

FIGURE 1.15-2 A PET scanner consists of a ring of radiation sensors that are designed to detect the simultaneously emitted, characteristically back-to-back (180 degrees apart) dual photons that are created by the annihilation of a positron and an electron. Opposing detectors are electronically coupled to form a coincidence circuit. Thus, when separate scintillation events in paired detectors coincide, an annihilation event is presumed to have occurred at some point along a line connecting the two. This information is registered by a computer and later used to reconstruct images using the principles of computed tomography. (Reprinted with permission from Malison RT, Laruelle M, Innis RB: Positron and single photon emission tomography: Principles and applications in psychopharmacology. In *Psychopharmacology: The Fourth Generation of Progress*, F Bloom, D Kupfer, editors. Raven, New York, 1995.)

then converted into an electrical pulse by an immediately adjacent photomultiplier tube, and the electrical pulse is then registered by the scanner's computer. When the scanner detects two electronic signals from two radiation detectors that coincide (to within 3-10 nsec), an annihilation event is presumed to have occurred at some point along an imaginary line connecting the detectors. In contrast, single events are ignored. Although any two crystal detectors may be activated by coincident photons, the most straightforward conceptual configuration for a PET camera is one in which only opposing detectors are electronically connected. Although it is true that two unrelated photons from spatially separate annihilation events can reach opposing detectors concurrently, such accidental coincidences are much less frequent than true ones. Nevertheless, random coincidences constitute one source of the background noise in PET images.

Because PET detects the site at which a positron annihilates and not the site of its emission, there exists an intrinsic theoretical limit on the spatial resolution of PET. Specifically, a positron generally travels a finite distance before coming to rest in a tissue and colliding with an electron. Thus, an annihilation typically occurs some distance away from the site of radioactive decay. This distance is proportional to the positron's average kinetic energy as it is emitted from the nucleus and is characteristic of the specific isotope employed (Fig. 1.15-1). For example, the range for ^{11}C decay is roughly 2 mm. An additional limitation placed on PET is that sometime photons are emitted at an angle slightly more or less than 180 degrees. This typically occurs if the positron is not entirely at rest when it annihilates. Thus, both remote positron annihilation and photon noncollinearity are factors that theoretically limit PET's achievable spatial resolution (approximately 2 to 3 mm); modern PET instruments fall within this realm.

In the case of SPECT, the opposite occurs. Instead of a proton-rich radionuclide ejecting a positron (i.e., e^+), it captures an orbiting electron (denoted e^-). Once again, the net result is transformation of a proton into a neutron. Most commonly, the radioactive progeny of this process remains in a residually excited, so-called metastable state. With the dissipation of this metastable arrangement, the daughter nucleus achieves a ground state, and a single γ -photon is pro-

duced. Thus, SPECT employs isotopes that decay by electron capture or γ -emission or both, including both 123-iodine (^{123}I) and the long-lived metastable nuclide 99m-technetium ($^{99\text{m}}\text{Tc}$). No comparable theoretical limit on spatial resolution exists for SPECT because the site of γ -emission and the site of radioactive decay are synonymous.

The emission of only a single photon fundamentally distinguishes SPECT from PET and necessitates an intrinsically different approach to ascertaining the origin of a decay event and therefore of camera design. Specifically, SPECT utilizes a method known as *collimation* (Fig. 1.15-3). In a manner analogous to the effects of a polarizing filter for visible light, a collimator is a physical filter that permits only γ -rays of a specific spatial trajectory to reach the SPECT scanner's detector. Most commonly, a collimator is a lead structure that is interposed between the subject and the radiation detector. The collimator contains many holes of sufficiently long and narrow dimension so that only photons of a parallel trajectory are allowed through. In contrast to parallel photons, γ -rays that deviate slightly are absorbed by the lead and go undetected (Fig. 1.15-3). Different collimators (e.g., parallel, fan-beam, and cone-beam) have holes of differing orientations (e.g., perpendicular to the detector, focused in two dimensions, and focused in three dimensions, respectively). Given a known geometric configuration for the specific collimator's holes, the original path of a detected photon is linearly extrapolated. Collimation is less efficient than coincidence detection because many potentially informative photons are lost. However, the sensitivity of SPECT has been largely enhanced by advances in collimator design and an increase in the number of detectors surrounding the body; SPECT is now sufficiently sensitive for routine use in nearly all the same applications as PET.

Image Reconstruction Although the nature of photon emission and detection are different in PET and SPECT, both techniques rely on the same principles of computed tomography when translating information about photon paths into brain images. Briefly, computed tomography is based on the premise that an appreciation of an object's two- or three-dimensional distribution in space may only

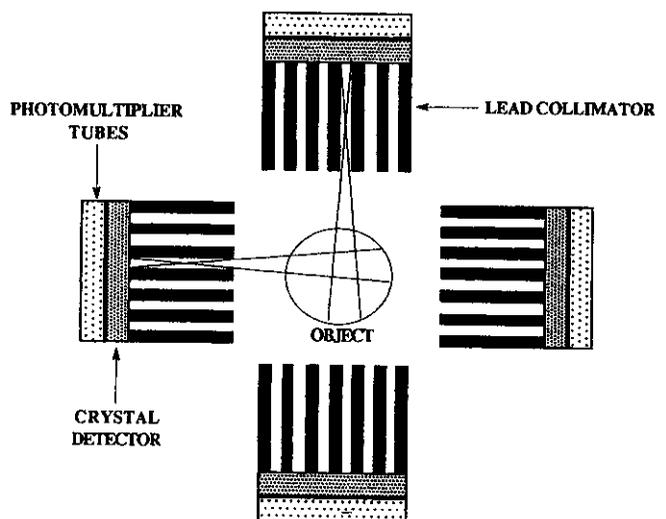


FIGURE 1.15-3 The method of image reconstruction from back projection in SPECT uses a collimator placed between the object and the crystal detector. The area of the object that is viewed by the underlying detector is decreased by having longer and narrower holes in the collimator. By moving the detector-collimator complex around the object, multiple views are obtained and provide the primary data for image reconstruction.

