Part I
Imaging Techniques

1 PET and SPECT

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Introduction

Nuclear medicine is a medical imaging subspecialty that uses administered radioactive materials to create images that assist in the diagnosis and treatment of disease. Positron emission tomography (PET) and single photon emission computed tomography (SPECT or SPET) are tomographic nuclear medicine techniques commonly used to diagnose malignant, inflammatory, degenerative and circulatory disorders.

Tomography is an imaging approach that involves reconstruction of a dataset into three-dimensional (3D) images. It allows higher contrast and improved visualization of structures that would obscure each other on planar images, such as superimposed lung, heart and thoracic spine on a conventional chest X-ray. Tomography first came into widespread use using X-rays in computed tomography (CT). The principle of tomography is now used in most 3D medical imaging techniques.

Both PET and SPECT use cameras to detect photons emitted by the radioactive decay of unstable isotopes, which can be radioactive elements themselves, radioactive isotopes synthesized into molecules of interest or radioactive isotopes attached to molecules, to create functional images. These radioactive materials are called *radiotracers* because they are able to trace processes of interest without perturbing the processes being followed. PET and SPECT differ in the type of isotopes they require, the way they detect the emitted signals and the way the data are reconstructed into images. SPECT is technically simpler, less expensive and has lower spatial and temporal resolution than PET. A forensic practitioner can encounter PET and SPECT scans introduced as evidence of abnormal brain function at various stages of legal proceedings.

A chemical element is defined by two parameters: atomic number and atomic mass. Atomic number is the number of protons present in an element and determines the chemical properties of that element. The number of protons and electrons in a given element are fixed. Atomic mass is the total mass of protons, neutrons and electrons in a single atom of a given element. The atomic mass can change based on the number of neutrons.

Atomic mass and atomic number are denoted in superscript and subscript, respectively before the capital letter that signifies the element. For example, $^{18}_{9}$F is an isotope of fluorine with an atomic mass of 18 and an atomic number of 9. Atomic mass can also be listed after the symbol of an element. For example, ^{18}F can also be denoted F-18 or Fluorine-18.

Neuroimaging in Forensic Psychiatry: From the Clinic to the Courtroom, First Edition. Edited by Joseph R. Simpson.

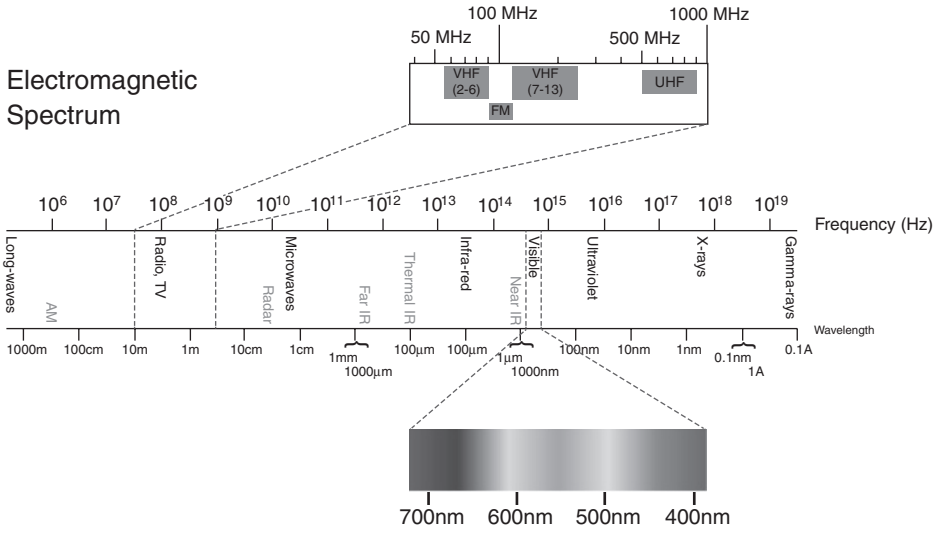

Figure 1.1 Electromagnetic spectrum. Images prepared by Ms. Sherry Wang.

Isotopes are atoms of the same chemical element that differ in the number of neutrons contained in their nuclei, which changes their atomic mass. The nucleus of the atom is made up of protons, which have positive charge, and neutrons, which have no charge. Because the positively charged protons repel each other, it takes a great deal of energy to hold the nucleus together. Further, it requires a delicate balance between the number of neutrons and the number of protons in a nucleus for that nucleus to remain intact. If a nucleus has too many or too few neutrons to remain intact, it is called *unstable* or *radioactive*.

Radioisotopes are unstable isotopes of chemical elements that become more energetically stable through the release of energy or particles (called *radioactive decay*). This radiation can be released in multiple forms including: α-particles, which are equivalent to He^{2+} helium nuclei and include two protons and two neutrons; β^- particles, which are electrons and allow a proton to convert to a neutron; β^+ particles, also called positrons, which are exactly the same physically as β^- particles except they have a positive charge (and form the basis for PET imaging); and γ-rays, which are high-energy photons physically the same as X-rays except that they originate from the nucleus whereas X-rays originate from the electron shell, and the range of γ-ray energies goes higher than that for X-rays, as shown in Figure 1.1 [1] Alpha and β^- particles typically travel a distance of microns to millimeters in tissue, making them difficult to detect externally, whereas γ-rays travel at the speed of light and are very likely to exit the tissue where they can be detected. Positrons (β^+ particles) have a very interesting fate: when a positron is ejected from the nucleus it briefly combines with an electron to form a quasi-atom called a positronium. However, this construct is unstable and lasts a tiny fraction of a second. The positron and electron then annihilate (that is, they both cease to exist) and their energy is released in the form of light. Specifically, the annihilation results in exactly two photons with 511 keV of energy moving in opposite directions. While there is a wide range of possible mechanisms for radioactive decay, each specific isotope has a characteristic mode or modes of decay.

Radioactive decay is an exponential process, meaning that for a given isotope there is a characteristic period of time during which one half of the atoms will undergo decay. This

is known as the *half-life* ($t_{1/2}$). Half-lives of known isotopes can range from fractions of a second to thousands of years, but almost all medically useful isotopes have half-lives in the range of minutes to days, with the most commonly used having half-lives from about 2 to 6 hours. For example, the half-life of ^{14}C, which is used in carbon dating, is 5730 years, which makes it excellent for estimating the age of pre-historic specimens but undesirable for most types of clinical imaging, whereas ^{18}F has a half-life of 110 minutes and decays by positron emission, making it ideal for PET imaging. In addition to the half-life of the isotope itself, called the *physical half-life*, when the isotope is given to a patient in some chemical form, that molecule may also be excreted from the body at some rate, called the *biologic half-life*. The effective half-life is the rate at which the radioactivity disappears from the body and is a combination of the physical decay and the excretion. For example, a radioactive molecule that has little or no excretion from the body will have an effective half-life very similar to the physical half-life, whereas a radioactive molecule that is very quickly excreted will have a very short effective half-life even if the physical half-life is very long. Because it is a combination of physical and biologic clearance from the body, the effective half-life is never more than the shorter of the physical or biologic half-life.

