PET Neuroimaging of Neurologic Disease: Methods, Clinical and Research Applications

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1. Background

Positron emission tomography (PET) is a functional imaging technique that can be used to visualize physiological activity or molecular processes in the whole body or specific organs. For several decades, PET imaging has been used to expand our understanding of neurobiology and neurologic disease. In addition to playing an increasing role in neuroscience research, PET imaging has become ubiquitous in the clinical setting. For example, PET neuroimaging is currently used to aid in differential diagnosis, monitor treatment effectiveness, and assist with surgical planning. While perhaps most well-known for its role in neurodegenerative disease, PET neuroimaging has also been used to care for and study patients with epilepsy, brain tumors, traumatic brain injury, schizophrenia, and other neuropsychiatric conditions. PET neuroimaging is currently undergoing a period of rapid development, particularly as it pertains to the visualization and quantification of neurodegenerative processes and neurotransmitter systems. Given that neuropsychologists are positioned to integrate neuroimaging findings with information derived from a clinical interview and cognitive testing, a fundamental understanding of PET neuroimaging applications and methods will likely prove useful.

PET neuroimaging makes use of radioactive molecules called radioligands or radiotracers that bind to molecules of interest, ideally with high affinity and specificity. PET images indicate the spatial distribution and amount of the radiotracer in the organs being imaged. PET neuroimaging was initially used to visualize and quantify cerebral blood flow (perfusion) and cerebral metabolism using radiotracers such as [^{15}O]-water, [^{11}C]CO, and [^{13}N]NH₃ (Nasrallah & Dubroff, 2013). Many additional radiotracers have since been developed to study normal neurophysiological and neurologic disease processes.

PET neuroimaging has facilitated tremendous advances in neuroscience research, and the clinical indications for this neuroimaging modality continue to grow. However, there are several disadvantages to PET imaging that need to be considered. Compared to functional magnetic resonance imaging and magnetoencephalography, which are techniques used to study neural activity, PET neuroimaging provides poorer spatiotemporal resolution, exposes participants to ionizing radiation, and is invasive in that it involves an intravenous injection. Radioisotopes that decay quickly are used to limit the subject's exposure to radiation. However, the short half-life of radioisotopes may necessitate that some be produced on-site in a particle accelerator called a *cyclotron*. Additionally, there is typically a high cost associated with PET scans due to their operational complexity and the necessary involvement of many specialized individuals.

2. Biophysics of PET

2.1. Introduction

Brain PET imaging involves the inhalation or peripheral intravenous injection of a radioactive substance, called a radiotracer (short for radioactive tracer). A radiotracer is a molecule that contains an atom with excessive nuclear energy due to a difference in the number of neutrons it contains compared to the stable form of the atom. This unstable atom is called a radioisotope.

Common radioisotopes in brain PET imaging are summarized in **Table 1**.

Table 1. Most common radioisotopes in brain PET imaging. Half-lives shown are approximate.

Isotope	Half-life (min)
^{11}C	20
^{15}O	2
^{18}F	110

The radiotracer is directly related to the biological phenomenon we seek to image: it can be a molecule that is naturally processed by the body or an analog thereof (for example, water or glucose), except that one of its atoms has been replaced by a radioisotope, or a radioisotope containing molecule that has been designed to bind to a specific target in the body. Radiotracers used in brain PET must be small lipophilic molecules to be able to cross the blood-brain barrier, but higher lipophilicity increases the likelihood that the tracer will bind to unintended targets in the brain. A frontier in radiotracer development for brain PET imaging is the use of antibodies, which have high specificity and affinity, that have been modified to enable their active transport into the brain tissue (Sehlin et al., 2019).

As the radiotracer is delivered to tissues and binds to its target, its radioisotope seeks to reach a stable form by undergoing radioactive decay. The rate of decay is characterized by the half-life of the radioisotope, which is the time it takes, on average, for the amount of radioactive material to be halved. For the radioisotopes used in PET, radioactive decay results in the emission of a positron (and a neutrino). A positron is a positively-charged particle that has the mass of an electron. After travelling a short distance (called the positron range), the emitted positron encounters an electron. The result of this encounter is mutual annihilation, which yields two (approximately) anti-parallel photons, each of which has 511 kiloelectron-volts (keV) of energy, the energy equivalent of the mass of an electron at rest (**Figure 1**). Both the positron range and the slight non-collinearity of the anti-parallel photons limit the spatial resolution of PET.

Figure 1. The radioisotope decays to a stable configuration by releasing a positron (e_+), which encounters an electron (e_-) after traveling a short path, as indicated by the dashed lines. Mutual annihilation results in the release of two (approximately) anti-parallel 511 keV photons.

PET scanners are built to exploit this annihilation phenomenon. They are, in essence, annihilation coincidence detectors. The computational machinery of the PET scanner identifies pairs of photons that reach opposing detectors at around the same time. Such a pair of coincident photons establish a line of response (LOR), on which lies the radioactive source. Image formation involves disentangling the detector coincidences, which are one-dimensional projections of the decaying radioisotopes, to determine the locations of the sources in three-dimensional space.

