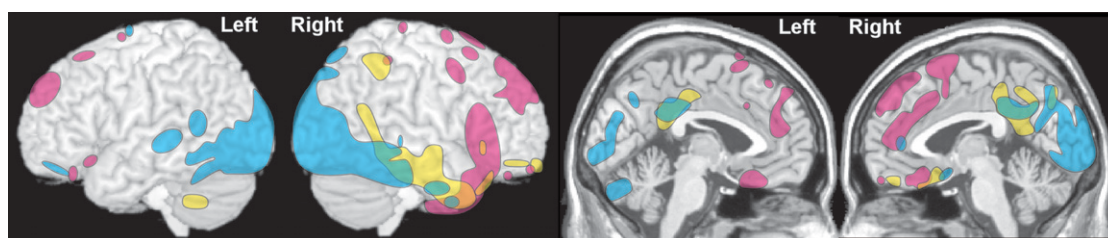


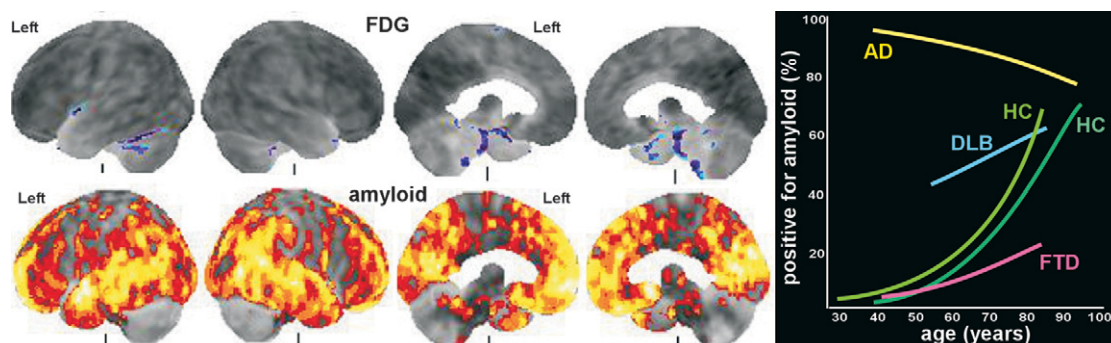
# Clinical Positron Emission Tomography (PET) Neuroimaging: Advantages and Limitations as a Diagnostic Tool

Courtney Slough, Pharm.D., Shane C. Masters, M.D., Ph.D., Robin A. Hurley, M.D., and Katherine H. Taber, Ph.D.

**COVER AND FIGURE 1.** A common analytical approach in positron emission tomography (PET) imaging is to statistically compare a patient's PET images on a voxel-by-voxel basis to a database of healthy individuals matched for age and gender (normative database). Voxels in which the patient differs by more than 2.5 standard deviations (Z-scores less than -2.5 or more than +2.5) indicate areas of significantly altered function.<sup>1</sup> Specificity and sensitivity of this approach can be affected by the size and patient population in the normative database, age adjustment, statistical methods, and the classification of the scan as normal or abnormal. Z score results are often displayed using a three-dimensional (3D) stereotactic surface projection system (3D-SSP). In this example, the Z-score results for fluorodeoxyglucose (FDG) PET imaging demonstrate the patterns of reduced metabolism characteristic of Alzheimer's disease (AD, yellow), frontotemporal dementia (FTD, pink) and dementia with Lewy bodies (DLB, blue) overlaid onto the lateral, medial and inferior surfaces of the brain. Note the predominately posterior pattern of hypometabolism in AD (asymmetric in this case, which is not unusual), involving the parietal and posterior temporal regions as well as the posterior cingulate gyrus. DLB has a similar pattern to AD. However, there is also involvement of the visual cortex. FTD has a predominantly anterior pattern involving the frontal lobes, anterior temporal lobes, and anterior cingulate gyrus.



**FIGURE 2.** Left. Representative PET Z score images of a patient with suspected AD. FDG PET (upper row) was obtained two years before the amyloid (F-18 florbetapir) PET (lower row). Note that there was no clear pattern of hypometabolism (purple-blue) on FDG PET. Amyloid PET was obtained two years later due to progressive worsening of dementia symptoms. Note that very extensive cortical uptake is present (yellow-red) indicating moderate to frequent amyloid plaques and supporting the clinical diagnosis of AD. Right. Although amyloid PET can be helpful in distinguishing AD from other dementing disorders, it is important to remember that presence of amyloid deposition alone is not diagnostic, as it is found in many cognitively healthy individuals.<sup>2-4</sup> Illustrated here is a comparison of the percentage of individuals positive on amyloid PET imaging by age and diagnostic state (AD, yellow; FTD, pink; DLB, blue).<sup>4</sup> The percentage of healthy individuals (HC) positive on amyloid PET (light green) and at autopsy (dark green) is very similar.<sup>2,4</sup>