be inferred by viewing it from multiple vantage points. Since information about a photon's direction, not depth, is known, views of photon trajectories from multiple angles around the entire head are required. In PET and SPECT, such a set of measurements from a given angle or viewpoint is referred to as a *projection*. A ring of essentially contiguous radiation detectors in a PET scanner provides multiple projections in this modality. In contrast, SPECT cameras usually rely on several (typically 2 to 4) detector "heads" that rotate around the subject in synchrony, collecting data over 360 degrees. A picture of the distribution of radioactivity within a given brain slice is then inferred by retracing or backprojecting the trajectories (typically thousands) of γ -rays across the field of view for every imaging angle. Conceptually analogous to the simple childhood puzzle in which numbers in a square grid (e.g., 3×3) are inferred from their sums along each row, PET and SPECT images require fast computer coprocessors and efficient mathematical algorithms (fast Fourier transformations) to handle the considerably larger matrices (e.g., 128×128 or 256×256 elements) of radiation density values and the correspondingly more intensive calculations. In this manner, individual radiation values (i.e., counts of detected events) are determined for each cell of the matrix (also known as a *picture element* or *pixel*), corresponding shades of color assigned, and an image of the distribution of radioactivity within the brain produced (Fig. 1.15-4).

Despite its complexity and computational intensity, backprojec-

tion is an imperfect process and introduces known artifacts into the images themselves. As the backprojection algorithm retraces a photon's path, it cannot be sure of the actual point of decay. The algorithm is thus forced to assume an equal probability of radioactive decay and hence of radiation value for every point along the line of trajectory. Areas of the brain in which radioactivity is highly concentrated will stand out as many trajectories from multiple projections are superimposed and their probability values are summed. In the process, however, those areas containing no radioactivity now bear the statistical imprint of the algorithm's guess. Thus, small but finite values are ascribed to areas where none should exist. By increasing the density of spatial sampling through greater numbers of projections, the impact of these spurious values on image quantitation can be minimized but not eliminated. Therefore, a filter is still required to restore quantitative accuracy to images by "erasing" counts in those areas that should have none. Several filters have been developed (e.g., Ramp, Butterworth, and Hanning) in an effort to overcome these limitations, and these techniques remain the mainstay of the field of image reconstruction. Trade-offs exist with respect to the relative impact of filters on spatial resolution and noise amplification, and filter selection depends on the imaging context. Alternative reconstruction methods (e.g., restorative and iterative techniques) are the current focus of much research, and simple filtered backprojection is likely to be superseded by more quantitatively accurate methods in the near future.