2.2. Instrumentation

Detector blocks used in PET consist of scintillation crystals backed by a matrix of photomultiplier tubes (PMTs) or silicon photomultiplier (SiPM) digital photon counting (DPC) detectors. In traditional PET scanners, detector blocks are arranged in adjacent rings or polygons to form a tube. In certain dedicated brain PET systems, detector blocks are arranged in a hemisphere (Catana, 2019).

2.2.1. Scintillation crystal. The scintillation crystals stop the incident photons and produce a burst of light that conveys information on the energy of the incident ray to the PMTs or DPC detectors. Scintillation crystals in modern PET scanners are generally made from cerium-doped lutetium oxyorthosilicate (LSO), lutetium-yttrium oxyorthosilicate (LYSO), or gadolinium oxyorthosilicate (GSO). Compared to thallium-doped sodium iodide (NaI), which is the material used in original commercial PET scanners, these materials have higher attenuation coefficients at 511 keV, allowing them to stop the incident photons with thinner crystals than would be required with NaI to have the same stopping power. LYO, LYSO, and GSO also have shorter decay times compared to NaI or bismuth germanate (BSO), enabling for the individual detection of incident photons separated by shorter time intervals. Each crystal is cut into smaller sections that are separated by opaque reflective layers to help contain the light bursts within one subcrystal.

2.2.2. Scintillation photon counting. Analog systems. In analog systems, the light burst generated in the scintillation crystal is channeled into an array of photomultiplier tubes (PMTs), which convert light to an electrical pulse. The pulse is amplified prior to the position logic circuit, which determines the location of the detected photon within the scintillation crystals. Locations of a coincident photon-pair on opposing detectors define a LOR. One way to localize the photon in the scintillation crystal is to compute a PMT output-weighted centroid as the position of the photon in the plane parallel to the surface of the crystal, and to set the depth of interaction (DOI) within the crystal to a pre-specified value (for example, as determined by the attenuation coefficient of the crystal). However, being able to measure the DOI improves the localization of photons in the scintillation crystals, and therefore the accuracy of the LORs (Mohammadi, Castro, Correia, Silva, & Veloso, 2019). This is especially important for

PET systems without septa between detector rings. An approach for incorporating DOI detection capability is to use multi-layered scintillation crystals.

An important disadvantage of PMTs is their incompatibility with magnetic fields, which renders them inappropriate for combined PET/MRI systems. Systems that have been developed to overcome this limitation of PMTs include avalanche photodiodes (APD) and silicon photomultipliers (SiPM).

Digital systems. A recent development in PET instrumentation is the use of SiPM digital photon counting (DPC) detectors instead of PMTs (Zhang, Maniawski, & Knopp, 2018). Each scintillation crystal is coupled with an SiPM DPC detector that can individually record each scintillation photon, and therefore, no position logic circuit is needed. DPC detectors yield significant improvements in photon detection accuracy and image quality.

2.2.3. Pulse height analyzer. The pulse height analyzer characterizes the number of photons incident on the scintillation crystals as a function of photon energy. This information is used to accept photons resulting from annihilation events and to reject scattered photons. In a PET scan, the greatest number of pulses will occur around the pulse height equivalent of 511 keV, which is called the photopeak (**Figure 2**). Due to the statistical fluctuations related to the conversion of photons to light, and light to electrical signal, photons that reach the detectors without scattering produce a range of pulse heights around the photopeak. Therefore, a window around the photopeak is used to define the acceptance window. The lower limit of this window is chosen to maximize the acceptance of the photons that reach the detectors directly from the source while minimizing the acceptance of scattered photons, which have lower energy.

Figure 2. Pulse height spectrum. The photopeak represents the energy deposited in the crystal by unscattered photons. An acceptance window (whose energy limits are represented by the dashed lines) is defined around the photopeak to minimize counting scattered photons as events.

2.2.4. Coincidence detection circuit. The coincidence detection circuit identifies pairs of counts detected at around the same time at opposing detectors, and all other counts are discarded as scattered photons. In systems with time-of-flight (TOF) capability, the slight differences in time at which anti-parallel photons reach opposing detectors can be used to estimate where along the LOR the annihilation event occurred (Vandenberghe, Mikhaylova, D’Hoe, Mollet, & Karp, 2016).

Inevitably, a fraction of the accepted pairs will be due to coincident photons from two separate sources. Such detections are referred to as random coincidences. The expected number of random coincidences can be computed given the count rates at a pair of opposing detectors and the coincidence acceptance time window. The expected number of true coincidences then can be computed by subtracting this number (as well as the expected number of scattered photon counts) from the total counts. Scatter and random correction is often embedded in the iterative

image reconstruction algorithm, with the scatter distribution being estimated using simulation techniques.

2.2.5. *Septa.* In PET scanners with a tubular detector block arrangement, adjacent detector rings can be separated by lead or tungsten septa, whose purpose is to stop scattered photons and to simplify image reconstruction as the individual reconstruction cross-sectional slices. Using septa during scanning is called the two-dimensional mode. Modern PET systems, however, operate in a three-dimensional mode, in which such septa are not used. This has the advantage of greatly increasing the number of detected photons, and thereby yielding higher quality images.