**FIGURE 3.** In the past decades, a wide array of PET ligands have been developed that target multiple aspects of brain functioning. The locations of several are approximated on this color-coded diagram. Ligands bind to many presynaptic (pink) targets including modulatory receptors (red boxes), neurotransmitter reuptake transporters (yellow boxes), and vesicular neurotransmitter transporters (black boxes). Ligands have been developed for many postsynaptic (purple) neurotransmitter and modulatory receptors (orange boxes). The TSPO receptor (gold boxes) resides on the outer mitochondrial membrane of microglial (green) and astroglial (blue) cells. Other targets include protein aggregates in the intracellular (tau, white squiggles) and extracellular (amyloid, red squiggles) spaces.

**P**ositron emission tomographic (PET) imaging of the brain has been used for many years in research and clinical settings. Many factors have contributed to increased demand including improved techniques, wider availability, reimbursement by third-party payers, and clinical application in oncology. PET imaging demonstrated a 57% annual growth rate after 2004.<sup>5</sup> PET neuroimaging has many applications for use in neurodegenerative disorders, movement disorders, and neuropsychiatric conditions. Through examining metabolism, enzyme activity, protein accumulation, and receptor binding, abnormalities on PET imaging may be detected before changes are apparent on structural imaging. As PET brain imaging is applied to clinical practice, it is important for clinicians to understand both the advantages and limitations as a diagnostic tool. Illustrative clinical examples will focus on the most mature application, the evaluation of patients with primary neurodegenerative disorders.

## Principles of PET

PET scanners detect and localize radiotracers (ligands labeled with a radioisotope) to produce semiquantitative images of in vivo brain functioning.<sup>6–8</sup> The radioisotopes decay through emitting a positron, which annihilates by colliding with an electron. Two gamma-photons traveling at 180 degrees away from each other result from the annihilation, each with energy of 511 keV. They strike opposite detectors nearly simultaneously resulting in a true coincidence event. The scintillator detector converts the 511 keV photon to light, which is detected by the attached photomultiplier tubes. The path between the two detectors hit in coincidence is termed the line of response (LOR). This is critical for the accuracy of the PET scan because the LOR provides additional information regarding position of the coincidence event compared with single photon imaging. An image reconstruction algorithm is applied to the raw data and the resulting spatial distribution of the radiotracer reflects the functional process. Spatial resolution is typically 5 to 10 mm. Although this is much better than single photon emission tomography (SPECT) imaging, companion structural imaging (magnetic resonance imaging, MRI; computed tomography, CT) is typically obtained for better mapping of function to anatomy.<sup>7</sup>

There are several methodological issues that can degrade PET images.<sup>9</sup> One of the most important is Compton scatter. Interaction of one or both of the photons with electrons causes varying degrees of change in direction, artifactually shifting the LOR. Since Compton scatter decreases the energy of the photons, some scatter can be removed by setting an energy threshold. However, some scattered photons are able to hit detectors with energy above the threshold. Therefore, mathematical scatter correction is also required. In addition, photons can be lost to photoelectric absorption or severe Compton scatter in the tissue, resulting in attenuation artifact. PET is particularly sensitive to attenuation

since two photons must be detected for each coincidence event. Attenuation correction is accomplished by measuring the composition of the body along the LOR, most commonly using CT (MRI attenuation correction is also starting to enter clinical use). Attenuation correction depends on matching two different scans, so it is important to instruct the patient to limit movement during scanning to avoid misregistration.<sup>10</sup> Random coincidence events occur when two photons from different annihilation events strike the detectors within the coincidence timing window. The random rate depends on count rate in the scanner and can be adjusted for mathematically. Previously, detector rings were separated with septa (lead or tungsten annular shields) to reduce scatter coincidence events. However, this also blocks cross plane true coincidence events, decreasing count rate and prolonging scan time. Removing the septa reduced data gaps and permitted the generation cross-plane data, allowing for three dimensions (3D) PET.<sup>9,11</sup>