PET radiochemistry

Radioisotopes used in clinical PET are energetically unstable forms (isotopes) of the main elements found in the body – carbon (C), oxygen (O) and nitrogen (N). The natural concentrations of those isotopes are extremely low, so they must be artificially generated in a cyclotron. In nuclear medicine, *radioligands* are molecules that carry the radioactive isotopes to their targets in the body. The process of inserting a radioactive isotope into a biologically active molecule is called *radiolabeling*.

Simple molecules normally used by the body, such as glucose, water or ammonia, as well as more complex molecules such as a substrate for the dopamine transporter [1, 2], can be used as radioligands. An isotope combined with a ligand is called a radiotracer or a radiopharmaceutical, which is administered to the patient.

Fluorine-18 (^{18}F) is the isotope most commonly used in clinical PET due to its many advantageous properties [3]. The $t_{1/2}$ of ^{18}F is 110 minutes, which is long enough to transport it over relatively long distances from the production site, but brief enough to limit radiation exposure from isotope remaining in the body after the scan. Moreover, radiolabeling glucose with ^{18}F by substituting the hydroxyl group in a regular glucose molecule to create the radioligand 2-deoxy-2-(18F)-fluoro-D-glucose (^{18}FDG) is a reliable and well-established process accessible to most qualified radiochemists. ^{18}FDG is a glucose analog that is taken up by brain cells like regular glucose, but it neither undergoes oxidative metabolism (glycolysis) nor is it released back into the circulation.

Other elements used in brain PET are significantly more difficult to use. For example, ^{15}O has a half-life of just over two minutes, making on-site production essential for ^{15}O (H_2O) PET. Moreover, since ^{15}O is used to label water, it provides information on regional brain blood flow, which is similar to what can be obtained by certain types of SPECT and MRI scans at much lower cost and technical complexity. While O-15 H_2O PET studies were critical in the early days of brain-imaging research, and data obtained with it may still be encountered in court, it is difficult to justify its clinical use today. Likewise, ^{13}N and ^{11}C have short half-lives of 10 and 20 minutes respectively and have higher energy.

Table 1.1 Half-lives and energy of the main isotopes used in PET

Isotope	$t_{1/2}$ (minutes)	Energy (kiloelectron volts)
^{11}C	20.4	960
^{15}O	2.07	1190
^{18}F	109.7	640
^{13}N	9.96	1720

Ionizing radiation deposits energy into tissues that is measured in joules/kg, a unit also known as a sievert (Sv). Table 1.1 lists the half-life and energy of the main isotopes used in PET.

SPECT radiochemistry

SPECT radioligands come in two general categories: brain blood flow tracers and molecular probes of brain receptors and neurotransmitters. The latter category is not yet commonly seen in forensic practice. Effective half-life of the radioligand is determined by the half-life of the radiotracer used to label it and the elimination rate of the biologically active compound that carries it.

Compounds used for SPECT are typically low-molecular weight and lipophilic, allowing them to easily cross the blood–brain barrier [4]. The blood flow (perfusion) tracers are distributed in the brain in accordance with regional blood flow over a known period of time, usually measured in minutes, providing an average image of brain perfusion over a fixed time period of a few minutes. SPECT image acquisition is timed to begin at the end of the estimated 'distribution time' of the radioligand.

The gamma ray-emitting radioligand most commonly used in brain SPECT is technetium-99m (^{99m}Tc) [5]. ^{99m}Tc is produced from molybdenum-99 (^{99}Mo), which itself has a half-life of 66 hours, making it easy to generate. ^{99m}Tc derived from ^{99}Mo is delivered on a weekly basis to most clinical nuclear medicine departments. ^{123}Iodine (^{123}I) is a SPECT radioisotope that used to be popular in perfusion SPECT [6]. While ^{99m}Tc has a half-life of six hours and emits a photon that has energy of 140 keV, ^{123}I has a distribution time of about one hour, half-life of 13 hours and a 159 keV photon. These characteristics make I-123 inferior to Tc-99 in brain perfusion SPECT [3].

Radiation exposure

Because the energy released by radioactive decay can cause ionization of molecules in living tissues, it is called *ionizing radiation*. The gray (Gy) is the SI unit of absorbed radiation dose, defined as the deposition of one joule of energy in one kilogram of tissue. The ionizations from radiation deposition can cause a range of effects, which are termed biological toxicity. Toxic effects may include: single-stranded DNA breaks, which can be repaired; double-stranded DNA breaks, which are lethal to the cell; and DNA base mutations, which can be carcinogenic. Biological toxicity varies both with the type of radiation and with the organ being exposed to the radiation. For example, the bone marrow and gonads are much more sensitive to the effects of ionizing radiation than brain tissue. Further, α-particles are far more likely to cause cell death than γ-rays. In order to be able

to compare radiation doses from different sources to different organs, a weighted quantity called the *effective dose* is used. The effective dose is expressed in SI units as sieverts (Sv) but in the US is still frequently reported in units of roentgen equivalent man (rem) or in millirem (mrem), which is one thousandth of a rem [7].

Rem and millirem can be converted in a straightforward way to the SI unit, sievert:

$$1 \text{ rem} = 0.01 \text{ Sv} = 10 \text{ mSv} = 10\,000 \ \mu\text{Sv}$$
$$1 \text{ millirem} = 0.00001 \text{ Sv} = 0.01 \text{ mSv} = 10 \ \mu\text{Sv}$$

Ionizing radiation is present in space and is attenuated, but not completely eliminated, by Earth's atmosphere. In addition, naturally radioactive isotopes are present in different concentrations in our environment. For example, Radon (Rn) has 36 radioactive isotopes with atomic masses ranging from 193 to 228 and is a common source of naturally occurring exposure to ionizing radiation. Thus, we are constantly exposed to low levels of radioactivity.

The average person in the U.S. receives an effective dose of about 3.6 mSv of radiation per year from naturally occurring materials and cosmic radiation. Due to reduced atmospheric protection, people are exposed to an additional 5 μSv of cosmic radiation per hour on an airplane flight at the common altitudes of 30 000 feet and higher.

In the U.S., the Occupational Safety and Health Administration (OSHA) limits workplace exposure to 50 mSv per year for non-pregnant adults with occupations involving radioactive materials. For minors working in or near radioactive materials, the limit is 5 mSv per year. For people of any age not working in occupations involving radiation, the limit is 1 mSv per year. The National Council on Radiation Protection and Measurements (NCRP) sets guidelines for pregnant workers [8]. The radiation dose to the embryo/fetus resulting from occupational radiation exposure to the mother should not exceed 5 mSv from the time when the pregnancy is declared to the radiation safety monitoring staff at the place of work until delivery. Women who may become pregnant should limit their occupational radiation dose to no more than 2.5 mSv per month, so if a pregnancy is confirmed, the total radiation dose received by the embryo/fetus during the first two months would not exceed the 5 mSv fetal dose limit. The council advises that pregnant workers should avoid or reduce radiation exposure in the workplace [8].

Doses of radiation below 1 Sv are unlikely to produce any immediate detectable changes in humans, though they have risk of inducing mutations which may lead or predispose to cancer formation at a later time. 1–2 Sv will cause illness but will rarely be fatal. Acute full body exposure of 5 Sv will kill 50% of people exposed, and doses that exceed 10 Sv are always fatal.