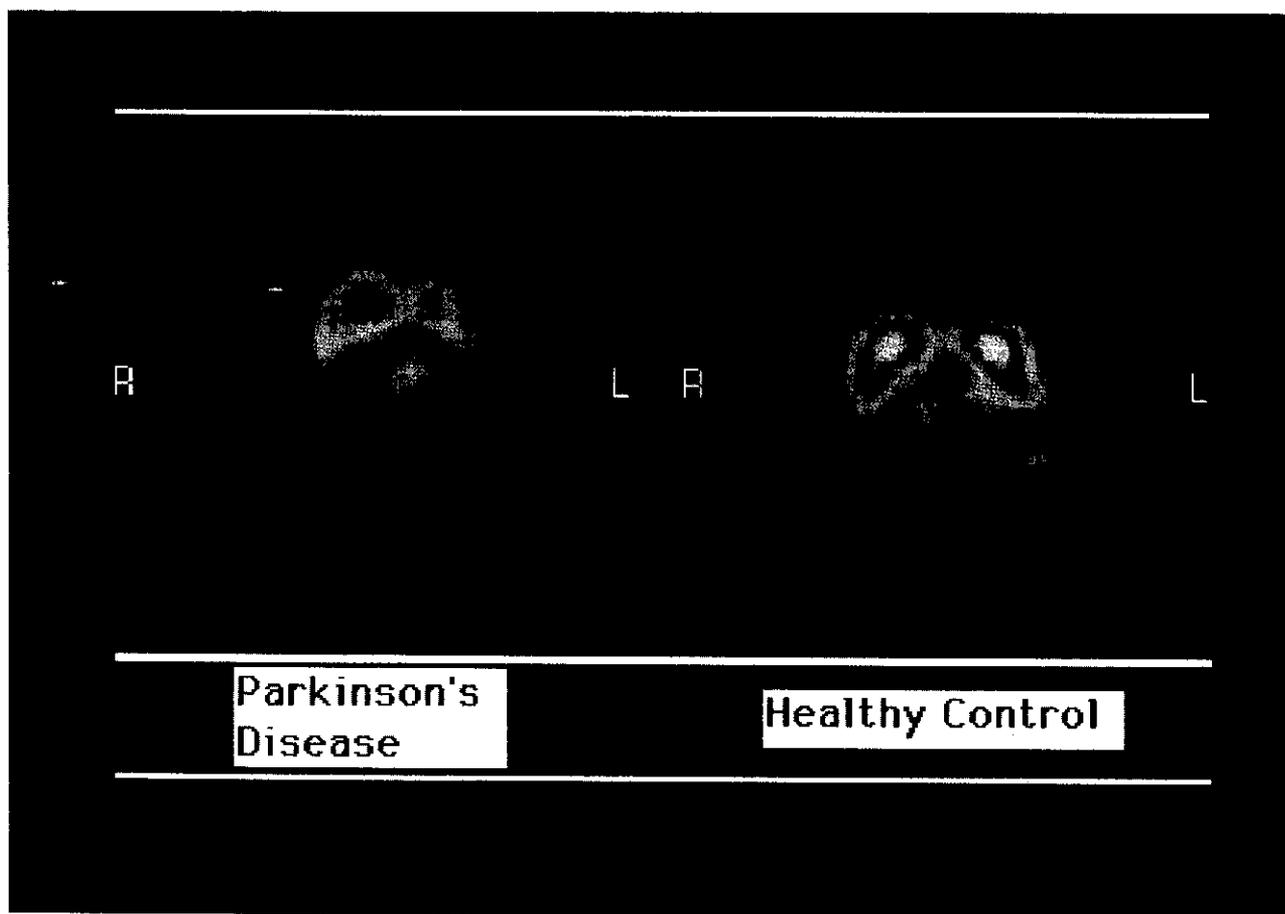


FIGURE 1.15-4 SPECT images of the distribution of $[^{123}\text{I}]\beta\text{-CIT}$ (cocaine-iodo-tropine) in a healthy subject and a patient with Parkinson's disease. $[^{123}\text{I}]\beta\text{-CIT}$ is a radiolabeled cocaine analogue and is a probe of dopamine transporters in the striatum. These transporters are located presynaptically on terminals of dopamine neurons projecting from the substantia nigra to the striatum. These transverse images show a high density of dopamine transporters in striatum and a marked reduction of these sites in an age- and sex-matched patient with idiopathic Parkinson's disease. The transporters are lost because the entire dopaminergic neuron, including its terminal projections in the striatum, degenerate in this disorder. (Courtesy of John Seibyl, Yale University.) (See Color Plate 1.)

Factors Affecting Image Quantitation Several physical factors affect the quantitative accuracy of PET and SPECT images. Among these are the statistics of radioactive decay, photon scatter, limited spatial resolution, and partial volume effects.

Statistics of Radioactive Decay Mathematically, radioactive decay is described by an exponential curve. The rate at which a specific radionuclide decays is expressed in terms of its radioactive half-life, or $T_{1/2}$ value, a parameter defined as the time required for half of the radioactive atoms to decay. Values of $T_{1/2}$ vary between species and are characteristic of a given nuclide. The characteristic $T_{1/2}$ values of several commonly used PET and SPECT isotopes are listed in Figure 1.15-1. Although a given isotope's half-life is constant, the nature of radioactive decay is intrinsically statistical. This phenomenon is most readily conceptualized by imagining an isotope of infinite half-life (i.e., unchanging levels of radioactivity). In struggling to measure the precise amount of radioactivity during a fixed period of time, variations in the individually recorded values invariably result. Only by taking the statistical average of multiple measurements is the true amount of radioactivity (and $T_{1/2}$ value) inferred. The variation in sampling derives from the intrinsic probabilistic nature (mathematically described by a Poisson distribution) of radioactive decay and the random fluctuation in individual decay events from moment to moment, and it occurs irrespective of detection method.

The manifestations of this effect are most readily appreciated by imaging an object which contains a uniform concentration of radioactivity. The swiss cheese appearance of the resulting images is the spatial equivalent of this temporal variation in PET and SPECT images. The probabilistic inaccuracies (or statistical noise) introduced is by virtue of its random nature easily surmountable through the collection counts. Longer sampling times and greater instrument sensitivity are the principle ways in which counting statistics are improved. Longer acquisition times improve statistical noise at the expense of temporal resolution. Conversely, increased sensitivity (e.g., larger collimator holes in SPECT) are traded for poorer spatial resolution (because slightly less than parallel photons are detected).

Photon Attenuation Although the high energies of photons emitted by PET and SPECT nuclides enable their penetration of brain structures, a significant number of γ -rays escape detection by both types of scanners based on their interactions with surrounding tissues. These interactions fall into two general categories—Compton scattering and photoelectric absorption. In *Compton scattering*, a collision occurs between the photon and an atomic electron. The photon is deflected from its original trajectory and, in the process, loses a fraction of its original energy. Alternatively, in *photoelectron absorption*, the photon's energy is completely absorbed by the atom, and an electron may be ejected from its orbit. For this reason, γ -radiation is said to be ionizing.

Because the chances of scatter or absorption decrease with increasing photon energy and increase with distance, photon attenuation is both energy- and depth-dependent. On both counts, PET has distinct advantages. Since photons in PET have higher energies (i.e., 511 keV) than those in SPECT (typically 80 to 160 keV), they are less prone to attenuation (Fig. 1.15-1). Moreover, linear attenuation is largely depth independent in PET because of coincidence detection. Nevertheless, activity at the brain's center is disproportionately underestimated (roughly fourfold to fivefold) in comparison to its surface for both PET and SPECT. Compensating for undetected photons is therefore crucial for comparing radioactive densities in different brain regions. The most commonly employed method with

SPECT is uniform attenuation correction. In *uniform attenuation correction*, an ellipse is fitted to the brain's contour and the same attenuation value (typically equal to that of water) is assigned to all points within the ellipse. A commonly used method for attenuation correction in PET (and with some recent SPECT devices) is *nonuniform attenuation correction*, which relies on a preceding transmission study similar to a computed tomography (CT) scan. An external source of radiation is transmitted through the subject's head, creating a precise attenuation map for that individual. Because the sizes and shapes of patients' heads vary and because the attenuation properties of bone, tissue, fluid, and air differ, such an approach has clear theoretical advantages. Although commercially available PET and SPECT scanners now support this technology, the conditions under which nonuniform methods offer clear advantages over uniform approaches remain to be established for practical brain-imaging applications.

Photon Scatter In both PET and SPECT, instrumentation and image reconstruction are based on the underlying assumptions that detected photons retain their linear paths. However, Compton effects cause photons to deviate from their original trajectories. Although these photons lose energy to atoms in the tissue, many scattered photons retain sufficient energy to enable their escape from the brain. The detection of scattered events therefore leads to errors in image reconstruction as a result of false assumptions about the photon's original path. Much like accidental coincidences, scattered photons increase the background noise and compromise image contrast.