Radiotracers are defined as molecules selective for biochemical processes labeled with a radioactive isotope. For PET, the radioactive moiety is commonly fluorine-18 (<sup>18</sup>F) or carbon-11 (<sup>11</sup>C).<sup>12–14</sup> These radioisotopes are produced by a cyclotron.<sup>15</sup> The short half-life of these isotopes, 20 min for carbon-11 and 110 min for fluorine-18, limits patients' exposure to radioactivity, but presents challenges to availability. The very short half-life of <sup>11</sup>C limits its use to centers with an on-site cyclotron. The longer half-life of <sup>18</sup>F provides sufficient time for regional shipping of radiotracers.<sup>13</sup> There are several requirements for developing a PET radiotracer useful for in vivo imaging.<sup>12,13</sup> The radiotracer should provide sufficient signal at a concentration low enough to prevent pharmacodynamics effects. It is important for the radiotracer to have highly specific binding to the target (high selectivity) and low nonspecific (off target) binding. The radiotracer should localize rapidly to the target. It is preferable that the radiotracer not be metabolized. If it is metabolized, metabolites should not bind with the target.<sup>12</sup> For brain imaging, the radiotracer must be able to reach its target by crossing the blood brain barrier. Important factors include molecule size, lipophilicity, protein binding, size, and polarity.<sup>12</sup>

## Clinical Applications

PET has clinical value when it can contribute to differential diagnosis, enable earlier diagnosis, monitor therapeutic efficacy, and/or alter clinical management.<sup>16</sup> There are many factors that are important to consider when using PET imaging as a clinical tool in neuro psychiatric conditions. These include the sensitivity and specificity of the radiotracer, the FDA approved use(s) of the radiotracer, and the evidence that the PET scan will provide clinically useful information. It is important to complete a full clinical assessment, including appropriate structural imaging and laboratory studies, before utilizing PET imaging. PET imaging alone does not provide conclusive diagnosis.<sup>17,18</sup>

## FDG PET

2- $^{18}\text{F}$ -fluoro-2-deoxy-D-glucose (FDG) is the mostly widely used PET ligand. FDG PET provides a measure of cellular glucose metabolism. FDG is a glucose analog that is taken into cells by membrane-bound glucose transporters. FDG undergoes only the first step in glucose metabolism (phosphorylation). It is trapped within the cell until it is dephosphorylated. FDG accumulation in brain is proportional to regional cerebral metabolic rate (rCMR), which is closely related to neuronal and synaptic function.<sup>16,19</sup> FDG PET is FDA approved for the identification of epileptic seizure foci, evaluation of malignancies, and for specific cardiology studies.<sup>20</sup> FDG PET has been used in studies of many neuropsychiatric conditions including depression, bipolar disorder, schizophrenia, traumatic brain injury, and neurocognitive disorders.<sup>21</sup>

In 2009, the Society of Nuclear Medicine released guidelines for the use of FDG PET in brain imaging.<sup>17</sup> The guidelines should be reviewed and used consistently to ensure accuracy and reproducibility of imaging. Multiple patient-related factors can alter FDG uptake, including blood glucose level, medications, and emotional state (e.g. angry, agitated, profoundly depressed).<sup>7,18,19</sup> Presence of some psychoactive medications (e.g. barbiturates, benzodiazepines) can alter uptake of FDG. Insulin can alter biodistribution of FDG by promoting uptake into muscle, so it is recommended that patients fast and have intravenous fluid containing dextrose or parenteral feedings withheld for 4–6 hours before administration of FDG. In patients with diabetes, blood glucose levels may become elevated to the point of competing with FDG for uptake into the brain. Blood glucose level should be measured prior to injection of FDG in all patients. If too high, rescheduling of the examination is recommended. Alternatively, short acting insulin can be administered with delay of the FDG injection to allow time for clearance of insulin. Good hydration is important to assure rapid renal clearance, which decreases background activity and patients' radiation exposure. FDG is taken up gradually, so the patient needs to remain in a stable environment (quiet darkened room, very limited activity) for at least 30 min after administration. Eyes open is preferred, as occipital lobe metabolism will be reduced under eyes closed conditions.<sup>7,18</sup>

FDG PET can be used clinically to assist in differentiating types of primary neurodegenerative disorders. These conditions affect more than half of individuals greater than 85 years of age and approximately 14% of individuals greater than 65 years.<sup>18</sup> The most prevalent are major neurocognitive disorder due to Alzheimer's disease (AD, 50%–60%), major neurocognitive disorder due to frontotemporal lobar degeneration (FTD, 15%–25%), and major neurocognitive disorder with Lewy bodies (DLB, 15%–25%).<sup>18</sup> FDG PET is currently not FDA approved to assist in the diagnosis of mild neurocognitive disorders or neurodegenerative disorders; thus it is considered an off-label use. However, evidence from clinical trials, national guidelines, and policies

from third party payers support its use under defined criteria. In 2001, the Centers for Medicare and Medicaid Services approved coverage for use of FDG PET in patients who meet the minimal requirements of having a decline in cognitive function for at least six months, meeting criteria for both FTD and AD, and cause of clinical symptoms is unclear.<sup>14,22</sup>