A PET scan of the brain with ^{15}O water exposes the subject to 1 mSv of radiation. In comparison, a SPECT scan with ^{99m}Tc HMPAO delivers 6.9 mSv of radiation. A whole body ^{18}FDG PET is associated with 7–14 mSv of radiation, depending on dose and technique. Thus, radiation exposure from any single nuclear medicine scan is far below levels associated with known harm and should not present a risk of any immediate radiation-induced illness. A single nuclear medicine scan is significantly below the annual limits for persons with occupational exposure to radiation, but clearly above the recommended limits for people not working with or near radioactive materials. There is also a lifetime limit. With an increasing number of scans in a single patient, an increase in cancer risk can be expected and should be included in risk/benefit ratio considerations. While the risk

of cancer induction from ionizing radiation from diagnostic imaging studies is real (and unnecessary exposures should be avoided), it is impossible to accurately estimate the risk from a given scan, though the risk is certainly very low. Therefore, diagnostic radiation exposures should be avoided if unnecessary, but useful studies should not be withheld due to giving too much weight to the risks of the radiation exposure.

A number of routine clinical procedures can be employed to minimize the patient radiation dose from PET or SPECT studies. Patients are requested to empty their bladder prior to injection with the tracer and again after the study to minimize radiation exposure to the urinary bladder, which is the organ that receives the largest radiation dose from many agents used.

While it is not possible to estimate an individual's risk of cancer related to a single PET or SPECT scan, the population-based increase in cancer risk has been estimated for the use of CT scanners. A recent study estimated that CT scanner use in the U.S. would expose patients to enough ionizing radiation to induce 1.5% to 2% of future cancers [9]. A second study estimated that development of cancer from CT scan exposure will vary widely depending on the specific type of CT examination and the patient's age and sex. According to this study, an estimated 1 in 270 women who underwent CT coronary angiography at age 40 years will develop cancer from that CT scan (1 in 600 men), compared with an estimated 1 in 8100 women who had a routine head CT scan at the same age (1 in 11 080 men). For 20-year-old patients, the risks were approximately doubled, and for 60-year-old patients, they were approximately 50% lower [10]. However, these estimates derive from mathematical models and have not been verified with empiric evidence. Furthermore, the lifetime risk of developing malignancy is so high (on the order of 1 in 2), that detecting an additional 1 in 270 risk above that high level would require an impossibly large sample size.

Currently, it is unknown whether increased use of nuclear medicine studies will one day be associated with actual increases in population-based cancer risk. To avoid unnecessarily increasing cancer incidence in future years, every clinician must carefully assess the expected benefits of each PET and SPECT scan ordered for forensic purposes and fully inform forensic evaluees of the known risks of radiation.

Physics of PET and SPECT signals

For both PET and SPECT scans, the radioactive tracer is almost always injected into a peripheral vein after placement of an intravenous line. Therefore, patients must be able to tolerate an intravenous line access. Once injected, the tracer distributes in the body based on its uptake, delivery, metabolism and excretion properties. In some cases, imaging is done during the distribution time to evaluate the kinetics of distribution, but in most cases, the patient waits in a basal state, sitting or lying quietly in a dimly lit room, during distribution and is imaged once the patient is at or near steady state. Distribution time varies based on the tracer. Some tracers take hours to distribute, whereas others distribute within minutes. After injection of a SPECT tracer a patient may wait in a waiting room or may leave and return to the clinic in time for the scheduled scan. In contrast, patients awaiting PET are typically isolated after injection to minimize radiation exposure to staff and the public as photons emitted after positron decay are much higher than those from ^{99m}Tc SPECT tracer decay: 511 keV versus 140 keV respectively. After the tracer has distributed, the patient is positioned in the scanner.

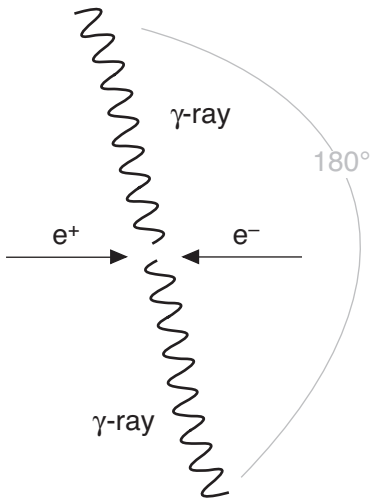

Figure 1.2 The annihilation process. Images prepared by Ms. Sherry Wang.

Though both PET and SPECT utilize photons emitted during nuclear decay for image formation, they differ in the source and nature of these photons. In SPECT, a single photon is emitted in the decay of ^{99m}Tc and detected by two or three gamma cameras rotating around the patient [11]. With PET, the process is more complicated. PET isotopes undergo radioactive decay via a process known as positron emission or positive beta decay. During this decay a positron and a neutrino are emitted from the radiotracer. The emitted positron travels through the tissue, until it collides with a random electron and both are annihilated (Figure 1.2). The distance the positron travels before annihilation depends on the positron energy (Table 1.1); the lower the energy, the less distance traveled. For ^{18}F, the positron range is less than 2 mm. The higher the positron energy, the farther the positron will travel before annihilation, and therefore the more uncertainty there is in where the positron actually originated, ultimately leading to lower spatial resolution. Therefore, lower energy positron emitters provide higher resolution imaging. During annihilation, two gamma-rays with energy of 511 keV are released in opposite directions at a 180° angle from each other and are detected by the PET scanner cameras that are arranged in a stationary ring around the patient. Below we will review separately how SPECT and PET scans capture, count the photons and turn data into images yielding important information about brain function.

SPECT image generation

The simplest form of photon tomography is rotational SPECT. This approach uses a single gamma camera rotating around a stationary patient in a circular or elliptical orbit. Most modern SPECT scanners are equipped with two or three cameras, reducing the time of acquisition and the distance each camera must travel around the patient for each image [12].

The rotation of the SPECT camera head subjects the SPECT system to forces not encountered in other tomographic systems. Thermal, magnetic and gravitational forces must be accounted for in the SPECT scan design.

Data acquisition for SPECT

Unlike in PET scans, the tracer used in SPECT emits gamma radiation that is measured directly by a scintillation counter also known as a *gamma camera*. The camera is made up of a collimator, a crystal and an array of photomultiplier tubes. The collimator, in most cases, is a block of lead with an array of parallel holes. These holes are perpendicular to the crystal and they allow only the photons that are perpendicular to the crystal to pass. The collimator design ensures that the scintillation camera records only the photons that come directly from the patient. However, a limitation of this design is that only a limited number of photons are actually detected, increasing the image noise and the image formation time [13]. The crystal is a material that emits flashes of visible light known as *scintillations* when high-energy X-ray or γ-ray photons strike it. The most commonly used gamma camera crystals today are sodium iodide crystals doped with thallium [14]. The light emitted by the scintillator hits the surface of the nearest photomultiplier tube. The photomultiplier tube converts a flash of light into an electrical signal that allows measurement of the energy of the incoming γ-ray. The array of photomultiplier tubes utilizes a method called Anger logic to accurately localize the point where the incident γ photon struck the crystal.