Because radionuclides emit photons of a known energy, scattered photons may be distinguished from true ones by the loss of energy they sustained from collisions with electrons. In an attempt to exploit this principle, PET and SPECT cameras measure the energy spectrum of their detected photons. In practice, however, accurately discriminating between true and scattered photons is often difficult because the energy resolution of current PET and SPECT scanners is limited. Also, the photopeak energies of true photons are not identical, but rather normally distributed about a mean value. Thus, scattered and photopeak photons inevitably overlap in their energy distributions. Current algorithms that subtract a *scatter fraction* from the photopeak counts are an attempt to compensate for this problem; however, these methods have obvious limitations. As for attenuation correction, advances in scatter correction offer the promise of incorporating *a priori* information about the head's structure and density in achieving more faithful image reconstruction.

Spatial Resolution In contrast to the fine visual detail seen in magnetic resonance images, pictures created using SPECT and PET appear blurred. The visual sense of imprecision is the qualitative consequence of limited spatial resolution. Equally important, however, is the quantitative impact of finite resolution on the measured radioactivity in individual brain regions. The latter partial volume effects have important consequences for image quantitation and require a clearer understanding of spatial resolution and its definition.

In PET and SPECT, spatial definition is defined in practical terms, the distance by which two objects must be separated to perceive them as discrete (Fig. 1.15-5). In a SPECT or PET camera with perfect resolution, a point source of radioactivity would be depicted as a vertical line of infinitely narrow width. In such an ideal device, two point sources could be distinguished from each other as long as they were not superimposed. In the real world, however, PET and SPECT scanners perceive the radioactivity from such a point source as a Gaussian curve and the radioactivity from the point is spread out. This *point spread function* characterizes a camera's resolving capacity. The spatial diffusion of imaged radioactivity is expressed

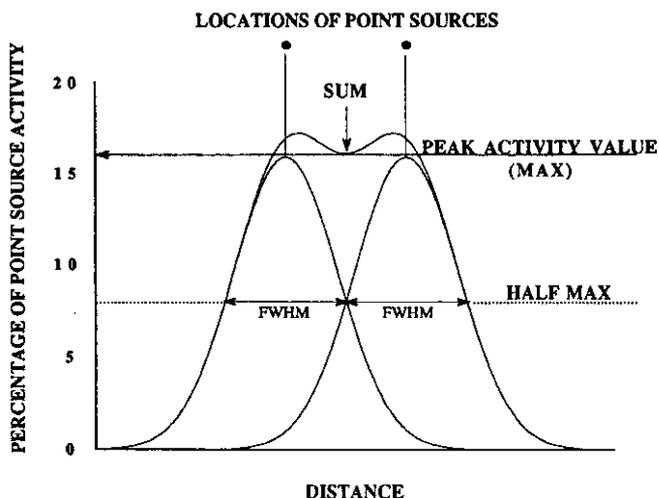


FIGURE 1.15-5 The limited resolution of PET and SPECT cameras blurs the activity of single point sources into adjacent regions with no activity. Viewed in just one dimension, a point source is visualized by the camera as a gaussian curve. Resolution is defined as the width of the curve at half maximum measured peak levels (FWHM). For two point sources of equal intensity separated by a distance equal to the FWHM of the camera, the sum of the activities begins to show a modest decrease at the midpoint. Thus, two point sources separated by a minimum distance equal to the FWHM will begin to appear as two separate points rather than just one.

in terms of the *full-width-at-half-maximum* (FWHM), or the width of the Gaussian curve at half of the curve's peak activity. The FWHM is the parameter most commonly used to define resolution in emission tomography because this is the distance at which the peaks of both sources become distinguishable from one another (Fig. 1.15-5).

Excluding issues of positron range, image resolution is primarily influenced by issues of instrumentation. For example, the precision of collimation, the number and size of detectors, and the accuracy with which scintillation events are localized within the crystalline elements all contribute to limited spatial resolution. In the case of PET, state-of-the-art devices have yielded resolutions close to the theoretical limits of accuracy (3 mm). However, the average PET and SPECT camera is currently capable of 5 to 6 mm and 7 to 9 mm FWHM, respectively.

Partial Volume Effects In the simplest terms, partial volume effects create one of two problems for image quantitation: the appearance of radioactivity where there was none, and the impression of less radioactivity than truly exists. For example, just as the brightness in a part of a room depends on the intensity and distance separating two lamps, so too will the measured radioactivity in a given brain region reflect the relative activity and proximity of nearby structures. Thus, brain regions with relatively lower concentrations of radioactivity will appear "hotter" in PET and SPECT images as imaged activity "spills over" from adjacent (more active) areas. Conversely, as the size of a radioactive region becomes smaller than two to three times the FWHM resolution, true activity is effectively diluted by nonradioactive areas within the field of resolution. In the latter case, regions containing equal concentrations of radioactivity will appear to have declining levels with decreasing size. Metaphorically speaking, together these two effects result in sharp peaks and steep canyons of brain activity being rendered as short hills and shallow valleys in PET and SPECT images.

Several approaches are currently taken to compensate for errors resulting from limited spatial resolution and partial volume effects. One method attempts to simulate errors created by partial volume effects by creating a plastic model or phantom. Models can be designed to approximate the structures or activity distributions of interest in the brain. For example, finely machined, polycarbonate brain phantoms are commercially available and can recreate the geometry of gray and white matter. Once imaged, regionally specific correction factors, or *recovery coefficients*, are derived that relate units of measured activity to known activity. Such methods, however, are unable to account for inter-subject variations in brain anatomy, whether pathological or nonpathological. For this reason, researchers are now beginning to use structural information (e.g., CT or MRI scans) to quantify functional information. More specifically, partial volume errors may be mathematically compensated for by registering subjects' MRI scans with their own PET or SPECT scans and incorporating a priori functional (e.g., relative blood flow ratios in gray and white matter) and physical information (e.g., a PET or SPECT camera's three-dimensional point spread function). The latter approach is more complicated than the former but has obvious advantages for conditions such as Alzheimer's disease, in which cortical atrophy is present.