Although presence of characteristic patterns of altered metabolism can improve diagnostic sensitivity, it is important to remember that there is sufficient variability to cause overlap between disease states. The most common pattern in AD is hypometabolism in the posterior cingulate cortex (PCC), precuneus and posterior temporoparietal areas including the angular gyrus (Figure 1).<sup>16,18,23,24</sup> PCC is often the earliest area affected. In advanced AD, metabolic activity is reduced in the prefrontal cortex with possible involvement of more posterior frontal lobe (sparing the sensorimotor cortex). Metabolic deficits are typically bilateral but may be asymmetric, and unilateral deficits are also seen. Metabolism is usually preserved in anterior cingulate and visual cortices, thalamus, basal ganglia and cerebellum. In contrast, the most common pattern in FTD is hypometabolism in the frontal and anterior temporal cortices. The anterior cingulate cortex is usually affected, whereas the parietal cortex is spared (Figure 1). The pattern of metabolic impairment in temporoparietal cortices is similar in DLB and AD. PCC is commonly preserved in DLB (although some studies disagree) but impaired in AD. Visual cortex is commonly impaired in DLB but preserved in AD (Figure 1).<sup>16,18,23,24</sup>

Multiple studies have evaluated the use of FDG PET in differentiating among dementing disorders. Sensitivity and specificity are generally favorable, but vary across studies and are affected by analytic methodology (e.g. axial sections versus surface projections, visual versus quantitative assessment).<sup>16,18,25,26</sup> The 2011 National Institute on Aging-Alzheimer's Association guidelines for the diagnosis of dementia due to AD stated that FDG PET and other biomarkers may be used to confirm that the pathophysiological process is consistent with AD in patients who meet the core clinical diagnosis for probable AD, but does not recommend for routine use in diagnosis.<sup>27</sup> FDG PET may be particularly useful when structural imaging is uninformative.<sup>26,28</sup> In some cases frontal and temporoparietal hypometabolism occur equally, complicating the clinical diagnosis. For these patients,  $\beta$ -amyloid PET (Figure 2) may provide additional guidance (discussed below).

## Amyloid and Tau PET

The hallmark pathologies of AD are cerebral  $\beta$ -amyloid plaques (extracellular) and tau neurofibrillary tangles (intracellular).<sup>14,29,30</sup> However, the relationship between these markers, neurodegeneration, and development of dementia remains controversial. Both autopsy and amyloid PET studies have reported that amyloid burden does not correlate with cognitive state, synaptic activity or neurodegeneration.<sup>30,31</sup> Many cognitively healthy elderly individuals have considerable



amyloid deposition (Figure 2).<sup>2–4</sup> Studies have reported that both cognitive state and neurodegeneration do strongly correlate with level of soluble  $\beta$ -amyloid oligomers and the density of tau neurofibrillary tangles.<sup>14,30,31</sup> It has been proposed that presence of  $\beta$ -amyloid facilitates hyperphosphorylation of tau, the first stage in the process that ends with deposition of aggregated tau as neurofibrillary tangles.<sup>30</sup>

In 2013 The Amyloid Imaging Task Force (a collaboration between the Alzheimer's Association and the Society for Nuclear Medicine) released appropriate use criteria for amyloid PET imaging: atypical symptom presentation (etiologically mixed or atypical clinical course), atypical age of onset (65 years or less), persistent or progressive unexplained mild cognitive impairment.<sup>32,33</sup> The cost of amyloid PET remains a factor in widespread clinical adoption. In 2013, the Centers for Medicare and Medicaid Services concluded that there was insufficient evidence to approve coverage for use of amyloid PET for the diagnosis of AD. Limited use in research was approved. A single amyloid PET scan is covered provided it is done as part of an approved clinical research study.<sup>34</sup> The most studied amyloid PET radiotracer is Pittsburgh Compound B (<sup>11</sup>C-PiB).<sup>14,33</sup> However, the short half-life (20 min) prohibited commercial use. There are currently three 18F amyloid PET radiotracers approved by the FDA: florbetaben, florbetapir, and flutemetamol. A recent meta-analysis found that all three tracers had high sensitivity and specificity.<sup>33</sup> There were no differences in diagnostic accuracy. The use of amyloid PET may enhance the development of treatments targeting  $\beta$ -amyloid plaques. Currently florbetapir is being used in a phase 1b clinical trial for adacanumab (a human immunoglobulin  $\gamma$ 1 monoclonal antibody selective for aggregated  $\beta$ -amyloid plaques) to identify amyloid positive patients. Of 278 patients evaluated with amyloid PET imaging, 39% were excluded due to a negative scan.<sup>35</sup> Multiple other radiotracers with improved characteristics, such as reduced binding in white matter, are under development.<sup>14</sup>