A series of images are produced as the cameras move around the patient and record data from multiple angles. Most SPECT scans use a 'stop and shoot' technique in which the camera briefly pauses at multiple steps in the orbit to allow for data recording. A 360-degree arc is usually needed to acquire an adequate image. The camera typically pauses to shoot an image every 3–6 degrees. The more angles obtained by the camera, the better the resolution of the image.

SPECT spatial resolution is approximately one centimeter using typical clinical instrumentation. The total scan time is typically around 20 minutes. Patient motion and the amount and specific activity of the radiopharmaceutical affect image quality [14]. Whereas longer imaging times give more data, reducing image noise, the longer the scan the more likely the patient is to move, which degrades the image significantly. While immobilization devices can be used to attempt to minimize patient motion, they are of limited effectiveness. Most patients cannot reliably keep their head still for longer than 20–30 minutes, so imaging times longer than this are usually counterproductive. In some patients, particularly those with neurologic or psychiatric disorders, even 20–30 minutes is difficult to achieve without motion. Periodic coaching and encouragement by the imaging team can help prevent patient motion.

Image reconstruction

In SPECT a number of corrections must be made for background and physical effects. First, the projection images need to be corrected for non-uniformity and axis-of-rotation misalignment. Once these corrections, which are beyond the scope of this chapter, are applied, the multiple projection images are reconstructed to form a three-dimensional image. The simplest reconstruction technique is filtered backprojection, which, for example, is routinely used to create X-ray computed tomography (CT) images. However, for images which have relatively low counts, filtered backprojection results in three-dimensional images that have many 'streaky' artifacts. Another approach, called *iterative reconstruction*, starts with a filtered backprojection image then uses mathematical models to essentially guess at a better solution. Doing multiple iterations of the algorithm arrives at a closer solution to how the image should appear. While iterative reconstruction is computationally demanding, modern computers permit its use and the gains from iterative reconstruction

have resulted in its almost entirely displacing filtered backprojection of SPECT image reconstruction.

The attenuation of γ rays by the tissues is a more significant issue for body imaging, but it affects brain SPECT and PET as well [15]. Attenuation leads to significant distortion of the true relationship between the raw image and imaged activity, such as blood flow. For example, a γ-ray originating in the center of the body may be absorbed or scattered along its way to the detector; in comparison a γ-ray originating at the tissue periphery is more likely to reach the detector because it is less likely to be absorbed or scattered as it travels a shorter distance to the detector. In the brain this can be seen in γ-rays originating in subcortical structures such as the putamen when compared to γ-rays originating in the cortex.

Methods for attenuation correction are the subject of continuous development and are outside the scope of this chapter. Briefly, attenuation correction requires an estimate of the relative density of the tissues of the imaged organ. This is achieved either by performing an additional scan using X-rays or by mathematically estimating the attenuation. Equipment for such a transmission scan is often incorporated into the nuclear medicine system. Some modern SPECT and PET scanners are integrated with an X-ray CT scanner that forms the attenuation map of the tissues. This map is then used to mathematically correct the raw SPECT or PET image for attenuation and used for additional anatomical information, if desired.

Reconstructed images typically are 64×64 or 128×128 pixels, with the pixel sizes ranging from 3–6 mm. In general, the resulting reconstructed images will be of lower resolution, have increased noise compared to planar images and be susceptible to artifacts. While SPECT scans are clearly inferior to PET scans in terms of image resolution, they are able to demonstrate brain function, are typically admitted in court and are less costly than PET scans. Furthermore, most SPECT scans have lower radiation dose to the patient and are more widely available than PET scans. Finally, spatial resolution is a description of how far apart two points need to be for them to be seen as two separate points rather than a conglomerate single point. For many imaging scenarios, spatial resolution is critical in determining whether a finding is seen. However, in some cases with nuclear imaging, the question is only whether there is binding of the radiotracer or not and in these cases, lower spatial resolution does not preclude excellent sensitivity.

Clinical uses of SPECT scans

The primary clinical use of brain SPECT with ^{99m}Tc-based blood flow ligands is to assist in the diagnosis and evaluation of cancer and neurodegenerative diseases. However SPECT is generally inferior to MRI for these applications. ^{99m}Tc-TRODAT-1 (TRODAT), a relatively inexpensive technetium-labeled dopamine transporter ligand, is one of the few clinically available tracers unique to SPECT that is superior to other modalities in the diagnosis of Parkinson's disease [16]. However, TRODAT SPECT is not yet generally clinically accepted. If a forensic practitioner chooses to use a modality that is not generally accepted by the medical community, he or she may face an evidentiary challenge. Recently, a related ^{123}I-labeled compound, ^{123}I-Ioflupane has been granted FDA approval for differentiation of essential tremor from Parkinsonian syndromes, which will strengthen the utility of such a study for forensic indications.

PET and SPECT also have a role in the evaluation of mild traumatic brain injury [17]. There is also significant optimism about the clinical potential of such nuclear medicine techniques in addiction, psychopathy, autism, paraphilias, psychoses and mood disorders; several of these applications are discussed elsewhere in this volume. Ordering

a nuclear medicine study to generate evidence supporting any of these diagnoses in court, however, is a controversial issue that thus far lacks a consensus approach. Despite this lack of consensus on clinical indications, nuclear imaging is becoming an important element in forensic evaluations of brain-based disorders.

Forensic uses of SPECT scans

SPECT scans are commonly utilized in so-called *toxic tort* cases, in which a plaintiff claims brain damage due to chemical exposure, as well as in personal injury litigation, such as in a claim of brain damage following an automobile accident. Many plaintiffs have been successful in introducing SPECT scans into evidence even when admissibility was subject to a *Daubert* or other scientific evidentiary challenge.

SPECT scans have been used to demonstrate the presence of brain injury. In *Rhilinger v. Jancsics et al*. SPECT imaging was admitted into evidence in a case considering whether Ms Rhilinger sustained brain injury after exposure to fumes emanating from chemicals stored in the basement of her apartment building [18].

The court stated that there was no dispute that SPECT scans show abnormalities in brain function. Nor is there a dispute that SPECT scans cannot conclusively establish the existence or non-existence of toxic solvent encephalopathy in a patient. The judge emphasized that the plaintiff's experts did not opine that the SPECT scan did, in fact, establish the diagnosis of toxic solvent encephalopathy, but was a tool that could be used to investigate this claim.

Likewise in *Fini v. General Motors Corp, et al*. the court concluded that the use of SPECT may have important implications for classification and management of patients with mild head trauma, such as closed head injury, providing 'clinical correlation' for the physical examination [19]. In Ms Fini's case, SPECT was used to show 'massive frontal lobe brain damage' sustained in a motor vehicle accident.