Radiopharmaceuticals The versatility and sensitivity of PET and SPECT arise largely from the ability of talented radiochemists to synthesize a radiopharmaceutical of high chemical purity, high radioactive yield, and small mass dose. Expressed differently, in order to ensure that a specific biological system of interest is adequately measured yet unperturbed by the tracer, high purity and high specific activity (expressed in units of radioactivity per chemical quantity: Ci/mmol) are paramount. However, the physical nature of radioactive decay and the short half-lives of most suitable radionuclides (Fig. 1.15-1) constantly challenge the radiochemist's efforts. Chemical yield generally improves with increasing reaction times; however, radioactivity and specific activity diminishes with increasing decay times. Thus, an optimal synthetic scheme is a balanced one in which chemical yield is maximized, radioactive byproducts are minimized, and the final product is capable of prompt purification. Given the high affinity of many radiopharmaceuticals (e.g., neurotransmitter receptor ligands) for their physiological targets, specific activities of greater than 2000 Ci/mmol are generally required. Most radiopharmaceuticals are still manually prepared by radiochemists racing against the clock of a nuclide's decay; however, a limited number of radiochemical syntheses are now automated and performed in robotically controlled hot cells (e.g., [^{18}F]-2-fluoro-2-deoxyglucose; [^{18}F]FDG).

In the case of positron-emitting radionuclides (e.g., ^{15}O , ^{13}N , ^{11}C , and ^{18}F), the particularly short half-lives (2, 10, 20, and 109 minutes, respectively) have special implications for the design of PET imaging facilities. Most PET centers have an on-site cyclotron that generates radionuclides for "real-time" utilization. An exception to this is ^{18}F , whose nearly 2-hour half-life permits a "local" regional facility to produce quantities for large metropolitan centers. The significant expense of a cyclotron (typically \$1 to \$2.5 million) and its highly skilled support staff are relative disadvantages for PET. In contrast, SPECT isotopes like $^{99\text{m}}\text{Tc}$ ($T_{1/2} = 6$ hours) may be obtained from inexpensive molybdenum generators located in many hospital radiopharmacies. Alternatively, ^{123}I has a sufficiently long half-life (13 hours) to permit centralized production at distant (>3000 miles) commercial reactors. The radionuclide may then be delivered via overnight express mail and still meet the radiochemical needs of high specific activity.

The choice of a candidate molecule for radiopharmaceutical development depends primarily upon the physiological process under

investigation. In the case of regional cerebral blood flow, relatively nonspecific and often nonorganic, diffusible tracers may be employed (e.g., the gaseous tracer ^{133}Xe). In contrast, the measurement of aspects of brain neurochemistry require much greater biochemical selectivity. Thus, PET and SPECT radiopharmaceuticals are most often naturally occurring substances, structural analogues, or ligands that selectively label a particular brain target. In this regard, PET has significant advantages over SPECT because ^{11}C can be directly substituted for ^{12}C in existing organic molecules without altering their intrinsic biochemical properties. Alternatively, fluorine is frequently substituted for native hydrogen atoms without significant isotopic effects (e.g. [^{18}F]FDG). In contrast, SPECT nuclides (i.e., ^{123}I and $^{99\text{m}}\text{Tc}$) are uncommon elements of organic substrates. The metallic nature and multiple valence states of $^{99\text{m}}\text{Tc}$ necessitate bulky complexing groups for its molecular stabilization. These barriers have largely limited the initial uses of $^{99\text{m}}\text{Tc}$ to nonselective processes (e.g., the blood flow agent [$^{99\text{m}}\text{Tc}$]-hexamethyl propyleneamine oxime; [$^{99\text{m}}\text{Tc}$]HMPAO). However, in 1997, $^{99\text{m}}\text{Tc}$ -labeled probes of the dopamine transporter were developed, and SPECT imaging has demonstrated appropriate labeling in human and monkey brain. Extension of these efforts is certain to result in the development of many other $^{99\text{m}}\text{Tc}$ -labeled probes in the future.

Many ^{123}I -containing radiopharmaceutical agents have been developed as a result of rapid advances in iodide metallation procedures and increasing knowledge of the structure-activity relationships of pharmacologically active compounds. The lipophilic nature of ^{123}I may actually facilitate transfer across the blood-brain barrier and, in some instances, improve affinity of the parent compound at its site of action. In particular, SPECT imaging of brain receptors and uptake sites with ^{123}I -containing radiopharmaceuticals is routine at several university medical centers.

Successful *in vivo* radiopharmaceuticals must fulfill several stringent pharmacokinetic criteria. Because a radiopharmaceutical must easily enter the brain, tracer binding to plasma proteins must be readily reversible, and its transport across the blood-brain barrier must be favorable. Although some tracers (e.g., [^{18}F]FDG) may have facilitated carriers, most ligands must be sufficiently lipid-soluble to permit passive diffusion across the blood-brain barrier. However, as the tracer's lipophilicity increases, its "signal-to-noise" properties may be degraded because nonspecific binding increases. Thus, lipophilicity (nonspecific binding) and affinity (specific binding) are important factors influencing an imaging agent's signal-to-noise ratio. Lastly, tracer metabolism may also limit a ligand's *in vivo* utility. For example, rapid degradation, lipophilic radioactive metabolites, and pharmacologically active metabolites may all confound central measurements.

Safety With regard to studies in humans, PET and SPECT methods give rise to similar safety concerns for radiation exposure and pharmacological toxicity of the injected radiopharmaceutical. The radiation exposures from typical PET and SPECT scans are thought to be reasonably safe within the context of the present knowledge of radiation biology. The Food and Drug Administration (FDA) has established limits of radiation exposure to various organs of the body and to the body as a whole, these limits are applied to research studies and are often lower than exposures in routine clinical nuclear medicine procedures. Although the FDA limits are presently thought to provide adequate safety, the long-term biological effects of ionizing radiation are an area of active investigation and even controversy. The estimation of the dose received by the body depends on multiple factors (including the amount of activity, the type of emission, and the residence time in the body), but the shorter half-lives of PET

radionuclides and the higher sensitivity of the method generally yield lower radiation burdens than did a comparable SPECT study. A useful guideline is to employ doses of radiotracer that are "as low as reasonably allowable" to provide useful results.