2.2.6. *Combined systems.* Certain PET scanners are designed as combined PET/CT systems. Such scanners enable the simultaneous acquisition of PET and CT scans, obviating the need for image registration. The CT scan provides anatomical information that can be helpful in the visual evaluation of the PET scan, and also provides tissue attenuation coefficients that can be used for correcting the PET image for attenuation. Similarly, simultaneous PET and MRI scans can be acquired using dedicated PET systems that can be inserted into MRI scanners or using combined PET/MRI systems, and various image analysis approaches exist for estimating tissue attenuation coefficients in such systems (Catana, Guimaraes, & Rosen, 2013).

2.3. *Image acquisition*

Image acquisition begins at the time of or after a certain time interval following the radiotracer administration. This scan is called the emission scan.

2.3.1. *Acquisition modes.* The information collected by the PET system can be stored using different approaches. One approach is to store the location, energy, and time of detection of each incident photon. This is called the list mode. List mode enables tremendous flexibility in data processing after acquisition; however, it requires a sizeable amount of storage space per scan.

Frame mode alleviates the storage space requirement by storing the number of counts detected at each location bin on the surface of the camera. Frame mode can be static or dynamic. In a static acquisition, only a single matrix of counts is recorded, whereas in a dynamic acquisition, scanning duration is split into time bins and a separate matrix is stored for each time bin. With a scan acquired over a sufficiently long period of time in list mode or dynamic frame mode, it is possible to study the chemical binding properties of the radiotracer or to assess biological phenomena as a function of time via kinetic modeling.

2.3.2. Attenuation coefficient image. The tissue that photons travel through prevents a fraction of the photons from continuing on their direct path towards the detectors. At 511 keV, the main reason for this is the scattering of photons (but at lower photon energies, tissues can also completely absorb a fraction of the photons). The fraction of photons that are absorbed or scattered per unit thickness, called the linear attenuation coefficient, differs across tissue types, with bone having a higher coefficient compared to soft tissue. Attenuation reduces the detected photon counts from locations deeper in tissues. To mediate this problem, attenuation correction is applied as part of image reconstruction. In order to perform attenuation correction, a separate scan is acquired to enable the calculation or approximation of the tissue attenuation coefficients (though attenuation coefficients can be estimated from the emission scan in certain systems). This scan can be a transmission scan (generally acquired prior to the emission scan), where a radioactive source with a long half-life, such as ^{68}Ge or ^{137}Cs , located in the scanner gantry, is rotated around the participant, a CT scan in a combined PET/CT system, or an MRI scan in a combined PET/MRI system.

2.4. Image reconstruction

Image reconstruction involves determining the number of photon counts as 2-D image slices, a 3-D image, or a sequence of 3-D images over time from their 1-D projections onto the detectors.

A 1-D projection is the summation of coincident photon counts along each LOR oriented at a given angle (**Figure 3**). The PET system captures 1-D projections at many different angles. The collection of these projections, represented as a function of the angle, makes up the sinogram.

Image reconstruction is the process that takes a sinogram (or list mode data) as its input and generates an image of counts. It can be thought of as the inversion of the 1-D projection.

Figure 3. A mutual annihilation event (*) within the radioactive object being imaged is shown. Dashed lines illustrate a few of the possible lines or response (LORs). 1-D projections are the summations of photon counts along LORs at a given angle θ as a function of the distance s from the center of the field of view. A sinogram is a collection of projections, visualized as a function of the angle θ and the distance s . A slice of the sinogram at an angle θ_0 (dotted line) is the 1-D projection at that angle. The contribution of the event * to the sinogram is indicated by the dash-dotted curve.

There are two major types of PET image reconstruction methods (for an overview, see Tong, Alessio, & Kinahan, 2010) Analytic methods such as filtered backprojection directly solve for the image using the inverse of the discrete Radon transform. However, because these methods do not take into account the noise structure accurately, they can yield lower resolution images with artifacts. Iterative methods such as ordered-subsets expectation-maximization (OSEM) address this limitation by framing image reconstruction as a statistical estimation problem and using a more realistic model of the imaging system, but they are computationally more expensive. Both methods incorporate attenuation correction. Iterative methods can also include various additional image correction techniques as part of image reconstruction (Iriarte, Marabini, Matej, Sorzano, & Lewitt, 2016). For example, participant motion or partial volume effects (see §1.5.2) can be included in the statistical model that the iterative reconstruction technique is based on, and be appropriately accounted for in the reconstruction rather than post-reconstruction. Other types of image reconstruction methods, such as deep neuronal networks that learn the parameters of a series of transformations that need to be applied to detector data to obtain images, are also being developed (Duffy, Boyle, & Vasdev, 2019).

2.5. Image quality

2.5.1. System sensitivity. Sensitivity of a PET system is defined as the fraction of photons emitted as a result of mutual annihilation that are detected by the scanner. Thicker crystals yield better sensitivity, as they are better at stopping high-energy photons, but this comes at the expense of poorer spatial resolution (in systems without DOI detection capability). Systems without septa between detector rings have higher sensitivity.

2.5.2. Spatial resolution. Various aspects of the physics of radioactive decay and photon propagation, as well as the hardware and software of a PET system introduce blurring effects in the reconstructed image. The blurring is characterized by the point spread function (PSF). The spatial resolution of a PET system is usually quantified as the minimum physical distance required between two point sources to be able to distinguish them in the reconstructed image. This concept is mathematically represented using the full width at half maximum (FWHM) of the PSF, which is measured in mm. Due to blurring, image intensity in areas of high radioactivity is reduced, and intensity in areas of low radioactivity is increased. These are referred to as spill in and spill out effects, and they reduce image contrast. Partial volume correction methods, applied during or after image reconstruction, can improve image contrast by recovering the true tissue activity by reverting or accounting for the blurring caused by the PSF.