Combining information from different ligands may provide a better understanding of some aspects of pathophysiology.<sup>36</sup> A recent longitudinal study obtained both FDG and amyloid (<sup>11</sup>C-PiB) PET as well as functional connectivity measures (resting state functional MRI) in patients with probable early stage AD.<sup>37</sup> Hypometabolism in areas of prefrontal cortex free of amyloid was associated with amyloid burden in areas with high functional connectivity to those areas.<sup>37</sup> As noted by the authors of this study, their results are consistent with the hypothesis that functional disconnection is the basis for neuronal dysfunction (as indicated by hypometabolism) in areas with little or no amyloid deposition.

Tauopathies (e.g. AD, progressive supranuclear palsy, corticobasal degeneration, chronic trauma encephalopathy, some FTD variants) are neurodegenerative conditions characterized by the accumulation of misfolded aggregates of the tau phosphoprotein.<sup>29–31</sup> AD is the most common tauopathy. Tau is critical for the assembly and stabilization of the microtubules which support the cytoskeleton and

intracellular transport.<sup>29</sup> As noted above, tau deposition is highly associated with cognitive impairment and neurodegeneration, so early detection is important for developing interventions. However, the characteristics of tau deposition pose many challenges for developing PET tracers in addition to the requirement of crossing the blood brain barrier. Deposition is intracellular, so PET tracers must be able to pass into the cells of the brain (tau aggregates can occur in neurons, astrocytes, and oligodendrocytes; Figure 3).<sup>38</sup> Further, there are six tau isoforms. Tau aggregates associated with specific tauopathies vary in their ultrastructural conformation and histopathological characteristics.<sup>31</sup> Tau aggregates also have multiple sites available for binding of tracers and conformational differences could result in variable binding affinity.<sup>30,31</sup> Binding to other misfolded proteins in addition to tau is also a concern. The PET tracer 18F-FDDNP, for example, binds to both amyloid plaques and tau neurofibrillary tangles.<sup>30</sup> The development of tau PET tracers is a rapidly growing field, and requires establishment of reference ranges, stability and applicable quantification methods.<sup>30,31</sup> The tau PET tracer [<sup>18</sup>F]-T807 (also known as [<sup>18</sup>F]-1451) is the most studied.<sup>31</sup> Several candidate ligands have been shown to have unexpectedly high retention in nontarget areas including the striatum, brainstem, fibria and cerebellar white matter.<sup>30</sup> Studies are underway in multiple conditions (e.g. AD, traumatic brain injury, depression).<sup>31</sup>

### Other Targets for PET Radiotracers

In recent decades, a wide array of PET ligands have been developed that provide a basis for assessing many aspects of presynaptic (e.g. neurotransmitter reuptake transporters, vesicular neurotransmitter transporters, neurotransmitter synthesis, modulatory receptors), postsynaptic (e.g. neurotransmitter receptors) and glial (e.g. mitochondrial receptor) functioning (Figure 3).<sup>14,16,39</sup> Most familiar are the ligands targeting postsynaptic neurotransmitter receptors. Parkinson's disease (PD) has been established to have decrease in nigrostriatal dopamine functioning, and provides a useful example of the diversity of presynaptic targets for PET ligands.<sup>14,39–41</sup> One is dopamine transporter (DAT) receptors in the striatum. These presynaptic receptors are responsible for dopamine reuptake, and levels decrease in PD due to both loss of terminals and adaptive changes.<sup>39,41</sup> A DAT SPECT tracer (<sup>123</sup>I-ioflupane) was approved by the FDA in 2011 as an adjunctive diagnostic tool in the evaluation of adult patients with suspected Parkinsonian syndromes.<sup>40</sup> Several DAT PET tracers are under development including both 11C and 18F forms of PE2I (a cocaine derivative) and <sup>11</sup>C methylphenidate.<sup>41,42</sup> Presynaptic dopamine functioning can also be assessed utilizing tracers for vesicular monoamine transporter type 2 (VMAT2) such as <sup>11</sup>C or <sup>18</sup>F DTBZ.<sup>14,39,41,43</sup> Dihydroxyphenylalanine (DOPA) is a final precursor for monoamine synthesis, so uptake of 18F-DOPA reflects local synthesis of dopamine, norepinephrine and/or serotonin (depending on the region examined).<sup>39,44</sup>

