useful for assessing overall brain structure. T1 is also the only sequence that allows contrast enhancement with the contrast agent gadolinium-diethylenetriamine pentaacetic acid (gadolinium-DTPA). As with the iodinated contrast agents used in CT scanning, gadolinium remains excluded from the brain by the blood–brain barrier, except in areas where this barrier breaks down, such as inflammation or tumor. On T1 images, gadolinium-enhanced structures appear white. T2 pulses last four times as long as T1 pulses, and the collection times are also extended to emphasize the signal from hydrogen nuclei surrounded by water. Thus, brain tissue is dark, and CSF is white on T2 images. Areas within the brain tissue that have abnormally high water content, such as tumors, inflammation, or strokes, appear brighter on T2 images. T2 images reveal brain pathology most clearly. The third routine pulse sequence is the proton density, or balanced, sequence. In this sequence, a short radio pulse is followed by a prolonged period of data collection, which equalizes the density of the CSF and the brain and allows distinction of tissue changes immediately adjacent to the ventricles. An additional technique, sometimes used in clinical practice for specific indications, is fluid-attenuated inversion recovery (FLAIR). In this method, the T1 image is inverted and added to the T2 image to double the contrast between gray matter and white matter. Inversion recovery imaging is useful for detecting sclerosis of the hippocampus caused by temporal lobe epilepsy and for localizing areas of abnormal metabolism in degenerative neurological disorders. MRI magnets are rated in teslas (T), units of magnetic field strength. MRI scanners in clinical use range from 0.3 to 2.0 T. Higher field-strength scanners produce images of markedly higher resolution. In research settings for humans, magnets as powerful as 4.7 T are used; for animals, magnets up to 12 T are used. Unlike the well-known hazards of X-irradiation,

exposure to electromagnetic fields of the strength used in MRI machines has not been shown to damage biological tissues. MRI scans cannot be used for patients with pacemakers or implants of ferromagnetic metals. MRI involves enclosing a patient in a narrow tube, in which the patient must remain motionless for up to 20 minutes. The radiofrequency pulses create a loud banging noise that may be obscured by music played in headphones. A significant number of patients cannot tolerate the claustrophobic conditions of routine MRI scanners and may need an open MRI scanner, which has less power and thus produces images of lower resolution. The resolution of brain tissue of even the lowest power MRI scan, however, exceeds that of CT scanning. Figure 5.8-3 reveals that a brain tumor is the cause of a patient’s depression. FIGURE 5.8-3 Three axial images from a 46-year-old woman who was hospitalized for the first time for depression and suicidality following the end of a long-standing relationship. A malignant neoplasm extending into the posterior aspect of the left lateral ventricle is clearly seen in all three images. Images A and B are T1 and T2 weighted, respectively. Image C demonstrates the effects of postcontrast enhancement. (Courtesy of Craig N. Carson, M.D., and Perry F. Renshaw, M.D.) MRI Applications to Dementia. Several MRI changes, including increased number of subcortical hyperintensities, generalized atrophy, and

ventricular enlargement, are associated with normal aging. However, it is well established that some changes seem more specific to the diagnosis of Alzheimer's disease and may be clinically useful in formulating the diagnosis and prognosis of the disorder. MRI evidence of medial temporal lobe (MTL) atrophy appears to be most closely associated with the disorder. One approach that may help to improve the clinical utility of MRI in the diagnosis and prognosis of Alzheimer's disease and other forms of dementia is to follow the rate of change in brain structure over time. Longitudinal follow-up studies have shown the rates of volume loss to be significantly greater in subjects with