Spatial resolution is affected by the characteristics of the radioisotope used as well as scanner elements (Moses, 2011). Radioisotopes with higher positron ranges yield poorer spatial resolution, since the PET system determines the location of the positron-electron mutual annihilation, not where the positron was emitted from. The non-collinearity of the photons emitted following mutual annihilation also degrades spatial resolution. Due to this non-collinearity, detector rings with larger diameters result in poorer spatial resolution. While thicker scintillation crystals are better at stopping photons (and therefore, improve system sensitivity), they degrade the spatial resolution because the light bursts generated in the crystal have to travel longer distances before reaching the PMTs or the SiPM DPC detectors. This in turn increases the error in the localization of the incident photons.

2.5.3. Dead time. After registering a photon count, there is a time interval in which the PET system cannot register another incident photon as a separate count. This time is called the dead

time. If successive photons hit the detector with a short time interval in between, the light bursts they generate in the scintillation crystal will pile up, and the system will treat this as a single count with energy equal to the sum of the energies of the individual photons. This means that increasing the amount of administered radiotracer will not translate into proportional gains in the number of counts, because more of the photons will be not counted due to dead time or will be rejected by the pulse height analyzer due to the pile up effect.

2.5.4. Energy resolution. Energy resolution describes the ability of a PET system to distinguish between photons with different energies. Systems with better energy resolution can better identify scattered photons as such, and therefore, have better spatial resolution. Energy resolution is quantified using the FWHM of the photopeak.

2.6. Kinetic modeling

PET images provide information about the amount of radiotracer in tissues¹. It is often desirable to extract additional information to quantify the physiological parameters that govern the uptake of the radiotracer by tissues and the binding properties of the radiotracer in tissues. A parameter of interest usually is, or is directly related to, the volume of distribution, which is the ratio of radiotracer concentration in tissue to in plasma at equilibrium. Equilibrium can be achieved through a sustained drip injection of the radiotracer over a sufficiently long period of time. However, this generally is not feasible due to the limitations of time and dose to the patient. Kinetic modeling enables the estimation of the volume of distribution and other tissue parameters without having to perform drip injections.

¹ If circulating radioactive metabolites can also be taken up by tissues, then the PET images reflect the combined amount of radiotracer and radioactive metabolites. Most brain PET radiotracers are processed by the liver to yield metabolites that cannot cross the blood-brain barrier, and therefore, brain tissue signal is not confounded by metabolites.

Kinetic models are mathematical descriptions of the movement of radiotracer from blood into tissues and back into blood as a function of time (for a review, see Carson, 2005). Models can also describe the binding of the radiotracer to its intended target (called specific binding) and to spurious off-targets (called nonspecific binding). The most commonly used type of kinetic model is a compartmental model, where a system of differential equations is used to describe the flow of radiotracer among compartments representing various physical locations and chemical states (bound vs. unbound) of the radiotracer. The rates of movement between the compartments are the unknown model parameters. Except for the uptake rate of the radiotracer by the tissue, these rate parameters generally cannot be estimated individually. However, an analytic expression can be derived for the volume of distribution in terms of the rate parameters, and this value can be reliably estimated with sufficient data.

Fitting a kinetic model requires dynamic PET scans and measurements of radiotracer concentrations in plasma over time. Dynamic PET scans are used to obtain time activity curves (TACs), which are the concentrations of radiotracer in tissues over time. Plasma measurements are obtained using arterial lines and are corrected for radioactive metabolite concentrations if necessary. TACs and metabolite-corrected plasma measurements are then used to estimate the uptake rate or lumped parameters such as the volume of distribution. Given that arterial lines are invasive, various compartmental models that do not require plasma measurements have been developed. One approach is to approximate the arterial input function from large arteries in the PET scan. Another approach is to use reference tissue models, where an anatomical region in the scan that is known to be free of specific binding is included in the compartmental model, and this strategy enables the computation of a value proportional to the volume of distribution.

3. Research and Clinical Applications

3.1. *FDG PET Neuroimaging*

Fluorine-18 (^{18}F) fluorodeoxyglucose (FDG) radiotracer (^{18}F]FDG) is a glucose analog widely used in PET imaging to estimate metabolic activity within the body. Glucose-using cells take up ^{18}F]FDG via a glucose transporter. By measuring the retention and clearance of ^{18}F]FDG, this radiotracer can be used as an indicator of regional glucose metabolic activity. The ^{18}F]FDG radiotracer has been FDA approved for clinical use for multiple indications. ^{18}F]FDG PET imaging is most commonly used in the oncology setting to identify malignant tumors, which tend to have higher metabolic activity (i.e., greater glucose transport and phosphorylation) than the surrounding tissue. However, the ^{18}F]FDG radiotracer has also seen widespread use for imaging of neurologic conditions. The healthy brain maintains a high level of metabolic activity, which corresponds to high levels of glucose use. By examining cerebral regional metabolic differences, researchers and clinicians have been able to make inferences about bioenergetic changes in neurologic disease.