PET ligands that bind to a similar array of targets are available for many other neurotransmitter systems. For example, PET tracers that bind to serotonin 2A (5-HT<sub>2A</sub>) receptors include <sup>18</sup>F setoperone, <sup>11</sup>C MDL 100907 and <sup>18</sup>F altanserin.<sup>14</sup> Decreased 5-HT<sub>2A</sub> binding has been reported in mania, aggression, and schizophrenia. Increased binding has been reported in obsessive-compulsive disorder and Tourette syndrome.<sup>14</sup> The endocannabinoid type 1 (CB1) receptor is present on all cell types in the brain (presynaptic terminals, astrocytes, microglia, oligodendroglia).<sup>14</sup> Increased binding of 18F-MK-9470 (an inverse agonist) has been reported in PD, anorexia nervosa, migraine, and following stroke.<sup>14,39</sup> Elevated binding of 11C-OMAR (a selective antagonist) has been reported in schizophrenia.<sup>14</sup>

The translocator protein (TSPO, previously called the peripheral-type benzodiazepine receptor) provides an example of an entirely different type of target. TSPO is an 18 kDa protein located on the outer mitochondrial membrane of microglia and astrocytes.<sup>14,45,46</sup> In healthy brain, expression is quite low. Expression increases with injury-induced microglial and astroglial activation.<sup>45,46</sup> The most widely utilized tracer has been <sup>11</sup>C (R)PK11195 (selective antagonist). Multiple new tracers are in development with better characteristics (e.g. higher brain permeability, lower nonspecific binding, <sup>18</sup>F for longer half-life).<sup>46</sup> A present limitation is the need to assess a genetic polymorphism that is associated with intrinsic differences in binding status (high, mixed, low).<sup>14,46</sup> Clinical studies suggest potential for evaluating and monitoring therapeutic interventions for brain injuring conditions.<sup>14,45,46</sup> Binding has been reported to be increased in the ischemic penumbra for several days to weeks after stroke onset. Focal increases in both lesions and surrounding white matter have been found in patients with multiple sclerosis. Increases have also been found in several neurodegenerative conditions (e.g. AD, FTD, PD, viral encephalitis). It may also serve as a useful biomarker in other disorders. A recent study reported that patients with schizophrenia had elevated TSPO binding in gray matter compared with healthy controls.<sup>47</sup> In the group with subclinical symptoms (high risk for psychosis), symptom severity was positively correlated with TSPO distribution volume in gray matter, suggesting potential as a biomarker for elevated risk during the prodromal stage. Although TSPO has been considered a marker for neuroinflammation, its presence on multiple cell types including astrocytes suggests a less specific role.

## Conclusions

Advances in PET imaging have increased its utilization in neuropsychiatry over the last few decades. Like all neuroimaging techniques, a thorough understanding of the strengths and weaknesses is essential for use as a clinical tool. For some neurodegenerative conditions, currently available radiotracers can provide important information about disease pathology and progression. As new radiotracers are validated in human

studies, PET's contributions to neuropsychiatric diagnoses are likely to increase.

## AUTHOR AND ARTICLE INFORMATION

Dr. Slough is affiliated with the Research and Academic Affairs Service Line and the Veterans Affairs Mid Atlantic Mental Illness Research, Education, and Clinical Center at the W.G. Hefner Veterans Affairs Medical Center in Salisbury, North Carolina. Dr. Masters is affiliated with the Department of Radiology at Wake Forest School of Medicine in Winston-Salem, North Carolina. Drs. Hurley and Taber are affiliated with the Research and Academic Affairs Service Line and the Veterans Affairs Mid Atlantic Mental Illness Research, Education, and Clinical Center at the W.G. Hefner Veterans Affairs Medical Center in Salisbury, North Carolina. Dr. Hurley is affiliated with the Departments of Psychiatry and Radiology at Wake Forest School of Medicine in Winston-Salem, North Carolina, and the Menninger Department of Psychiatry and Behavioral Sciences at Baylor College of Medicine in Houston, Texas. Dr. Taber is affiliated with the Division of Biomedical Sciences at the Via College of Osteopathic Medicine in Blacksburg, Virginia, and the Department of Physical Medicine and Rehabilitation at Baylor College of Medicine in Houston, Texas.

Corresponding author: Send correspondence to Dr. Hurley; e-mail: Robin.Hurley@va.gov.