prodromal Alzheimer's disease (up to 5 percent brain volume per year) compared with those experiencing normal age-related reductions (0.1 percent brain volume per year). MRI Applications to Alcohol Dependence. MRI studies have been the principal tool to describe in vivo the many sources of neurotoxicity associated with alcoholism, including (1) the direct neurotoxic and gliotoxic effect of ethanol, (2) the neurotoxic effects of poor nutrition that often accompany the abuse of alcohol, (3) the excitotoxicity associated with the ethanol withdrawal state, and (4) the possible disruption in adult-neurogenesis–associated ethanol intoxication and withdrawal. These studies documented a striking age dependence of the overall neurotoxicity associated with alcoholism. Magnetic Resonance Spectroscopy Whereas routine MRI detects hydrogen nuclei to determine brain structure, magnetic resonance spectroscopy (MRS) can detect several odd-numbered nuclei (Table 5.8-1). The ability of MRS to detect a wide range of biologically important nuclei allows the use of the technique to study many metabolic processes. Although the resolution and sensitivity of MRS machines are poor compared with those of currently available PET and SPECT devices, the use of stronger magnetic fields will improve this feature to some extent in the future. MRS can image nuclei with an odd number of protons and neutrons. The unpaired protons and neutrons (nucleons) appear naturally and are nonradioactive. As in MRI, the nuclei align themselves in the strong magnetic field produced by an MRS device. A radiofrequency pulse causes the nuclei of interest to absorb and then emit energy. The readout of an MRS device is usually in the form of a spectrum, such as those for phosphorus-31 and hydrogen-1 nuclei, although the spectrum can also be converted into a pictorial image of the brain. The multiple peaks for each nucleus reflect that the same nucleus is exposed to different electron environments (electron clouds) in different molecules. The hydrogen-1 nuclei in a molecule of creatine, therefore, have a different chemical shift (position in the spectrum) than the hydrogen-1 nuclei in a choline molecule, for example. Thus, the position in the spectrum (the chemical shift) indicates the identity of the molecule in which the nuclei are present. The height of the peak with respect to a reference standard of the molecule indicates the amount of the molecule present. Table 5.8-1 Nuclei Available for In Vivo Magnetic Resonance Spectroscopya

The MRS of the hydrogen-1 nuclei is best at measuring N-acetylaspartate (NAA), creatine, and choline-containing molecules; but MRS can also detect glutamate, glutamine, lactate, and myo-inositol. Although glutamate and γaminobutyric acid (GABA), the major amino acid neurotransmitters, can be detected by MRS, the biogenic amine neurotransmitters (e.g., dopamine) are present in concentrations too low to be detected with the technique. MRS of phosphorus-31 can be used to determine the pH of brain regions and the concentrations of phosphorus-containing compounds (e.g., adenosine triphosphate [ATP] and guanosine triphosphate [GTP]), which are important in the energy metabolism of the brain. MRS has revealed decreased concentrations of NAA in the temporal lobes and increased concentrations of inositol in the occipital lobes of persons

with dementia of the Alzheimer's type. In a series of subjects with schizophrenia, decreased NAA concentrations were found in the temporal and frontal lobes. MRS has been used to trace the levels of ethanol in various brain regions. In panic disorder, MRS has been used to record the levels of lactate, whose intravenous infusion can precipitate panic episodes in about three-fourths of patients with either panic disorder or major depression. Brain lactate concentrations were found to be elevated during panic attacks, even without provocative infusion. Additional indications include the use of MRS to measure concentrations of psychotherapeutic drugs in the brain. One study used MRS to measure lithium (Eskalith) concentrations in the brains of patients with bipolar disorder and found that lithium concentrations in the brain were half those in the plasma during depressed and euthymic periods but exceeded those in the plasma during manic episodes. Some compounds, such as fluoxetine and trifluoperazine (Stelazine), contain fluorine-19, which can also be detected in the brain and measured by MRS. For example, MRS has demonstrated that it takes 6 months of steady use for fluoxetine to reach maximal concentrations in the brain, which equilibrate at about 20 times the serum concentrations.

MRS in Dementia. MRS presents the opportunity to noninvasively obtain measures of several neurochemicals related to neurotransmission, energy metabolism, and cellular function. Studies using MRS have shown a trend for a general reduction in NAA measures with increasing age in MTL and frontal cortical brain regions. The studies in MCI and Alzheimer's disease report patients with these disorders have decreased levels of NAA and increased levels of myo-inositol (a form of inositol normally found in the brain that contributes to osmotic regulation) compared with those of age-matched comparison subjects. MRS in Schizophrenia. MRS has been applied widely in studies of cortical chemistry in schizophrenia. These studies documented reductions in NAA levels in many cortical and limbic brain regions in schizophrenic individuals and smaller reductions in family members of people diagnosed with schizophrenia. Other metabolites have been measured in MRS studies of schizophrenic patients. The most interesting finding may be the description of normal or low levels of glutamate and increased levels of glutamine in medication-free patients with schizophrenia. One preliminary study suggested that glutamine elevations were not present in medication-free patients who were receiving benzodiazepines, drugs that would be predicted to suppress excitatory neurotransmission. MRS in Alcohol Dependence. MRS studies evaluating NAA and choline have provided neurochemical evidence that complements the MRI findings related to the emergence and recovery from alcohol-related neurotoxicity. MRS studies of GABA have provided insights into alterations in cortical inhibitory neurotransmissions associated with the recovery from alcohol dependence. During acute withdrawal, cortical GABA levels appear to be normal. With recovery from alcohol dependence, cortical GABA levels appear to decline and may be significantly below the level seen in healthy subjects with extended sobriety. Functional MRI Recent advances in data collection and computer data processing have reduced the acquisition time for an MRI image to less than 1 second. A new sequence of particular interest to psychiatrists is the T2 or blood oxygen level–dependent (BOLD) sequence, which detects levels of oxygenated hemoglobin in the blood. Neuronal activity within the brain causes a local increase in blood flow, which in turn increases the local hemoglobin concentration. Although neuronal metabolism extracts more oxygen in active areas of the brain, the net effect of neuronal activity is to increase the local amount of oxygenated hemoglobin. This change can be detected essentially in real time with the T2 sequence, which thus detects the functionally active brain regions. This process is the basis for the technique of fMRI. What fMRI detects is not brain activity per se, but blood flow. The volume of brain in which blood flow increases exceeds the volume of activated neurons by about 1 to 2 cm