^{18}F]FDG PET neuroimaging has been particularly valuable in research for understanding the pattern of reduced regional glucose metabolism that occurs in the context of neurodegenerative conditions such as Alzheimer's disease (AD), frontotemporal lobar degeneration (FTLD), and dementia with Lewy bodies (DLB). With the progression of neurodegenerative disease, changes in ^{18}F]FDG tracer uptake are observable in brain regions with known pathogenic protein deposition and neuronal dysfunction. In the context of autosomal dominant AD, for example, a reduction in ^{18}F]FDG PET-defined cerebral metabolism occurs in the precuneus as early as 17 years before the estimated time of symptom onset (McDade et al., 2018). This reduction in glucose metabolism that occurs across the spectrum of

neurodegenerative conditions is believed to represent a final common disease pathway resulting from synaptic failure and reduced glucose utilization.

3.1.1. Clinical Applications for FDG PET. In clinical practice, FDG PET neuroimaging is widely used to aid in differential diagnosis of neurodegenerative disease. Signature patterns of reduced [^{18}F]FDG uptake are discernable for patients with underlying AD, DLB, and FTLT. For example, individuals with AD typically show bilateral hypometabolism in temporo-parietal, posterior cingulate, and medial temporal brain regions (Rice & Bisdas, 2017). [^{18}F]FDG PET can aid in distinguishing individuals with AD from neurologically healthy individuals and patients with other neurodegenerative conditions, including FTLT (Rice & Bisdas, 2017; Shivamurthy, Tahari, Marcus, & Subramaniam, 2015).

[^{18}F]FDG PET neuroimaging is also used as a tool to aid seizure localization. Although seizures themselves can cause a surge in brain metabolic activity, interictal [^{18}F]FDG PET imaging shows a pattern of hypometabolism around the seizure focus. In the context of temporal lobe epilepsy, use of [^{18}F]FDG PET to detect the epileptogenic focus has shown a sensitivity ranging from 85-90%. However, the sensitivity was found to be as low as 45-60% for epilepsy occurring outside of the temporal lobe (Drzezga, Schön, Vogtareuth, Minoshima, & Noachtar, 1999). For patients with temporal lobe epilepsy, FDG PET has also demonstrated some value as a tool to predict postoperative cognitive outcomes. For example, presurgical bilateral hypometabolism and hypometabolism extending outside of the temporal lobe has been associated with poorer postoperative cognition after unilateral resection of a temporal lobe epileptogenic lesion (Lotan, Friedman, Davidson, & Shepherd, 2020).

3.2. *Amyloid PET Imaging*

In 2004 Pittsburgh Compound B ($[^{11}\text{C}]\text{PiB}$) was identified as the first PET tracer to bind selectively and with high affinity to amyloid- β ($\text{A}\beta$) plaques, a core feature of Alzheimer's disease. $\text{A}\beta$ peptides, which initially emerge as monomers, can go on to form $\text{A}\beta$ oligomers, and $\text{A}\beta$ fibrils, the latter of which forms aggregates known as $\text{A}\beta$ plaques (Savonenko, Melnikova, Tong, Price, & Wong, 2015). $[^{11}\text{C}]\text{PiB}$ PET neuroimaging allowed $\text{A}\beta$ plaques to be visualized in-vivo for the first time, and in doing so, ushered in a new era Alzheimer's disease research. Since the development of $[^{11}\text{C}]\text{PiB}$, a number of additional PET radiotracers have been developed to image $\text{A}\beta$ aggregates, several of which have already been approved by the FDA for clinical use: $[^{18}\text{F}]$ Florbetapir, $[^{18}\text{F}]$ Florbetaben, and $[^{18}\text{F}]$ Flutemetamol (Villemagne, Doré, Burnham, Masters, & Rowe, 2018).

Although these radiotracers have demonstrated high reliability and accuracy as measures of cortical $\text{A}\beta$ deposition, a number of methodological challenges remain to be addressed (Clark et al., 2012). For example, there is currently a lack of consensus about the procedures and methods used to estimate the level of cortical $\text{A}\beta$, which limits comparability between studies and the establishment of a generalizable threshold for defining $\text{A}\beta$ positive status (Meyer, McSweeney, Gonneaud, & Villeneuve, 2019). $\text{A}\beta$ PET images can be assessed using a visual or a quantitative assessment. To quantify brain $\text{A}\beta$ levels, many centers now use the standardized uptake value ratio (SUVR) approach, a normalization method calculated by dividing the amount of tracer uptake in a region of interest by the person-specific level of non-specific binding in a region of the brain that is known to be free of $\text{A}\beta$ pathology based on autopsy studies (typically the cerebellum or a white matter region). This semi-quantitative method has been validated for PiB, Florbetapir (**Figure 4**), and other radiotracers (Landau et al., 2013).

Figure 4. Florbetapir PET images from two non-demented older adults. The top row displays elevated florbetapir uptake, suggestive of elevated amyloid- β ($A\beta$). The bottom row displays minimal florbetapir uptake, suggestive of an amyloid-negative scan. An area of cerebellar gray matter was used as the reference to calculate standardized uptake value ratios (SUVRs), as described in Wong et al., 2010.