In contrast, in *Summers v. Missouri Pacific Railroad System*, the court did not admit a SPECT scan into evidence in a Federal Employers Liability Act (FELA) case where plaintiffs were passengers on a train where diesel exhaust fumes entered the cabin of the train. The plaintiffs were diagnosed with an injury to the central nervous and respiratory systems that the physician termed 'chemical sensitivity.' The court noted a lack of reliable scientific and medical data to support the use of SPECT technology to diagnose neurotoxic exposure and excluded the scan from evidence. This evidentiary exclusion of SPECT was primarily due to the court's skepticism of a related, controversial disease entity termed multiple chemical sensitivity (MCS) [20].

SPECT scans have been used as mitigating evidence in criminal trials for capital murder. In *Smith v. Mullin*, 379 F.3d 919 (2004), the court ordered a re-sentencing hearing for Mr Smith, a man found guilty and sentenced to death for murdering his wife and her four children from a prior relationship [21]. The court found that the defendant was prejudiced by his counsel's failure to present evidence of his cognitive abilities and brain damage. The court noted that evidence of his brain damage was shown in SPECT scans authorized by the court but not raised by counsel in the original trial.

SPECT has also been used in at least one case to prove 'diminished actuality' (similar to diminished capacity) in a California murder trial [22]. Mr Peter Chiesa was a 65-year-old man with multiple medical problems including vascular dementia, epilepsy, strokes and a history of complicated coronary artery bypass surgery. Chiesa called 911 informing police of his plan shortly before he shot and killed two female neighbors in 2002. The defense used a SPECT scan to illustrate to the jury how Mr Chiesa's brain was 'misshapen' and

'contained holes' to argue against a pre-meditated first-degree murder charge. Despite the evidence of the 911 call, the jury convicted Chiesa of two counts of second-degree murder, rather than first-degree (i.e., premeditated) murder [23].

PET methodology

As described in prior sections, the PET tracer undergoes positron emission decay (beta decay) resulting in the production of two photons, which are γ-rays, traveling at a 180-degree angle away from each other. Like SPECT, PET uses a crystal scintillator to detect the γ-rays. However, in PET, hundreds or thousands of small crystals are formed into a ring that surrounds the patient. Typically, the scanner ring has an opening of 60–85 cm and the crystal ring is typically 15–24 cm wide, which is sufficient to image the entire brain at one time. There are dedicated brain-imaging instruments with scanner openings large enough only for the head. Because the incident photons in PET have higher energy than those used in SPECT, the crystals need to have higher density so that the photons will deposit their energy in the crystal and cause scintillation. The most commonly used PET crystals are bismuth germanate (BGO), lutetium oxyorthosilicate (LSO) and yttrium-doped lutetium oxyorthosilicate (LySO); the latter two have much faster light output, permitting greater sensitivity. Most modern scanners utilize LSO or LySO crystals. Unlike SPECT, PET does not use a collimator to block off angles photons, though the crystals are coupled to PMTs. Like in SPECT, the PMTs (Figure 1.3) are able to multiply the incident energy on the order of 10^6, allowing the solitary flash of light to be converted to a measureable electrical current [24].

One example of a PET detector design is made up of 64 individual elements, each $4 \times 4 \times 30$ mm in size, coupled to four 3/4"-diameter photomultiplier tubes, and is capable of high spatial resolution of approximately 3 mm [25]. The spatial resolution in most modern PET scanners is around 5 mm after adjusting for all factors that influence resolution. A typical set of images from an ^{18}FDG-PET of the brain is shown in Figure 1.4.

Rather than using physical collimators, PET imaging is based on collimating with time. That is, each PET scanner (Figure 1.5) contains an extremely precise clock allowing a

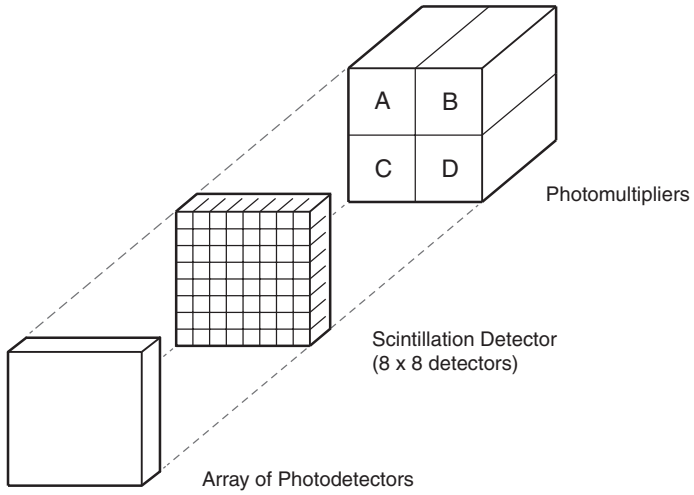

Figure 1.3 A photomultiplier tube system. Images prepared by Ms. Sherry Wang.

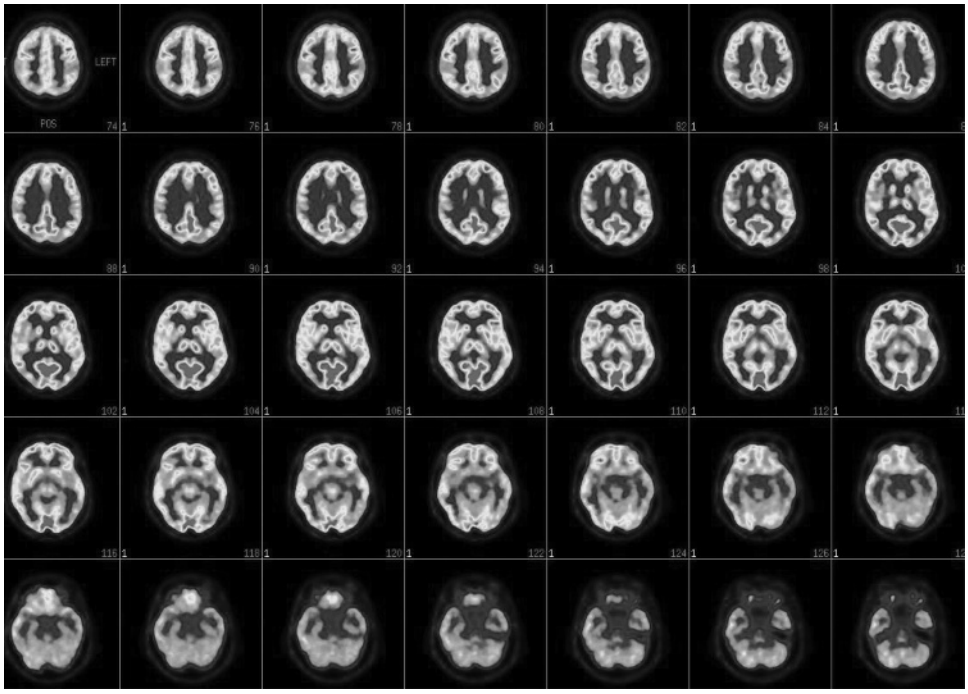

Figure 1.4 A typical set of images from an ^{18}FDG-PET scan of the brain. Please see Plate 1 for color figure.