*J Neuropsychiatry Clin Neurosci* 2016; 28:A4–71; doi: 10.1176/appi.neuropsych.16030044

## REFERENCES

- Shokouhi S, Claassen D, Riddle W: Imaging Brain Metabolism and Pathology in Alzheimer's Disease with Positron Emission Tomography. *J Alzheimers Dis Parkinsonism* 2014; 4:143
- Rowe CC, Ellis KA, Rimajova M, et al: Amyloid imaging results from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging. *Neurobiol Aging* 2010; 31:1275–1283
- Jansen WJ, Ossenkoppele R, Knol DL, et al: Amyloid Biomarker Study Group: Prevalence of cerebral amyloid pathology in persons without dementia: a meta-analysis. *JAMA* 2015; 313:1924–1938
- Ossenkoppele R, Jansen WJ, Rabinovici GD, et al: Amyloid PET Study Group: Prevalence of amyloid PET positivity in dementia syndromes: a meta-analysis. *JAMA* 2015; 313:1939–1949
- Smith-Bindman R, Miglioretti DL, Johnson E, et al: Use of diagnostic imaging studies and associated radiation exposure for patients enrolled in large integrated health care systems, 1996–2010. *JAMA* 2012; 307:2400–2409
- Basu S, Kwee TC, Surti S, et al: Fundamentals of PET and PET/CT imaging. *Ann N Y Acad Sci* 2011; 1228:1–18
- Byrnes KR, Wilson CM, Brabazon F, et al: FDG-PET imaging in mild traumatic brain injury: a critical review. *Front Neuroenergetics* 2014; 5:13
- Hu Z, Yang W, Liu H, et al: From PET/CT to PET/MRI: advances in instrumentation and clinical applications. *Mol Pharm* 2014; 11: 3798–3809
- Zanzonico P: Positron emission tomography: a review of basic principles, scanner design and performance, and current systems. *Semin Nucl Med* 2004; 34:87–111
- Cohade C, Wahl RL: Applications of positron emission tomography/computed tomography image fusion in clinical positron emission tomography-clinical use, interpretation methods, diagnostic improvements. *Semin Nucl Med* 2003; 33:228–237
- Turkington TG: Introduction to PET instrumentation. *J Nucl Med Technol* 2001; 29:4–11
- Pike VW: PET radiotracers: crossing the blood-brain barrier and surviving metabolism. *Trends Pharmacol Sci* 2009; 30:431–440
- Brust P, van den Hoff J, Steinbach J: Development of (18)F-labeled radiotracers for neuroreceptor imaging with positron emission tomography. *Neurosci Bull* 2014; 30:777–811