and limits the resolution of the technique. Sensitivity and resolution can be improved with the use of nontoxic, ultrasmall iron oxide particles. Thus, two tasks that activate clusters of neurons 5 mm apart, such as recognizing two different faces, yield overlapping signals on fMRI and so are usually indistinguishable by this technique. fMRI is useful to localize neuronal activity to a particular lobe or subcortical nucleus and has even been able to localize activity to a single gyrus. The method detects tissue perfusion, not neuronal metabolism. In contrast, PET scanning may give information specifically about neuronal metabolism. No radioactive isotopes are administered in fMRI, a great advantage over PET and SPECT. A subject can perform a variety of tasks, both experimental and control, in the same imaging session. First, a routine T1 MRI image is obtained; then the T2 images are superimposed to allow more precise localization. Acquisition of sufficient images for study can require 20 minutes to 3 hours, during which time the subject's head must remain in exactly the same position. Several methods, including a frame around the head and a special mouthpiece, have been used. Although realignments of images can correct for some head movement, small changes in head position may lead to erroneous interpretations of brain activation. fMRI has recently revealed unexpected details about the organization of language within the brain. Using a series of language tasks requiring semantic, phonemic, and rhyming discrimination, one study found that rhyming (but not other types of language processing) produced a different pattern of activation in men and women. Rhyming activated the inferior frontal gyrus bilaterally in women, but only on the left in men. In another study, fMRI revealed a previously suspected, but unproved, neural circuit for lexical categories, interpolated between the representations for concepts and those for phonemes. This novel circuit was located in the left anterior temporal lobe. Data from patients with dyslexia (reading disorder) doing simple rhyming tasks demonstrated a failure to activate Wernicke's area and the insula, which were active in normal subjects doing the same task (see Color Plate 5.8-4). Sensory functions have also been mapped in detail with fMRI. The activation of the visual and auditory cortices has been visualized in real time. In a recent intriguing study, the areas that were activated while a subject with schizophrenia listened to speech were also activated during auditory hallucinations. These areas included the primary auditory cortex as well as higher-order auditory processing regions. fMRI is the imaging technique most widely used to study brain abnormality related to cognitive dysfunction. fMRI of Dementia. fMRI methods provide information that can potentially be used in the study, diagnosis, and prognosis of Alzheimer's disease and other forms of dementia as well as proving insights into normal age-related changes in cognitive processing. Evidence that aging is associated with weaker and more diffused activations as well as decreased hemispheric lateralization suggests either a compensation for lost regional intensity or a dedifferentiation of processing. The weaker activation, especially prefrontal, suggests potential encoding-stage dysfunctions associated with aging. fMRI

studies have consistently demonstrated that patients with Alzheimer's disease have decreased fMRI activation in the hippocampus and related structures within the MTL during the encoding of new memories compared with cognitively intact older subjects. More recently, fMRI studies of subjects at risk for Alzheimer's disease, by virtue of their genetics or evidence of minimal cognitive impairment, have yielded variable results with some studies suggesting there may be a phase of paradoxically increased activation early in the course of prodromal Alzheimer's disease. fMRI of Alcohol Dependence. fMRI studies have provided insights into the functional consequences of alcoholism-related neurotoxicity. Studies suggest that recovering alcohol-dependent patients show abnormal activation patterns in frontal cortex, thalamus, striatum, cerebellum, and hippocampus related to impairments in attention, learning and memory, motor coordination, and inhibitory