Recently, an effort known as the Centiloid project was initiated to improve the comparability of $A\beta$ PET measurements and facilitate data harmonization (Klunk et al., 2015; Navitsky et al., 2018). The Centiloid project proposes a standardized set of $A\beta$ PET acquisition and pre-processing methods and the use of a transformation that places cortical $A\beta$ levels on a scale ranging from 0 to 100 (Klunk et al., 2015; Meyer et al., 2019). Centiloids were initially developed for [^{11}C]PIB PET, but this approach has since been expanded to incorporate other $A\beta$ radiotracers (Navitsky et al., 2018).

3.2.1. Clinical Applications for Amyloid PET. Currently, $A\beta$ PET neuroimaging can be used to support the diagnosis of probable AD and to reduce diagnostic ambiguity. Appropriate use criteria for the clinical use of $A\beta$ PET neuroimaging have been put forth by the Amyloid Imaging

Task Force (AIT). These criteria highlight the need for a) patients to have had a previous clinical assessment suggesting possible AD, b) evidence of subjective or objective cognitive problems, and c) a set of circumstances in which knowledge of cortical A β deposition would clarify a diagnosis and direct clinical care (Johnson et al., 2013). Furthermore, the Alzheimer's Association has recommended that A β PET scans not be used for patients older than age 65 who appear to clearly meet the clinical criteria for AD; for patients with subjective cognitive impairment for which there is no objective evidence of cognitive impairment; on the basis of an AD family history or *APOE* ϵ 4 status; or for insurance, employment, or other non-medical reasons (<https://www.alz.org/media/Documents/health-care-pros-faqs-beta-amyloid-imaging.pdf>).

Current use of A β imaging in clinical care is limited. At the time this chapter was drafted, the out-of-pocket cost of a single A β scan was approximately \$3,000, and Medicare had not extended its coverage to support A β PET imaging, despite accumulating evidence that it can result in clinically meaningful changes to patient care. The largest study to date of the utility of A β , the Imaging Dementia-Evidence for Amyloid Scanning (IDEAS) study, found that A β PET imaging findings led to changes in the clinical management of 60% and 64% of patients with MCI and dementia, respectively, who met the AIT's appropriate use criteria for A β PET scan eligibility (Rabinovici et al., 2019). Although A β PET neuroimaging has improved AD diagnostic accuracy, a positive A β PET scan cannot rule out the presence or co-occurrence of neurodegenerative conditions. It is also the case that the prevalence of elevated A β among older adults is much higher than that of clinically defined AD, and not all individuals with elevated A β deposits will go on to develop clinically defined AD (Jack et al., 2019). For these reasons,

correlating clinical symptoms and neuropsychological test findings with A β PET findings remains essential.

3.3. Tau PET Imaging

A number of PET radiotracers have been recently developed for imaging pathologic forms of tau in the brain, including multiple first-generation tau radiotracers, such as Flortaucipir (aka [^{18}F]T807, aka AV-1451), ^{18}F -THK5351, ^{18}F -THK5317, ^{11}C -PBB3, and ^{18}F -FDDNP (Villemagne et al., 2018). Tau is an intracellular protein found in neurons, which participates in the stabilization of axonal microtubules and has been implicated in numerous neurodegenerative conditions, including AD, some forms of FTLT, corticobasal degeneration (CBD), and progressive supranuclear palsy (PSP). In the context of neurodegenerative disease, abnormal phosphorylation of tau can occur, causing phospho-tau to detach from the microtubule and self-aggregate to form insoluble aggregates of paired-helical, straight, and/or twisted filaments, which can, in turn, form neurofibrillary tangles (NFTs). Tau can take the form of six different isoforms comprised of three isoforms of 3-repeat (3R) tau and three isoforms of 4-repeat (4R) tau (Brunden, Trojanowski, & Lee, 2009). Tau isoforms are differentially expressed in distinct neurodegenerative diseases and possess structural properties that influence the binding of PET radiotracers (Leuzy et al., 2019). Efforts to develop an optimal tau tracer have been met with a great number of challenges, among which include variable binding of specific radiotracers across distinct tau isotypes, and nonspecific binding to A β aggregates, white matter, and the choroid plexus (Okamura et al., 2014; Villemagne et al., 2018).

The tau radiotracer Flortaucipir has received the most attention to date. Flortaucipir has demonstrated an ability to differentiate between patients with AD and neurologically healthy individuals (Johnson et al., 2016), although several studies have demonstrated excess off-target

binding of Flortaucipir in the basal ganglia, and in melanin-containing cells, calcifications, and iron deposits (Betthauser, 2019; Marquie et al., 2015). A recent autopsy study found a strong correspondence between Flortaucipir imaging patterns and tau pathology, and demonstrated further that visual reads of Flortaucipir PET images by trained visual raters can accurately identify the AD pathological pattern of tau NFT that corresponds with Braak stages V and VI (Fleisher et al., 2020).