Figure 1.5 PET scanner.

determination of whether the two rays hit detectors at the same time – a process known as *coincidence detection*. Only photons that arrive within a few nanoseconds of one another are recorded as coincidental hits. Once a coincidental hit is registered, a computer calculates the straight line between the two rays, called a *line of response*; the positron that generated the coincidence rays originated somewhere along the line of response. By counting millions of these coincidental hits around a large number of cross-bearings, the size and position of the structure that has taken up the radioligand is determined. By combining the lines of response from many different angles, the data can be reconstructed into cross-sectional images, using the principles of tomographic imaging similar to those discussed for SPECT scans [26].

^{18}FDG-PET achieves high contrast between gray and white matter, and subcortical structures are easily identified. The 2–4 mm pixels are arranged into a matrix. The final resolution of the image varies between 2.5–10 mm full width at half maximum (FWHM). This level of resolution is generally adequate for image resolution and signal-to-noise ratios. Three-dimensional co-registration with MRI images can help localize lesions and areas of abnormality. Furthermore, most new PET scanners are equipped with CT scanners (PET/CT scanners) that acquire both a PET scan and a CT. The CT provides attenuation correction, as was discussed for SPECT, and also provides very accurate structural localization and an excellent adjunct for co-registration with MRI.

Limitations of PET

Several factors limit the spatial resolution available on a PET scan. First, the 180-degree emission of the two 511-keV gamma-rays is not exact, because the positron and electron are not completely at rest when they annihilate each other. The motion degrades spatial resolution by approximately 2 mm [27]. Further limiting resolution is a set of factors collectively known as *noise effective count rate* (NECR). NECR includes the true sensitivity of detectors; scatter; random coincidences, which are two photons detected at the same time that did not originate from a single positron annihilation; and detector dead time [28]. A number of correction procedures are routinely applied to raw PET data to preserve the quantitative relationship between a PET image and the biological process it reflects, e.g. distribution of glucose or occupancy of opiate receptors. Figure 1.6 demonstrates the processes required to convert raw PET data into quantitative images.

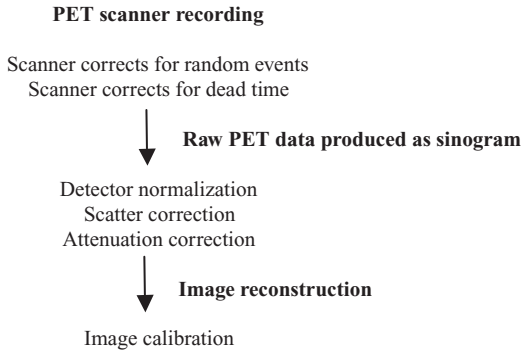

Figure 1.6 PET data correction and image reconstruction.

Correction for random events is necessary when two gamma-rays that are not coincident strike detectors within close proximity. These random events will be subtracted out by a delayed coincident window technique that is standard in modern PET scanners. Another correction that is standard in modern scanners is dead time correction. Dead time is the time when a scanner is processing counts and is unable to record coincident rays that hit during processing. The dead time correction is made by measuring the count rate on the detectors and having knowledge of each step in the electronic processing [29]. Without dead time, the relationship between the count rate and tracer concentration would be linear. However, due to dead time, there are a finite number of counts that can be recorded per unit time, and increasing the radioligand dose does not result in increasing count. Therefore, the injected dose of a PET tracer should be chosen to maximize the count while minimizing radiation exposure to the patient [26]. As crystal designs and electronics continue to improve, the amount of radioactivity that can be imaged before dead time becomes an important factor continues to increase.

Detector normalization is necessary, as each detector within the PET scanner will have slightly different efficiency. Efficiencies can be measured and corrected for by producing a uniform level of radiation from a source and calibrating detectors accordingly. It is also possible that coincident gamma-rays will bend from their straight path, a process known as *scatter*, on their way out of the head. Scatter decreases the resolution of the PET image and is particularly problematic in 3D images [30]. Correction factors to reduce scatter result in higher contrast images and more accurate quantification.

The largest correction factor is for gamma-ray attenuation by body tissue. In the case of ^{18}FDG-PET of the brain, gamma-rays emitted near the surface of the brain will reach the detectors more easily than gamma-rays emitted from deep within the brain tissue. Typically only 20% of gamma-rays emitted from the deep brain tissue are recorded. Formulas for attenuation have been developed to account for this [31].

Raw PET data are often stored in a 2D matrix called a *sinogram*. Each element of the sinogram represents the number of counts detected along a particular line of response. The vertical axis of the 2D image is the angle of the line of response and the horizontal axis represents the displacement from the center of the field of view. Because the sinogram sums all events during the image acquisition period, nothing can be learned about the rate of counts in a particular area at different points during the reconstruction. As computing power has increased, it has been increasingly possible to collect PET data in what is called *list mode*. List mode records each individual coincidence pair including both the line of response and the time that the event occurred. This allows the data to be split into arbitrary periods of time after the fact to better understand dynamic processes. Reconstruction of list mode data follows essentially the same process as that for sinogram data, but is much more computationally intensive.

The process of image reconstruction converts the coincident events detected by the PET scanner into cross-sectional images. There are two methods for reconstructing the sinogram data into cross-sectional images. The first and most common algorithm used in tomography is known as *filtered backprojection*. The backprojection process involves distributing the counts from a sinogram along the line in image space. The second method is known as the *iterative method*, which will find the image that best matches the measured projection data using a maximization/minimization technique. This process allows for better noise and/or resolution performance because *a priori* knowledge of the system can be taken into account. This is the type of analysis that is used when an MRI image is used to enhance the reconstruction process. A further description of filtered

backprojection and comparison of the iterative technique is summarized by Reinders *et al*. [32].

Detecting brain abnormalities with PET scans

In court, the approach to examining brain scans sometimes differs based on whether the expert is working for the defense or prosecution. Defense experts tend to complete a complex parametric analysis. The prosecution expert, on the other hand, may use a standard clinical visual read of the scan. There are points in favor of each method. In a study that compared two methods of visual analysis and a technique known as Statistical Parametric Mapping with two different smoothing filters, all four approaches had a similar sensitivity and accuracy, but specificity was highest using Statistical Parametric Mapping with a 16-mm smoothing filter [33].

There are two main approaches to diagnosing a brain abnormality with PET. First, a subject scan can be compared to a previously obtained study in the same individual. Second, the scan can be compared to a pre-existing normative study or a group average [34, 35]. In order to validly diagnose metabolic or blood flow abnormalities, there must be a clearly defined normal population. Each PET facility should have an accessible database of normal controls to which scans are compared [36]. Such databases are commercially available or can be generated at each individual site. Typically at least ten subjects are needed to generate a database, though more subjects will improve the ability of the database to differentiate normal inter-subject variability from disease [37, 38]. When quantitative comparisons are made to normal databases, the patient's image data must first be co-registered to the normal database. Because many persons with variations in brain shape make up the database, non-linear transformations of the image data are necessary to force all the images into the same shape. This process can introduce errors.

Forensic reports should specify whether reported outcomes are absolute or relative. Absolute metabolic rates for glucose using ^{18}FDG-PET require arterial blood sampling. Determinations of the absolute rate of glucose metabolism are usually limited to the research setting. In the forensic setting, most reported abnormalities are derived from relative comparisons of the whole brain average to regions of interest [39].

