Brain: Positron Emission Tomography Tracers Beyond [^{18}F] Fluorodeoxyglucose

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KEYWORDS

• Positron emission tomography • Brain • Central nervous system • Positron • Dementia
• Parkinson disease • Epilepsy • Neuroinflammation

KEY POINTS

- Positron emission tomography (PET) has led to significant insights into nervous system biology, physiology, and pathophysiology in health and disease.
- Several PET radiopharmaceuticals beyond fluorodeoxyglucose (FDG) have been used to study the physiology and pathophysiology in neurosciences.
- Future studies on the use of advanced PET imaging in delineating neural pathophysiology, drug development, and altering patient management and outcomes across the disciplines of neurosciences are needed.

INTRODUCTION

Positron emission tomography (PET) is a molecular imaging technique used for generating maps of functional and biochemical activity in target tissues in vivo.[1] PET has led to significant insights into nervous system biology, physiology, and pathophysiology in health and disease. Several of these insights and applications have a direct usefulness for the neurologist.[2] Although fluorine 18 [^{18}F]fluorodeoxyglucose (FDG) has remained a workhorse of clinical PET imaging, many other radiolabeled biomolecules have been studied using PET.[3] In this article, brain PET ligands beyond FDG, across the spectrum of neurologic subspecialties, including dementias, movement disorders, epilepsy, brain tumors, and neuroinflammation, are reviewed. Of the numerous available PET radiopharmaceuticals, a few have been selected that have been extensively studied in common neurologic disorders.

DEMENTIA

There is widespread deposition of amyloid in the cerebral cortex in Alzheimer disease (AD). Carbon 11 (^{11}C) Pittsburgh compound B (PiB) is a radiolabeled analogue of thioflavin dye, which has been established as a valid biomarker for amyloid deposition in the human brain.[4] Given the short half-life of ^{11}C, limiting its availability, several ^{18}F-labeled amyloid-binding PET radiopharmaceuticals have been developed, including ^{18}F-florbetapir, ^{18}F-flutemetamol and ^{18}F-florbetaben, which have recently been approved by the US Food and Drug Administration (FDA) for clinical use.[5–7] However, no single diagnostic test or imaging is considered sufficient. Amyloid imaging and cerebrospinal fluid CSF Aβ levels are considered markers of the neuropathologic process, whereas FDG-PET is considered a marker for neuronal damage, and their combined interpretation may aid a diagnosis of AD in the right clinical context.[8]

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There has been a controversy regarding the overall and relative usefulness of these PET agents with respect to FDG-PET for diagnosing AD.[9–11]

^{18}F-Florbetapir is a fluorine-labeled stilbene derivative. The recommended dose for ^{18}F-florbetapir is 370 MBq (10 mCi). For routine clinical use, the scan is obtained as a 10-minute acquisition, starting 40 to 50 minutes after intravenous injection (**Table 1**). The effective radiation dose after a 10-mCi injection in an adult is 7.0 mSv.[12] An excellent correlation between ^{18}F-florbetapir and ^{11}C-PiB uptake has been shown.[13]

Normal amyloid scans show a clear gray-white matter contrast, with more radioactivity concentration in white matter. In patients with AD, uptake is increased in the orbitofrontal cortex, anterior cingulate, precuneus, posterior cingulate, and lateral temporal cortex, consistent with autopsy findings in direct comparison studies (**Fig. 1**).[2,14] According to some recommendations, the ^{18}F-florbetapir scan is considered positive if either (1) 2 or more brain areas (each larger than a single cortical gyrus) show reduced or absent gray-white matter contrast, or (2) there are 1 or more areas in which gray matter uptake is intense and clearly exceeds the uptake in adjacent white matter. A potential pitfall of scan interpretation using these criteria is in cases with brain atrophy, in which the gray-white matter contrast may be lost because of atrophy rather than abnormal accumulation in the gray matter. Alternatively, the ratio of radiotracer concentration in the region of disease to either the whole brain or to pons has been proposed as a semiquantitative index of ^{18}F-florbetapir uptake.[15]

On correlation with disease, a negative amyloid scan corresponded to a neuropathologic amyloid deposition rating (Consortium to Establish a Registry for Alzheimer's Disease) of none to sparse, whereas a positive amyloid scan corresponded to a rating of moderate to frequent amyloid plaque deposition in the cortex.

Amyloid imaging can be useful in differentiating AD from frontotemporal dementia. Patients with frontotemporal dementia do not show significant amyloid deposition. However, abnormal amyloid deposition may be seen in 50% to 70% of patients with dementia with Lewy bodies (DLB) (**Table 2**).[16] Negative ^{18}F-florbetapir PET scans have been reported for some clinically diagnosed patients with AD, consistent with literature reports that 10% to 20% of clinically diagnosed patients with AD do not have amyloid disease at autopsy.[17]

False-positive results may be obtained in apparently healthy persons and are found in 12% of those in their 60s, 30% of those in their 70s, and approximately 50% of those older than 80 years.[16] Carriers of the ApoE-4 allele, constituting 27% of the general population, have almost 3 times the risk of a positive ^{11}C-PiB scan, even if cognitively normal, and a similar increase in the risk of developing AD. Overall accuracy of amyloid imaging for AD is estimated to be more than 90% for patients younger than 70 years, about 85% for patients in their 70s, and 75% to 80% for those older than 80 years.[16]

Amyloid imaging also has a role in evaluation of patients with mild cognitive impairment (MCI). Patients with MCI have a 70% chance of progression to AD over a 3-year period if the amyloid scan is read as positive, as opposed to only a 10% chance if the scan is deemed to be negative. Similarly, there is a high likelihood of AD being a cause of

Table 1
Imaging protocols

^{18}F-Florbetapir	10-min acquisition starting 40–50 min after intravenous injection of 10 mCi
^{11}C- or ^{18}F-Flumazenil	Dynamic list mode acquisition for 60–90 min after injection of 10 mCi
^{11}C-Methionine or ^{18}F-fluoroethyltyrosine	Dynamic acquisition or 10-min acquisition performed 20 min after injection of 10 mCi
^{18}F-Fluorothymidine	Dynamic acquisition obtained for 60–90 min after injection of radiopharmaceutical or static imaging obtained for 10 min 60 min after injection of 5–10 mCi
^{18}F-Fluorodopa	Ki values obtained from dynamic imaging performed over 90 min. Static imaging performed 60–70 min after injection for striatal imaging in movement disorders but earlier (approximately 20 min) for brain tumor evaluation
^{18}F-Fluoropropyl-(+)-dihydrotetrabenazine	10-min acquisition 90 min after intravenous injection of 10 mCi or dynamic acquisition
^{11}C-PK11195	Dynamic acquisition over approximately 60 min