Tau PET has improved the understanding of the spatiotemporal progression of aggregated tau in AD and has added to the information made available by CSF studies. The overlap between CSF tau measures and tau PET is typically modest, but varies by disease stage, brain region, and specific form of tau (Barthélemy et al., 2020; Betthauser, 2019). Consistent with the sequence of AD biomarkers as proposed by Jack and colleagues, the detection of abnormal A β using PET imaging typically occurs earlier than the detection of PET-defined tau NFTs. In the context of AD, PET NFTs demonstrate a neuroanatomical distribution that is distinct from that of A β and includes temporoparietal (angular gyrus) and medial temporal regions (Johnson et al., 2016). While Flortaucipir has been proven to be fairly accurate at labeling tau in patients with AD, results have been far less consistent for imaging tau in non-AD tauopathies, such as PSP and CBD (Leuzy et al., 2019; Marquie et al., 2017). Flortaucipir was recently approved by the FDA for clinical use in patients with suspected AD.

3.4. PET Imaging of Microglial Activation

There is increasing recognition of the importance of neuroinflammation in a wide range of neurologic conditions, including neurodegenerative disease, traumatic brain injury, stroke, and epilepsy. With this understanding has come an increased interest in imaging microglia activation, which is believed to represent a proxy measure of neuroinflammation. Activated microglia take

on a distinct morphology and upregulate the expression of benzodiazepine receptor on the outer mitochondrial membrane (Scarf & Kassiou, 2011). This protein, which is referred to as the peripheral-type benzodiazepine receptor (PBR), or alternatively as 18-kDa translocator protein (TSPO), has served as the molecular target for radiotracers used to quantify microglial activation. The first wave of TSPO imaging employed the [^{11}C]PK11195 radiotracer, which used a non-benzodiazepine isoquinoline carboxamide compound to bind to microglial TSPO (Camsonne et al., 1984). Early studies found regional increases in [^{11}C]PK11195 uptake in patients with AD, multiple sclerosis, and Parkinson's disease (Alam, Lee, & Lee, 2017). Although [^{11}C]PK11195 has since been used for the study of neurological and psychiatric disease, several properties have limited its success in the research realm, including poor penetrance of the blood-brain barrier, short half-life, and non-specific binding due to its lipophilic properties (Best, Ghadery, Pavese, Tai, & Strafella, 2019).

Dozens of second-generation TSPO tracers have also been produced and evaluated, including [^{18}F]-PBR06, [^{18}F]-FEDAA1106, and [^{11}C]-PBR28. Though many of the second-generation tracers show a comparatively better signal-to-noise ratio than that observed using [^{11}C]PK11195, some have demonstrated kinetic properties which necessitate extended scanning time and result in inaccurate estimates of TSPO binding (Best et al., 2019). An additional limitation of second-generation radiotracers is the heterogeneity of binding affinity defined by a single nucleotide polymorphism (rs6971) on the *TSPO* gene (Owen et al., 2012). This genetic variant influences the binding affinity of all second-generation TSPO radiotracers and causes either high-affinity, mixed-affinity, or low-affinity TSPO binding based on the specific genetic polymorphism. As a result of this genetically determined difference in TSPO binding, investigators using second-generation TSPO radiotracers have either excluded low-affinity

binders from analyses or analyzed these participants as a separate group. Recent efforts have been directed toward developing a series of third generation of TSPO tracers less sensitive to the rs6971 genotype, including [^{11}C]-ER176 and Flutriciclamide ([^{18}F]-GE180)) (Fan et al., 2016; Ikawa et al., 2017).

The majority of PET studies of microglial activation have been relatively small and have relied on first generation of TSPO tracers, namely [^{11}C]PK11195. Several studies have demonstrated that patients with AD show elevated [^{11}C]PK11195 binding, particularly in the cingulate, entorhinal, and temporoparietal regions (Cagnin et al., 2001). Individuals with MCI and elevated cortical amyloid also show greater levels of [^{11}C]PK11195 binding. Consistent with the hypothesis that A β deposition may trigger or exacerbate neuroinflammation, [^{11}C]PK11195 levels tend to correlate positively with PET-defined cortical amyloid (Best et al., 2019). Elevated TSPO PET microglial activation has also been observed in cortical regions in the early stages of DLB, early Parkinson's disease, and in the substantia nigra in individuals with idiopathic rapid-eye-movement (REM) sleep behavior disorder (Edison et al., 2013; Stockholm et al., 2017; Surendranathan, Rowe, & O'Brien, 2015). In addition, regional increases in TSPO binding have been demonstrated in acquired neurological conditions, including traumatic brain injury and ischemic stroke (Donat, Scott, Gentleman, & Sastre, 2017; Gulyás et al., 2012).

3.5. PET Dopaminergic Imaging

Several PET tracers have been used to measure the functionality of specific neurotransmitter systems, including dopaminergic cells, glutamate receptors (mGluR5), and serotonergic receptors (5-HT_{1A} and 5-HT_{2A}) (Park et al., 2015; Truchot et al., 2007; Versijpt et al., 2003). Tracers used to visualize dopamine signaling have received a great deal of attention in the literature due to their utility as diagnostic aids and research tools in Parkinson's disease and other

conditions characterized by a progressive loss in dopaminergic neurons. The PET tracer fluorine-18-dihydroxy-phenylalanine ($[^{18}\text{F}]\text{F-DOPA}$) has been widely used to characterize the loss of dopaminergic neurons that occurs in the substantia nigra and basal ganglia of patients with Parkinson's disease or atypical Parkinsonisms (Calabria, Calabria, Gangemi, & Cascini, 2016). $[^{18}\text{F}]\text{F-DOPA}$ binding represents the activity of the L-aromatic amino acid decarboxylase (AADC) decarboxylating enzyme and the dopaminergic neuron storage capacity, and is broadly considered a measure of the presynaptic viability of dopaminergic neurons (Rubello, Nanni, & Fanti, 2007). To prevent the decarboxylation of F-DOPA in peripheral tissue before it crosses the blood-brain barrier, $[^{18}\text{F}]\text{F-DOPA}$ is typically administered following a dose of carbidopa, a DOPA decarboxylase (DDC) inhibitor.