Fortunately, the pharmacological toxicity of radiopharmaceuticals is usually not a significant issue. The sensitivity of functional imaging is so high that minuscule mass doses of compound may be injected, although that small mass is associated with significant levels of radioactivity. For example, some radiopharmaceuticals are injected at mg/kg doses that are a millionfold lower than the minimal dose required to have any pharmacological effect. In such situations no pharmacological toxicity would be expected and only an unusual immunological adverse effect could be anticipated. Nevertheless, the potential pharmacological effects and toxicity of radiopharmaceuticals needs to be evaluated relative to previously established criteria for nonradioactive pharmaceuticals. The final formulation of any radiotracer must meet established guidelines for purity, sterility, and lack of pyrogenicity.

RESEARCH APPLICATIONS

The uses of PET and SPECT brain imaging can be roughly divided into measurements of local neuronal activity, neurochemistry, and *in vivo* pharmacology.

Local Neuronal Activity Local neuronal activity is associated with energy consumption and can be directly measured with glucose metabolism or indirectly with cerebral blood flow. Local cerebral blood flow is coupled with glucose metabolism and neuronal activity via mechanisms that are not completely elucidated. PET tracers for measurement of local neuronal activity include [^{18}F]FDG (fluoro-deoxyglucose for glucose metabolism) and [^{15}O]H₂O (blood flow). SPECT does not have a comparable tracer for glucose metabolism but does have $^{99\text{m}}\text{Tc}$ - and ^{123}I -labeled agents, as well as ^{133}Xe to provide measures of blood flow.

Neuronal metabolic demands are believed to primarily reflect terminal rather than cell body activity. In any given volume of brain, the majority of [^{18}F]FDG uptake is believed to be in terminals rather than in cell bodies, a conclusion that is based upon a limited number of studies in which the cell bodies are anatomically distant from their terminals. Metabolic rate will not distinguish activity of excitatory and inhibitory neurons. Although increased [^{18}F]FDG uptake is usually interpreted as increased functional activity of a region, it may reflect an overall decreased activity based upon increased firing of inhibitory interneurons.

The clinical uses of PET and SPECT imaging to measure local neuronal activity are largely restricted to neurological disorders and include localization of cerebral ischemia, localization of epileptic foci, and distinguishing radiation necrosis from tumor growth. These imaging results can directly impact clinical care. For example, the neurosurgical treatment of patients with medically refractory epilepsy critically depends upon accurate localization of the seizure focus, which is often distant from the surface of the brain and poorly localized by scalp electrode EEG. The seizure focus is hypometabolic with decreased blood flow during the interictal period, but is hypermetabolic with increased blood flow during the ictal period. PET and SPECT imaging has been used either as a primary means of localization or as a confirmation of other diagnostic tests to select the portion of the brain that is subsequently resected.

PET imaging using [^{15}O]H₂O has been elegantly combined with neuropsychological activation studies to localize cognitive and sensory functions, including reading, speaking, word associations, visua

identification, and spatial localization. The short half-life of ^{15}O ($T_{1/2}$ of 2 minutes) allows multiple (often 8 to 10) bolus injections of the tracer in one experimental session. Thus, both baseline scans and those following neuropsychological tasks can be repeated and averaged.

Recently developed techniques in functional fMRI offer great promise to provide measures of local neuronal activity similar to that from PET and SPECT imaging. The primary signal from functional MRI is believed to derive from the concentration of deoxyhemoglobin. Functional MRI is superior to PET and SPECT in that it involves no radiation exposure and has greater temporal (<1 second) and spatial (<1 mm) resolutions. If these methods are fully developed with adequate quantitation, they may supplant PET and SPECT for measures of local neuronal activity.

Neurochemistry Two major attributes of both PET and SPECT are high sensitivity and chemical selectivity, both of which are critically important for *in vivo* neurochemical measurements. The sensitivity of PET and SPECT to detect radiotracers is less than 10^{-12} M, which is several orders of magnitude greater than that of nuclear magnetic resonance (NMR) methods. "Sensitivity" refers to the minimal concentration of the target compound that can be reliably measured. For example, the minimal concentration of [^{11}C]chlorpromazine that can be measured with PET in the human brain within a reasonably acceptable imaging time (e.g., 15 to 30 minutes) is less than 10^{-12} mol. In contrast, the minimal concentration of γ -aminobutyric acid (GABA) that can be measured with MRS is about 10^{-4} mol.

In a manner exactly analogous to nonradioactive drugs, radiotracers that label specific target sites in the brain can be developed. These specific tracers can thereby provide measures of multiple neurochemical pathways in the brain, including synthesis and release of transmitters, receptors, reuptake sites, metabolic enzymes, and possibly even second messenger systems. Of these multiple neurochemical systems in the brain, the greatest effort has been devoted to imaging of dopaminergic transmission; it is an example of the types of measurements provided by these methods.

Synthesis 6- ^{18}F Fluoro-L-3,4-dihydroxyphenylalanine (^{18}F -FDOPA) has been successfully used in animal and human studies to provide a measure of dopamine terminal innervation of the striatum. These studies have demonstrated decreased striatal uptake in parkinsonian patients as compared to healthy subjects. Furthermore, these studies have questioned the widely held notion that symptoms develop only after 85 to 90 percent depletion of endogenous dopamine levels. Imaging studies of patients with early signs of the disorder suggest that symptoms may begin with only a 50 to 60 percent decrease in striatal dopamine terminal innervation.