PET reports are not solely the result of a visual scan of the image; rather, quantitative or semi-quantitative analyses are reported. Most clinical scan reports are the result of a semi-quantitative analysis in which the results are based on regional concentrations of measured radioactivity, normalized to an internal reference standard, such as whole brain activity, corrected to the actual time of imaging. This is known as the *standardized uptake value* (SUV) [40]. The technique may involve warping the patient's anatomic structure obtained in the MRI to the PET scan to obtain regions of interest on the PET scan. The regions of interest can then be compared to whole brain glucose metabolism, yielding the region of interest to whole brain ratio [39].

Some researchers use absolute quantitative values, which are derived from biologically-based mathematical models that partition radioactivity into compartments that reflect physiologic boundaries, such as vascular space, blood–brain barrier and plasma membrane of neurons or biochemical processes such as enzymatic anabolism, enzyme degradation and transport molecules.

In ^{18}FDG-PET studies, the biologic parameter that is being estimated is the rate of regional glucose use, which is based on a method described by Sokoloff [41]. Early measures

of regional glucose use rates in the human brain estimated cerebral glucose metabolism at 5.5 mg glucose/min/100 g, with a range of 3.6 to 5.2 mg glucose/min/100 g in white matter structures and 5.8 to 10.3 mg glucose/min/100 g in gray matter structures [40].

A number of factors must be considered when comparing metabolic patterns across brains. For standardization purposes, gender, age, handedness, environmental conditions at the time of the scan, level of alertness, presence of medications, serum glucose levels and the amount of tracer that passes into the brain are all important variables that must be considered when comparing one individual's brain scan to a group of controls.

The composition of the control group is essential to the analysis, as this is a comparison of the patient's brain function to that of normal brains. Furthermore, great care must be taken in applying a normal database to a specific patient whose disease presentation is demographically unusual, for example, if a patient is much younger than those who typically have a particular disease and therefore younger than the controls used to generate the database. A common line of questioning regarding nuclear scans involves detailed characterization of the cohort used as controls to ensure that they are truly normal. Occasionally, attorneys will request to see the raw imaging and other data of the control group, including individual demographics. Common challenges to the appropriateness of the control group are age and gender mismatch with the subject.

A concern that the control data have been collected on a different imaging system is also common, though easier to defend against, given the robust standardization techniques commonly employed in nuclear medicine. Courts prefer that the control group data have been published in the peer-reviewed literature, which is raised under the *Daubert* standard for scientific evidence admissibility [42]. Such a standard for comparison may prejudice some courts in favor of nuclear medicine studies performed at academic medical centers with strong relevant research activity.

In *Penney v. Praxair*, the defense presented evidence that PET scan results can be affected by a person's age, medical history and medications. The plaintiff was 66 years old at the time of the scan. His scan was compared to a control group with thirty-one individuals whose ages ranged from 18–70 years. The court felt that the wide age range for the controls was not an accurate comparison for brain metabolism of the litigant. For this and other reasons the scan was not admitted into evidence [43].

Practical issues in forensic nuclear scans

A common line of questioning during deposition and on direct and cross-examination is whether the nuclear medicine examination was handled similarly to scans performed for clinical indications. Thus, the forensic practitioner should be familiar with and adhere to the relevant clinical standard of care when requesting, performing, analyzing and reporting a forensic scan.

Most states require nuclear medicine studies to be ordered by a physician licensed to practice medicine in the state where the scan will take place. Some states allow non-M.D. researchers to order scans for approved research studies and a few allow researchers to order scans for forensic purposes. Some nuclear scan facilities will accept prescriptions for PET and SPECT scans from out-of-state physicians. A savvy prosecutor could accuse the out-of-state forensic expert of practicing medicine without a license in his jurisdiction. However, forensic psychiatry is not covered under the rubric of the practice of medicine in all states. In 1998, the American Medical Association (AMA) conducted

a comprehensive survey of states' definitions of the practice of medicine and found that Alaska, Arizona, Arkansas, California, Colorado, Connecticut, Delaware, Georgia, Idaho, Illinois, Indiana, Iowa, Kansas, Louisiana, Minnesota, Montana, Nebraska, Nevada, New Hampshire, North Dakota, Ohio, Oregon, Rhode Island, South Carolina, South Dakota, Tennessee, Vermont and Wyoming consider expert witness testimony to be the practice of medicine (see http://www.aapl.org/state_law_prac_med.htm). These states could require an expert testifying in a case to obtain a state medical license.

As is standard in clinical practice, a medical history detailing current illnesses and including a list of medications taken by the patient/examinee must be considered prior to ordering the scan. Medications that alter blood flow to the brain could affect the scan. Therefore, if practical, the patient should be off all medications and not under the influence of psychoactive drugs, including caffeine, nicotine and alcohol prior to a nuclear medicine scan. Many imaging facilities request that patients discontinue all psychoactive medications for at least seven days prior to a SPECT or PET scan. The Society for Nuclear Medicine advises that anti-seizure medications, chemotherapy for brain tumors, anti-cholinesterase drugs for memory impairment and psychotropic pharmaceuticals can influence regional brain metabolic rates and should be discontinued prior to a PET scan [44].

Obviously, in many cases, it may not be safe or advisable to withhold some or all of a patient's medications. In such cases, the forensic practitioner will likely be asked to comment on whether any of these medications affected the scan results. The forensic practitioner may also be asked to consult with the patient's treating physician to choose the safest methods for tapering and restarting medications in conjunction with the nuclear medicine scan. A rule of thumb is that 96% of an active substance is washed out in five half-lives. Notably, some psychoactive medications cannot be restarted safely following the scan at the previous effective dose and will require titration back to an effective dose.

Many jail and prison inmates are treated with psychoactive medications during their incarceration. In our experience, it may be difficult to coordinate with the practitioner prescribing the medications. Lawyers and mitigation specialists can be helpful in coordinating such conversations. Written documentation of the consulting forensic psychiatrist's recommendations is commonly requested for the prisoner's medical record. A urine test for illicit drugs of abuse is recommended to confirm their absence.

Indeed, a patient's use of medications during a PET scan has been grounds for excluding PET data from courtroom evidence. This was a factor in the *Penney* case discussed above. The 8th Circuit Court of Appeals upheld the exclusion of a PET scan where the 66-year-old plaintiff was taking his regular dose of heart medications around the time of the scan. The court acknowledged that it was not clear whether the medication impacted the results, but the plaintiff had failed to carry his burden of establishing a reliable foundation for his PET scan reading compared to controls, who were not taking medication.

Special considerations for FDG PET

As abnormal glucose metabolism may affect an ^{18}FDG-PET image, an individual patient's history of abnormal glucose metabolism, as occurs in diabetes mellitus, and current fasting plasma glucose levels should be obtained prior to the ^{18}FDG-PET. An optimal scan requires that the patient's blood glucose be between 60–200 mg/dl. If plasma glucose is over 200 mg/dl, ^{18}FDG would be driven into peripheral fat and muscle, resulting in decreased

^{18}FDG uptake by the brain. Hypoglycemia (blood glucose < 60 mg/dl) is also undesirable, as it leads to increased uptake of the ^{18}FDG by the brain.