14. George N, Gean EG, Nandi A, et al: Advances in CNS Imaging Agents: Focus on PET and SPECT Tracers in Experimental and Clinical Use. *CNS Drugs* 2015; 29:313–330
15. Granov A, Tiutin L, Schwarz T: Positron Emission Tomography. Edited by Granov A, Tiutin L, Schwarz T. Berlin, Heidelberg, Springer, 2013, pp 3–24
16. Eisenmenger LB, Huo EJ, Hoffman JM, et al: Advances in PET Imaging of Degenerative, Cerebrovascular, and Traumatic Causes of Dementia. *Semin Nucl Med* 2016; 46:57–87
17. Waxman A, Herholz K, Lewis D, et al: Society of Nuclear Medicine Procedure Guideline for FDG PET Brain Imaging. Reston, VA, Society of Nuclear Medicine, 2009. [cited 2016 March 9], Available from <http://www.snmmi.org/ClinicalPractice/content.aspx?ItemNumber=6414>
18. Brown RK, Bohnen NI, Wong KK, et al: Brain PET in suspected dementia: patterns of altered FDG metabolism. *Radiographics* 2014; 34:684–701
19. Sarikaya I: PET studies in epilepsy. *Am J Nucl Med Mol Imaging* 2015; 5:416–430
20. Triad Isotopes I: FLUDEOXYGLUCOSE F 18 (fludeoxyglucose f-18 injection, solution). Bethesda, MD, National Library of Medicine, 2015. [cited 2016 March 9], Available from <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=5d05df4a-463e-4e66-9387-f3a842e20cd0>
21. Schöll M, Damián A, Engler H: Fluorodeoxyglucose PET in Neurology and Psychiatry. *PET Clin* 2014; 9:371–390, v
22. Centers for Medicare and Medicaid Services: Decision Memo for Positron Emission Tomography (FDG) and Other Neuroimaging Devices for Suspected Dementia #CAG-00088R. Baltimore, CMS; 2004. <https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=104>.
23. Herholz K: Guidance for reading FDG PET scans in dementia patients. *Q J Nucl Med Mol Imaging* 2014; 58:332–343
24. Marcus C, Mena E, Subramaniam RM. Brain PET in the diagnosis of Alzheimer's disease. *Clin Nucl Med* 2014; 39:e413–422; quiz e423–416
25. Morbelli S, Piccardo A, Villavecchia G, et al: Mapping brain morphological and functional conversion patterns in amnesic MCI: a voxel-based MRI and FDG-PET study. *Eur J Nucl Med Mol Imaging* 2010; 37:36–45
26. Segobin S, La Joie R, Ritz L, et al: FDG-PET Contributions to the Pathophysiology of Memory Impairment. *Neuropsychol Rev* 2015; 25:326–355
27. McKhann GM, Knopman DS, Chertkow H, et al: The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011; 7:263–269
28. Kerklaan BJ, van Berckel BN, Herholz K, et al: The added value of 18-fluorodeoxyglucose-positron emission tomography in the diagnosis of the behavioral variant of frontotemporal dementia. *Am J Alzheimers Dis Other Dement* 2014; 29:607–613
29. Querfurth HW, LaFerla FM: Alzheimer's disease. *N Engl J Med* 2010; 362:329–344
30. Villemagne VL, Fodero-Tavoletti MT, Masters CL, et al: Tau imaging: early progress and future directions. *Lancet Neurol* 2015; 14: 114–124
31. Okamura N, Harada R, Furukawa K, et al: Advances in the development of tau PET radiotracers and their clinical applications. *Ageing Res Rev* 2016; S1568–1637(15)30045-3 (Epub ahead of print, Jan 21, 2016)
32. Johnson KA, Minoshima S, Bohnen NI, et al: Alzheimer's Association; Society of Nuclear Medicine and Molecular Imaging; Amyloid Imaging Taskforce: Appropriate use criteria for amyloid PET: a report of the Amyloid Imaging Task Force, the Society of Nuclear Medicine and Molecular Imaging, and the Alzheimer's Association. *Alzheimers Dement* 2013; 9:e-1–e-16
33. Morris E, Chalkidou A, Hammers A, et al: Diagnostic accuracy of (18)F amyloid PET tracers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis. *Eur J Nucl Med Mol Imaging* 2016; 43:374–385
34. Centers for Medicare and Medicaid Services: Decision Memo for Beta Amyloid Positron Emission Tomography in Dementia and Neurodegenerative Disease (CAG-00431N). Baltimore, 2013. <https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=265>
35. Sevigny J, Suhy J, Chiao P, et al: Amyloid PET Screening for Enrichment of Early-Stage Alzheimer Disease Clinical Trials: Experience in a Phase 1b Clinical Trial. *Alzheimer Dis Assoc Disord* 2016; 30:1–7
36. Gialleonardo VD, Wilson DM, Keshari KR: The Potential of Metabolic Imaging. *Semin Nucl Med* 2016; 46:28–39
37. Klupp E, Grimmer T, Tahmasian M, et al: Prefrontal hypometabolism in Alzheimer disease is related to longitudinal amyloid accumulation in remote brain regions. *J Nucl Med* 2015; 56: 399–404
38. Villemagne VL, Okamura N: In vivo tau imaging: obstacles and progress. *Alzheimers Dement* 2014; 10(suppl):S254–S264
39. Weingarten CP, Sundman MH, Hickey P, et al: Neuroimaging of Parkinson's disease: Expanding views. *Neurosci Biobehav Rev* 2015; 59:16–52
40. Gayed I, Joseph U, Fanous M, et al: The impact of DaTscan in the diagnosis of Parkinson disease. *Clin Nucl Med* 2015; 40:390–393
41. Brooks DJ: Molecular imaging of dopamine transporters. *Ageing Res Rev* 2016; S1568–1637(15)30043-X (Epub ahead of print, Jan 21, 2016)
42. Appel L, Jonasson M, Danfors T, et al: Use of IIC-PE2I PET in differential diagnosis of parkinsonian disorders. *J Nucl Med* 2015; 56:234–242
43. Hsiao IT, Weng YH, Lin WY, et al: Comparison of 99mTc-TRODAT-1 SPECT and 18 F-AV-133 PET imaging in healthy controls and Parkinson's disease patients. *Nucl Med Biol* 2014; 41:322–329
44. Holland JP, Cumming P, Vasdev N: PET radiopharmaceuticals for probing enzymes in the brain. *Am J Nucl Med Mol Imaging* 2013; 3:194–216
45. Chen MK, Guilarte TR: Translocator protein 18 kDa (TSPO): molecular sensor of brain injury and repair. *Pharmacol Ther* 2008; 118:1–17
46. Vivash L, O'Brien TJ: Imaging microglial activation with TSPO PET: lighting up neurologic diseases? *J Nucl Med* 2016; 57:165–168
47. Bloomfield PS, Selvaraj S, Veronese M, et al: Microglial activity in people at ultra high risk of psychosis and in schizophrenia: an [(11)C]PBR28 PET brain imaging study. *Am J Psychiatry* 2016; 173: 44–52