Release A potential method for the measurement of transmitter release involves the displacement of receptor radiotracers by the endogenous transmitter. On first consideration, this displacement may seem impossible because the endogenous transmitter tends to have a much lower affinity than the tracer for the receptor. For example, [^{11}C]raclopride has a IC_{50} value (concentration of drug required to occupy 50 percent of sites) for the dopamine type 2 (D_2) receptor of approximately 1 nM. In contrast, the IC_{50} value for dopamine itself may be as high as 1 μM . How then could dopamine effectively compete with [^{11}C]raclopride for binding to the D_2 receptor? Differ-

ent affinities, which are inversely related to IC_{50} , will influence the speed at which equilibrium is achieved. However, after equilibrium is achieved, dopamine demonstrates effective competition with high-affinity tracers. In an equilibrium state, if the displacer dopamine is present at a concentration equal to its IC_{50} value, then 50 percent of receptors will be occupied by the drug and 50 percent of the radioligand (which is associated with only tracer receptor occupancy) will be displaced. Thus, the real questions of feasibility will be determined by physiological concentrations of dopamine in the synapse, the *in vivo* inhibition constant (K_i) of dopamine for the receptor, and whether adequate time has elapsed to establish equilibrium binding conditions. Several investigators have provided evidence from *in vivo* labeling studies in rodents that both the resting levels of synaptic dopamine and stimulant-induced dopamine release are associated with significant D_2 receptor occupancy, which is mirrored by comparable displacement of radiotracer from the receptor. Recent PET and SPECT D_2 receptor imaging studies in humans and monkeys have been combined with a pharmacological challenge of dextroamphetamine (Dexedrine), which causes a massive release of dopamine into the synapse. The release of dopamine can be monitored by displacement of tracer binding to the D_2 receptor. These studies have shown that the amount of displacement in healthy subjects is correlated with psychological reports of activation and feeling high. Similar studies in patients with schizophrenia have shown that the amount of dopamine released is two and a half times higher and that the amount of the release is correlated with a transient increase in positive symptoms. These dopamine receptor imaging studies combined with amphetamine challenge have provided further evidence of dopamine playing a role in psychotic symptoms.

Receptors Receptor studies have probably received the greatest effort among the various targets of neurochemical imaging. If a receptor is selectively altered in a specific disease, then imaging of this site may provide diagnostic information about the disorder. For the dopamine receptor system, the Johns Hopkins PET group has reported that drug-naïve schizophrenia patients have an elevation of D_2 receptor density in the striatum of two and a half times as measured by the virtually irreversible tracer [^{11}C]N-methylspiperone and kinetic modeling. In contrast, the PET group at the Karolinska Institute, Sweden has reported normal levels of D_2 receptor densities in drug-naïve schizophrenia patients using the reversible radiotracer [^{11}C]raclopride and an equilibrium approach. Reasons for these disparate results have been investigated but remain disappointingly elusive. Elevated D_2 receptors are certainly not a *sine qua non* of schizophrenia but may be associated in an as yet unknown way with aspects of psychosis in subsets of patients. Research imaging of the D_2 receptor has more recently focused on the interaction with synaptic dopamine, both basal levels and stimulant-induced release.

Transporters The transporter is located presynaptically on terminals of dopamine projections from substantia nigra to striatum. Thus, the transporter is a marker for dopamine terminal innervation, which is decreased in patients with idiopathic Parkinson's disease. Several radiotracers for the dopamine transporter have been developed: [^{11}C]cocaine, [^{11}C]methylphenidate, [^{11}C]CFT (also designated WIN 35,428), and [^{123}I] β -CIT (also designated RTI-55). The striatal uptake of both [^{11}C]CFT and [^{123}I] β -CIT have recently been shown to be markedly decreased in patients with Parkinson's disease in comparison to healthy subjects of similar mean age (Fig. 1.15-4). Imaging with these tracers may be useful research tool for early diagnosis and for monitoring the progression of the disorder.

Metabolism The fate of a neurotransmitter can be studied by injection of selective inhibitors of the catabolic enzymes. For example, selegiline (Edepryl) is an irreversible inhibitor of monoamine oxidase (MAO) type B, and imaging with ^{11}C -labeled selegiline has been reported to provide a measure of regional enzyme activity in the brain. PET scanning with [^{11}C]selegiline may provide useful dosage-response measurements in patients treated with MAO inhibitors (MAOIs). Furthermore, reversible MAOIs such as [^{11}C]Ro 19-6327 may have advantages relative to the irreversible agents in terms of data analysis and ease of performing in vivo occupancy studies.

In Vivo Pharmacology Since receptors are frequently the targets of therapeutic medications, several investigators have argued that receptor imaging may be used to monitor drug treatment more accurately than is possible with measurement of plasma levels of the medications. However, the rationale for this argument is flawed from a theoretical perspective. Under steady-state conditions achieved with long-term treatment, the level of free (i.e., not protein bound) drug in plasma should be in equilibrium with the free level of drug in the extracellular space of the brain. Thus, under steady-state conditions there is little apparent value in performing expensive neuroreceptor imaging studies instead of simple measurements of the free level of drug in plasma. However, for non-steady-state conditions (e.g., beginning or discontinuing treatment), receptor imaging can provide valuable kinetic information. The brain uptake and washout of many psychoactive agents can be markedly delayed compared to a rapid peak and fast clearance of the drug from plasma. For example, the maximal brain uptake of the potent cocaine analogue cocaine-iodo-tropane occurs about 12 hours after intravenous administration as compared to plasma levels, which peak at 2 minutes. In addition, significant D_2 receptor occupancy has been reported to last for several weeks following discontinuation of antipsychotic agents, even when plasma levels are almost undetectable.

Several pharmaceutical companies and academic researchers have begun to explore the role of receptor imaging in new drug development. The two basic methods are the radiolabeling of the target compound (e.g., with ^{11}C) or the in vivo screening of the effects of the intravenously administered nonradioactive compound with previously developed radiotracers. An example of the first method would be the use of ^{11}C -labeled fluoxetine (Prozac); an example of the second method would be the use of nonradioactive fluoxetine to interact with a different radiolabeled probe (e.g., [^{11}C]citalopram) for the 5-HT transporter. The first method is probably better suited to PET radiochemistry, which can more easily provide a pharmacologically identical radiolabeled form of the target compound than SPECT, which would probably use an iodinated analogue. However, the second method may be equally well performed with PET or SPECT provided that an appropriate radiotracer has been developed for each method.