Though hypo- or hyperglycemia precludes an accurate measurement of absolute glucose utilization, it is still possible to assess regional distribution in brain glucose relative to the brain as a whole [45]. Thus, PET scanning a patient with diabetes or other, less common disorders of glucose metabolism is challenging and requires special attention and preparations well in advance of the scan. In general, insulin-dependent diabetics should be injected with FDG at least 90 minutes after short-acting insulin injection but can be on a basal level of long-acting insulin.

Costs and indications

The cost of conducting an ^{18}FDG-PET scan, not including the interpretation, is usually between $1000 and $3000, however this cost can be significantly higher if an unconventional radiotracer is used or a professional interpretation fee is added. SPECT scans using commercially available radiopharmaceuticals usually cost below $1000. In general, insurance companies do not cover the cost of scans done for forensic purposes. However, studies ordered for clinical purposes and reimbursed by insurance may be used by forensic practitioners.

Applications of PET scans

Later chapters in this book discuss in depth the clinical indications for nuclear scans. Briefly, PET has virtually infinite growth potential through the development of new ligands. However, at this time, there are few commonly accepted non-^{18}FDG brain PET indications. Currently, ^{18}FDG-PET is a universally accepted clinical test in the diagnosis and follow up of malignancy [46, 47], myocardiac viability, epilepsy [48, 49] and dementia and other degenerative brain disease [50–54]. Other relatively common clinical uses include pre-surgical planning, post-stroke evaluation [55] and moderate to severe traumatic brain injury [56, 57]. Even in the case of mild traumatic brain injury where no specific imaging pattern has been established, PET scans are routinely admitted as part of the brain injury assessment performed by and relied upon by the testifying physician [36]. The physician may use PET scans to rule out other known pathologies with a characteristic pattern on PET and testify that the PET study is consistent with other medical evidence supporting the diagnosis.

PET scans are commonly admitted in death penalty litigation [22]. The defendant will argue that a brain abnormality should be considered as a mitigating factor supporting a sentence of life in prison rather than the death penalty. As such, in criminal trials, PET scans are generally introduced at the sentencing phase.

In Florida, defendant Hoskins challenged the trial court's judgment convicting him of multiple felonies, including first-degree murder, as well as the imposition of the death sentence [58]. Mr Hoskins had an IQ of 71 and an examining physician recommended a PET scan be ordered as part of the work-up for brain damage. The trial court refused to grant a defendant's motion seeking transport to a hospital to have a brain scan performed. This limited his defense expert's ability to evaluate the degree of his mental impairment, which is a statutory mitigating factor under Florida law [59]. The appellate court remanded

the case, ordering that a brain scan be obtained and consideration of a new penalty phase, in effect overturning Hoskins's death sentence.

In *People v. Weinstein* the court determined that a doctor's testimony regarding the metabolic imbalances surrounding a large arachnoid cyst in Mr Weinstein's frontal lobe was admissible [60]. Shortly thereafter, the prosecution offered Mr Weinstein, charged with strangling and defenestrating his wife, a plea bargain to manslaughter.

To be admitted into evidence, a PET scan must demonstrate information that is not otherwise available to the clinician. In *People v. Goldstein*, the defendant Goldstein, a man apparently suffering from schizophrenia, pushed a woman in front of an oncoming subway train, killing her [61]. All parties agreed that the defendant had schizophrenia. A PET scan was proffered by a defense expert to show that his brain imaging was consistent with schizophrenia. As the PET scan was not offered to further probe into the impact of schizophrenia on the defendant's cognition and behavior, it was excluded from evidence. In contrast, other courts have allowed PET scan evidence as part of a substantive defense [62].

In a recent California case, a PET scan was admitted at a hearing for competence to stand trial. The judge stated that PET scans are 'generally accepted in the scientific community and . . . are certainly accepted as tools used in clinical settings. And in forensic settings it seems . . . there could be testimony as to the areas of the brain that are relevant to the issue of [trial competency]' [63].

Nuclear scans are also increasingly being admitted into evidence in civil trials where brain injury is claimed. In fact, there have been cases in which litigants were penalized for failing to undergo nuclear scans. *Harris v. U.S.* was brought by a law student who was struck by a US Postal Service truck while driving to his law school final exam. He filed a claim under the Federal Tort Claims Act asking for damages based on his diagnosis of mild traumatic brain injury (TBI) resulting from the accident. The court noted that although a PET or a SPECT scan could be used to confirm a diagnosis of mild TBI, Harris had not offered a scan as evidence of his injury. In part due to the lack of neuroimaging evidence, the court found that the plaintiff failed to prove that he suffers from continued cognitive impairment as a result of the car accident [64]. It is possible in this case that the court was suspicious of neuropsychological testing alone being used to corroborate a claim of brain injury. Courts are sometimes fearful that a sophisticated plaintiff could 'fake' a neurocognitive deficit on clinical interview and pen-and-paper-based tests. Courts also assume that since it would be difficult or impossible for an individual to manipulate their brain blood flow and metabolism, imaging evidence is safe from malingering.

In contrast, attempting to use PET scans for novel purposes in court can be risky. In *Jackson v. Calderon*, the court stated that PET scans are not generally accepted tools to diagnose chronic PCP use. In *United States v. Mezvinsky*, a PET scan was not admitted to suggest that the defendant, a former congressman charged with 66 counts of fraud, was incapable of deception, an element necessary to prove fraud [65]. The court opined that the relevance of the evidence was outweighed by its capacity to mislead the jury.

Further, an expert's testimony and scan are likely to be excluded if the expert overstates the causal links that can be inferred from the PET scan. In the case of *Palazzolo v. Hoffman la Roche*, the plaintiff's expert witness claimed that a PET scan could provide evidence linking a patient's depression and subsequent suicide to the medication Accutane that the decedent had been taking for acne [66]. The PET scan was excluded from evidence as plaintiffs and defendants had stipulated that PET scans were not tools used in the diagnosis of depression.

Conclusion

Positron emission tomography (PET) and single photon emission computed tomography (SPECT or SPET) are clinical nuclear medicine imaging techniques that are commonly admitted into evidence when a brain abnormality is relevant to the legal issue. PET and SPECT scans provide data on brain function that are complementary to other neuroimaging techniques, such as magnetic resonance imaging (MRI) and computed tomography (CT).

Functional scans have characteristic activation patterns in activation in cancer [46, 47], epilepsy [48, 49], some types of dementia [50–53], moderate to severe traumatic brain injury [54, 67] and stroke [55]. In disorders that lack a characteristic signal, PET and SPECT scans can serve to support conclusions made by medical history, clinical examination and neuropsychological evaluation. The testifying expert will link aberrant blood flow or metabolism in given brain structures to the cognitive and behavioral processes associated with those brain regions.

Abnormal brain function is a mitigating factor that the court may consider in a death penalty sentencing hearing. Likewise, demonstration of functional brain abnormalities may be persuasive when brain injury is claimed in civil litigation. Since general clinical acceptance and medical risk/benefit are important criteria when considering a forensic brain-imaging study, it is advisable that the practitioner rely on independent experts to help determine whether and which nuclear medical imaging study may be indicated.

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