control of behavior. Studies have begun to explore pharmacological modulation of resting circuit activity to probe mechanisms underlying circuit dysfunction in alcoholism, illustrated by blunted responses to benzodiazepines. SPECT Scanning Manufactured radioactive compounds are used in SPECT to study regional differences in cerebral blood flow within the brain. This high-resolution imaging technique records the pattern of photon emission from the bloodstream according to the level of perfusion in different regions of the brain. As with fMRI, it provides information on the cerebral blood flow, which is highly correlated with the rate of glucose metabolism, but does not measure neuronal metabolism directly. SPECT uses compounds labeled with single photon-emitting isotopes: iodine-123, technetium-99m, and xenon-133. Xenon-133 is a noble gas that is inhaled directly. The xenon quickly enters the blood and is distributed to areas of the brain as a function of regional blood flow. Xenon-SPECT is thus referred to as the regional cerebral blood flow (rCBF) technique. For technical reasons, xenon-SPECT can measure blood flow only on the surface of the brain, which is an important limitation. Many mental tasks require communication between the cortex and subcortical structures, and this activity is poorly measured by xenon-SPECT. Assessment of blood flow over the whole brain with SPECT requires the injectable tracers, technetium-99m-D,L-hexamethylpropyleneamine oxime (HMPAO [Ceretec]) or iodoamphetamine [Spectamine]). These isotopes are attached to molecules that are highly lipophilic and rapidly cross the blood–brain barrier and enter cells. Once inside the cell, the ligands are enzymatically converted to charged ions, which remain trapped in the cell. Thus, over time, the tracers are concentrated in areas of relatively higher blood flow. Although blood flow is usually assumed to be the major variable tested in HMPAO SPECT, local variations in the permeability of the blood–brain barrier and in the enzymatic conversion of the ligands within cells also contribute to regional differences in signal levels.

In addition to these compounds used for measuring blood flow, iodine-123–labeled ligands for the muscarinic, dopaminergic, and serotonergic receptors, for example, can be used to study these receptors by SPECT technology. Once photon-emitting compounds reach the brain, detectors surrounding the patient’s head pick up their light emissions. This information is relayed to a computer, which constructs a two-dimensional image of the isotope’s distribution within a slice of the brain. A key difference between SPECT and PET is that in SPECT a single particle is emitted, whereas in PET two particles are emitted; the latter reaction gives a more precise location for the event and better resolution of the image. Increasingly, for both SPECT and PET studies, investigators are performing prestudy MRI or CT studies, then superimposing the SPECT or PET image on the MRI or CT image to obtain a more accurate anatomical location for the functional information (see Color Plate 5.8-5). SPECT is useful in diagnosing decreased or blocked cerebral blood flow in stroke victims. Some have described abnormal flow patterns in the early stages of Alzheimer’s disease that may aid in early diagnosis. PET Scanning The isotopes used in PET decay by emitting positrons, antimatter particles that bind with and annihilate electrons, thereby giving off photons that travel in 180-degree opposite directions. Because detectors have twice as much signal from which to generate an image as SPECT scanners have, the resolution of the PET image is higher. A wide range of compounds can be used in PET studies, and the resolution of PET continues to be refined closer to its theoretical minimum of 3 mm, which is the distance positrons move before colliding with an electron. Relatively few PET scanners are available because they require an onsite cyclotron to make the isotopes. The most commonly used isotopes in PET are fluorine-18 (18F), nitrogen-13, and oxygen-15. These isotopes are usually linked to another molecule, except in the case of oxygen-15 (15O). The most commonly reported ligand has been

[18F]fluorodeoxyglucose (FDG), an analogue of glucose that the brain cannot metabolize. Thus, the brain regions with the highest metabolic rate and the highest blood flow take up the most FDG but cannot metabolize and excrete the usual metabolic products. The concentration of 18F builds up in these neurons and is detected by the PET camera. Water-15 (H215O) and nitrogen-13 are used to measure blood flow, and 15O can be used to determine the metabolic rate. Glucose is by far the predominant energy source available to brain cells, and its use is thus a highly sensitive indicator of the rate of brain metabolism. 18Flabeled 3,4-dihydroxyphenylalanine (DOPA), the fluorinated precursor to dopamine, has been used to localize dopaminergic neurons. PET has been used increasingly to study normal brain development and function as well as to study neuropsychiatric disorders. With regard to brain development, PET studies have found that glucose use is greatest in the sensorimotor cortex, thalamus, brainstem, and cerebellar vermis when an infant is 5 weeks of age or younger. By 3 months of age, most areas of the cortex show increased use, except for the frontal and