3.5.1. Clinical Applications Dopaminergic PET. $[^{18}\text{F}]\text{F-DOPA}$ PET neuroimaging has demonstrated utility for discriminating individuals with Parkinson's disease and DLB from individuals without Parkinsonian syndromes (Hu et al., 2000). $[^{18}\text{F}]\text{F-DOPA}$ studies of disease progression suggest that the onset of PD occurs near the time that $[^{18}\text{F}]\text{F-DOPA}$ uptake is 75% of normal in the caudate and 91% of normal in the putamen (Morrish, Rakshi, Bailey, Sawle, & Brooks, 1998). In the clinical setting $[^{18}\text{F}]\text{F-DOPA}$ images are typically interpreted visually by examining the extent of binding in the striatum and the shape of the tracer signal. Patients with Parkinson's disease show reduced $[^{18}\text{F}]\text{F-DOPA}$ binding in the basal ganglia, particularly within the posterior region of the putamen contralateral to the side of symptom onset (Calabria et al., 2016; Rinne et al., 2001).

Although $[^{18}\text{F}]\text{F-DOPA}$ has been synthesized for research purposes since the 1980s, this radiotracer was only recently approved by the FDA for clinical use in adults with suspected Parkinsonian syndromes. The dopamine transporter scan, or DaTscan (^{123}I -ioflupane), which

uses single-photon emission computed tomography (SPECT), was approved for a similar indication in 2011. [^{18}F]F-DOPA and DaTscans have demonstrated comparable accuracy for differentiating individuals with Parkinson's disease from those who were neurologically normal (Eshuis et al., 2009). Although [^{18}F]F-DOPA PET provides better image quality than DaTscans, there are several drawbacks that are specific to [^{18}F]F-DOPA imaging, including higher costs and limited accessibility to PET radiotracers. [^{18}F]F-DOPA neuroimaging has also been used outside the context of Parkinson's disease for other neurologic indications, namely to aid in the visualization of gliomas, neuroendocrine tumors, and other types of neoplasms (Pretze, Wängler, & Wängler, 2014).

4. Software for PET Imaging

An up-to-date online list of software used in PET image simulation, reconstruction, partial volume correction, kinetic modeling, radiomics, dosimetry and visualization is maintained by NNMIttools: Tools for Nuclear Medicine and Molecular Imaging Research (<https://nmmitools.org/>).

5. Future Directions

In recent years, a great deal of effort and resources have been directed toward improving upon the current set of available PET radiotracers and expanding the potential applications for PET neuroimaging. For example, as tau PET radiotracers continue to be evaluated and validated for AD, the development of radiotracers for imaging non-Alzheimer's tauopathies such as PSP and CBD remain an active area of study. Additional efforts are being directed toward the development of PET radiotracers for alpha-synuclein, a protein found in Parkinson's disease,

DLB, and multiple system atrophy. While progress has been made on this front, these efforts have been met with numerous challenges that have led to limited success (Kotzbauer, Tu, & Mach, 2017). Given its potential to inform a wide range of neurologic conditions, continued development and improvement of microglial activation imaging also remain a priority. Though TSPO radiotracers have been successfully utilized to an extent, there are several alternatives to TSPO currently being considered as targets for in vivo visualization of microglial activation with PET. Among the promising candidates is a radiotracer that binds to type 2 endocannabinoid (CB2) receptors ($[^{11}\text{C}]\text{NE40}$), a molecule primarily expressed by activated immune cells. In addition, PET imaging of specific neurotransmitter systems and synaptic density (e.g., synaptic vesicle glycoprotein 2A [SV2A]) will remain a scientific priority relevant to many neurodegenerative and neuropsychiatric conditions. As a result of the development of new radiotracers, the expansion of clinical and research indications, and the reduction of associated costs, PET neuroimaging will likely take an increasingly large foothold in clinical practice and neurosciences research in the coming years. For further reading on the topic of PET neuroimaging, please refer to **Table 2**.

Table 2. Essential review articles for PET neuroimaging

Description	References
Overview of PET physics, instrumentation, and image quantification, with future directions	(Vaquero & Kinahan, 2015)
A broad overview of PET neuroimaging for neurologic conditions	(Nasrallah & Dubroff, 2013)
A review of A β and tau PET neuroimaging for Alzheimer's disease and other neurodegenerative conditions	(Villemagne et al., 2018)
A review of FDG PET neuroimaging for neurodegenerative disease	(Shivamurthy et al., 2015)
A broad review of TSPO PET neuroimaging with a focus on new generation radiotracers	(Alam et al., 2017)

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