Brain imaging studies of antipsychotic medications provide an example of the advantages and limitations of the PET and SPECT methods. Several pharmaceutical companies are trying to develop so-called atypical medications like clozapine (Clozaril) and risperidone (Risperidone) that would have superior efficacy and fewer adverse effects than older antipsychotic medications. Studies with [^{11}C]clozapine have been relatively disappointing because of the high non-specific uptake of the radioactivity. These results may prove to be typical, since only a small percentage of potential compounds prove to be useful in vivo radiotracers with low nonspecific binding. Studies of nonradioactive antipsychotic medications with established and selective receptor tracers have provided valuable information on the receptor occupancy profiles and the pharmacokinetics of brain up-

take. For example, researchers have shown that, in comparison to several typical antipsychotic medications, clozapine is associated with a disproportionately high occupancy of D_1 relative to D_2 receptors. Novel therapeutic compounds could be examined for both the pharmacokinetics of entry into the brain and their receptor occupancy profiles, which will provide the combined effect of the parent compound and any active metabolites; this potential application is receiving growing attention.

SUGGESTED CROSS-REFERENCES

Brain-imaging techniques, including electroencephalography and magnetoencephalography, are discussed in Section 1.16. Neuroimaging in clinical practice is discussed in Section 2.13, and neuroimaging in geriatric assessment is discussed in Sections 51.2e and 51.2f. The other sections of Chapter 1 discuss related neural sciences, particularly Section 1.2 on functional neuroanatomy and Section 1.14 on applied electrophysiology.

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▲ 1.16 Principles of Neuroimaging: Magnetic Resonance Techniques

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Most atoms have a nuclear magnetic moment. A strong external magnetic field will align the magnetic moment of atoms along the axis of the magnetic field. The magnetic moment of atoms aligned with a strong external field can be deflected off axis by a radiofrequency pulse at the *nuclear resonant spin frequency* or *Lamour frequency*. In turn, a detectable radiofrequency signal will be generated by the realignment of magnetic moments with the external magnetic field once the radiofrequency pulse is turned off. The detection of this signal forms the basis of all magnetic resonance experiments. In *magnetic resonance imaging* (MRI), magnetic field gradients are used to encode the locations from which these radiofrequency signals arise. In *magnetic resonance spectroscopy* (MRS), slight differences in the resonance frequencies of particular atoms in different molecular environments can be used to measure the concentrations of specific neurochemicals.

Once the magnetic moment of an atom has been deflected off the axis of the main magnetic field, it will return to its equilibrium orientation. The rate at which the magnetic moment returns to equilibrium is described by two relaxation time constants. The realignment of atomic spins with the external magnetic field is characterized as T1 (spin-lattice) relaxation; T2 relaxation describes the rate at which the coherence of the magnetization decays after an initial radiofrequency pulse deflects the spins off axis. In MRI, images may be collected using different acquisition parameters and the resulting images may be described as being either T1- or T2-weighted.

MRI first became available for clinical studies in the 1980s and

allows for detailed in vivo study of brain structure. Today, the use of MRI to rule out overt structural changes in the brain resulting from neurological illness remains the only agreed-upon clinical use for any magnetic resonance technique in the practice of psychiatry.

Magnetic resonance spectroscopy constitutes a second group of relevant magnetic resonance techniques. The first magnetic resonance experiments involved the spectroscopic detection of MRS signals from in vitro samples more than 50 years ago. At the present time, both in vitro and in vivo MRS experiments are feasible, and clinical scanners may be used to measure the concentration of many molecules in virtually any organ system based on the detection of radiofrequency signals from magnetic resonance-visible nuclei (Table 1.16-1). An example of an in vitro application would be the study of extracts from frozen brain tissue. In vivo MRS studies to evaluate human neurochemistry typically exploit the magnetic properties of the principle isotopes of hydrogen (^1H or proton) or phosphorus (^{31}P) atoms. Proton MRS can provide information about the concentration of several neurochemicals in tissue, including *N*-acetyl aspartate (NAA), an established neuronal marker. Phosphorus MRS provides data about the concentration of bioenergetic phosphates such as phosphocreatine (PCr) and adenosine triphosphate (ATP) in the brain. Finally some MRS-visible atoms like fluorine (^{19}F) and lithium (^7Li) are found in the molecular structure of psychotropic medications, that is, fluoxetine (Prozac) and lithium (Eskalith), respectively, and the concentration of these medications and their metabolites may be determined spectroscopically.

Since the late 1980s ultrafast scanning techniques such as echo planar imaging that allow the collection of complete image planes in less than 100 ms have become clinically available. It has been demonstrated that by exploiting the high-temporal resolution of these methods, it is possible to construct images that are sensitive to changes in regional cerebral metabolism. This family of MR techniques is often referred to as *functional MRI* (fMRI). Current interest in fMRI methods for psychiatric research reflects the opportunity to probe brain activity in vivo without the need for ionizing radiation. Repeated studies of individual subjects, as well as studies of women and children, are now feasible. Additionally, there will be widespread availability of fMRI because every high-field MRI scanner can be equipped with a high-speed imaging coil.

Clinical MRI, MRS, and fMRI have evolved as separate disciplines. The rate of technical development continues at a rapid pace. Improvements in signal-to-noise ratios continue, not only with the fast scanning techniques, but with the introduction of human magnets that operate at higher field strengths, such as 3 or 4 tesla. And, unlike other neuroimaging techniques, the end of this evolution is not in sight, suggesting that MRI may eventually dominate psychiatric neuroimaging in a way that could not have been imagined only a short time ago.



Table 1.16-1
Relative NMR Sensitivities

Nucleus	Spin Quantum Number	NMR Frequency at 10 kG (Mhz)	Relative Sensitivity at Constant Field
^1H	1/2	42.58	1.00
^{19}F	1/2	40.05	0.83
^7Li	3/2	16.55	0.29
^{23}Na	3/2	11.26	0.09
^{31}P	1/2	17.25	0.06
^{13}C	1/2	10.71	0.02
^{39}K	3/2	1.99	0.0005