association cortices, which do not begin to exhibit an increase until the infant is 8 months of age. An adult pattern of glucose metabolism is achieved by the age of 1 year, but use in the cortex continues to rise above adult levels until the child is about 9 years of age, when use in the cortex begins to decrease and reaches its final adult level in the late teen years. In another study, subjects listened to a rapidly presented list of thematically related words. When asked to recall words in the thematic category that may or may not have been on the list, some subjects falsely recalled that they had heard words that actually were not on the list. By PET scanning, the hippocampus was active during both true and false recollections, whereas the auditory cortex was only active during recollection of words that were actually heard. When pressed to determine whether memories were true or false, subjects activated the frontal lobes. FDG studies have also investigated pathology in neurological disorders and psychiatric disorders. Two other types of studies used precursor molecules and receptor ligands. The dopamine precursor dopa has been used to visualize pathology in patients with Parkinson’s disease, and radiolabeled ligands for receptors have been useful in determining the occupancy of receptors by specific psychotherapeutic drugs. Neurochemical findings from PET radiotracer scan are listed in Table 5.8-2. Table 5.8-2 Neurochemical Findings from Positron Emission Tomography Radiotracer Scans For example, dopamine receptor antagonists such as haloperidol (Haldol) block almost 100 percent of D2 receptors. The atypical antipsychotic drugs block serotonin 5HT2 receptors in addition to D2 receptors; hence, they are referred to as serotonindopamine receptor antagonists. The case study presented illustrates the potential

diagnostic value of three-dimensional PET imaging. Patient A is a 70-year-old man who had gotten more forgetful, to the point that his family was worried about him. The patient’s family was interested in getting a diagnostic workup to evaluate the possible causes for his memory disorder. His PET scan showed that he had functional parietotemporal decrease, which corroborated other neurological evaluations, suggesting that he had Alzheimer’s disease. The patient was treated with tacrine (Cognex) and benefited from some stabilization of his symptoms. (Courtesy of Joseph C. Wu, M.D., Daniel G. Amen, M.D., and H. Stefan Bracha, M.D.) Pharmacological and Neuropsychological Probes With both PET and SPECT and eventually with MRS, more studies and possibly more diagnostic procedures will use pharmacological and neuropsychological probes. The purpose of such probes is to stimulate particular regions of brain activity, so that, when compared with a baseline, workers can reach conclusions about the functional correspondence to particular brain regions. One example of the approach is the use of PET to detect regions of the brain

involved in the processing of shape, color, and velocity in the visual system. Another example is the use of cognitive activation tasks (e.g., the Wisconsin Card Sorting Test) to study frontal blood flow in patients with schizophrenia. A key consideration in the evaluation of reports that measure blood flow is the establishment of a true baseline value in the study design. Typically, the reports use an awake, resting state, but there is variability in whether the patients have their eyes closed or their ears blocked; both conditions can affect brain function. There is also variability in such baseline brain function factors as sex, age, anxiety about the test, nonpsychiatric drug treatment, vasoactive medications, and time of day. REFERENCES Arnone D, McKie S, Elliott R, Thomas EJ, Downey D, Juhasz G, Williams SR, Deakin JF, Anderson IM. Increased amygdala responses to sad but not fearful faces in major depression: Relation to mood state and pharmacological treatment. Am J Psychiatry. 2012;169(8):841. Beck A, Wüstenberg T, Genauck A, Wrase J, Schlagenhauf F, Smolka MN, Mann K, Heinz A. Effect of brain structure, brain function, and brain connectivity on relapse in alcohol-dependent patients. Arch Gen Psychiatry. 2012;69(8):842. Björklund A, Dunnett SB. Dopamine neuron systems in the brain: an update. Trends Neurosci. 2007;30:194. Borairi S, Dougherty DD. The use of neuroimaging to predict treatment response for neurosurgical interventions for treatment-refractory major depression and obsessive-compulsive disorder. Harvard Rev Psychiatry. 2011;19(3):155. Cahn B, Polich J. Meditation states and traits: EEG, ERP, and neuroimaging studies. Psychol Consciousness Theory Res Pract. 2013;1(S):48–96. Fornito A, Bullmore ET. Does fMRI have a role in personalized health care for psychiatric patients? In: Gordon E, Koslow SH, eds. Integrative Neuroscience and Personalized Medicine. New York: Oxford University Press; 2011:55. Holt DJ, Coombs G, Zeidan MA, Goff DC, Milad MR. Failure of neural responses to safety cues in schizophrenia. Arch Gen

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