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PET/CT in diagnosis of dementia

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Abstract

Clinical use of positron emission tomography (PET) is now well established in neurodegenerative disorders, especially in the diagnosis of dementia. Measurement of cerebral glucose metabolism is of significant value, and it facilitates early diagnosis, appropriate differential diagnosis, and the evaluation of drug treatment in patients with dementia. In addition, tracers offer new perspectives for studying the neuropathology of underlying dementia, such as the accumulation of amyloid proteins, tau-proteins, or the presence of neuroinflammation. Finally, PET tracer studies of different neurotransmitter systems in dementia may not only increase the understanding of pathophysiologic mechanisms of the different disorders, but also improve diagnostic accuracy. In conclusion, PET imaging with different tracers offers reliable biomarkers in dementia, which can assist clinicians in the diagnosis of different dementing disorders, especially in the situation of overlapping phenotypes.

Keywords

PET/CT; dementia; Alzheimer's disease

Introduction

Positron emission tomography (PET) is now well established for clinical use in neurodegenerative disorders. Measurements of cerebral glucose metabolism, as done with [¹⁸F]Fluorodeoxyglucose ([¹⁸F]FDG) PET, are of unequivocal value in early diagnosis, differential diagnosis, and the evaluation of drug treatment for patients with dementia. Additionally, several other PET tracers have been developed to study the neuropathology and alterations of neurotransmitter systems underlying dementia, to advance our understanding of the pathophysiology of dementia, and to improve diagnostic accuracy.

The use of computed tomography (CT) in conjunction with PET is a remarkable technical improvement for this imaging modality because it provides an accurate map for attenuation correction and a suitable anatomical substrate for coregistration with magnetic resonance

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Conflicts of interest

The authors declare no conflicts of interest.

imaging. Moreover, the CT scan acquired right before the PET scan allows a concurrent evaluation of possible structural abnormalities (i.e., stroke), which are often the secondary causes of dementia.

Here, PET tracers of diagnostic interest are reviewed, which have been used for evaluating functional activity, pathological processes, and neurotransmitter systems in the major dementing disorders, including Alzheimer's disease (AD), frontotemporal lobar degeneration (FTLD), and Lewy body disease (LBD) (see Tables 1 and 2).

Alzheimer's disease

AD is the most prevalent neurodegenerative disorder and the leading cause of dementia in the elderly, with a steadily increasing incidence.^{1,2}

Neuropathological hallmarks of AD include beta-amyloid (A β) deposition in the form of senile plaques (SPs) and accumulation of neurofibrillary tangles (NFTs), which induce a series of toxic events that result in synaptic dysfunction, neuronal loss, and brain atrophy.³ The neuropathological changes of AD are known to precede the clinical expression of disease by many years.⁴

Clinically, AD is characterized by progressive memory loss and impairment of other cognitive functions that significantly interfere with activities of daily living.⁵ Research criteria for AD diagnosis include the presence of at least one of the following: abnormal biomarker detectable by structural neuroimaging, PET imaging of brain glucose use and of amyloid accumulation, or cerebrospinal fluid (CSF) evaluation of A β or tau-proteins.⁶ The inclusion of PET imaging among AD diagnostic biomarkers highlights the increasing importance of PET as a reliable and accurate technique to evaluate AD at early, and possibly preclinical, phases.

Full-blown dementia in AD is often preceded by a diagnosis of mild cognitive impairment (MCI), which is characterized by impairment of one cognitive domain with preserved activities of daily living and no dementia.⁷ Depending upon the presence of memory impairment, MCI patients can be divided into amnesic (single- or multiple-domain) and nonamnesic (single- and multiple-domain) subtypes.⁷ Amnesic MCI (30% of MCI patients) likely represents a prodromal form of AD, with about 12% converting to AD each year.⁸

[¹⁸F]FDG PET imaging in AD

[¹⁸F]FDG PET imaging is used to measure cerebral metabolic rates of glucose (CMR_{glc}), an index of brain synaptic activity and density.⁹ Several [¹⁸F]FDG PET studies have been performed to qualitatively and quantitatively estimate AD-related brain changes. These studies have consistently shown widespread metabolic deficits in the neocortical association areas, with sparing of the basal ganglia, thalamus, cerebellum, primary sensory motor cortex, and visual cortex.¹⁰ Specifically, the so-called "AD metabolic pattern" is characterized by hypometabolism in associative parietotemporal areas,¹¹ posterior cingulate cortex, and precuneus,¹² as well as medial temporal lobes, mostly entorhinal cortex¹³ and hippocampus (Fig. 1).¹⁴ With advancing disease, hypometabolism extends to prefrontal cortex.¹¹

The brain hypometabolism finding in PET scans of AD patients correlates with clinical symptoms of cognitive impairment,^{15,16} as well as CSF markers of AD pathology such as concentrations of phosphorylated TAU protein and A β .^{17,18}

Longitudinal studies in AD patients have demonstrated that CMRglc reductions in AD-related regions worsen along with dementia progression, with an average decline of 16–19% over a three-year period.^{16, 19} Due to its sensitivity to detect changes over time, [¹⁸F]FDG PET can be useful not only for AD diagnosis, but also to monitor disease progression and therapeutic interventions.

Additionally, [¹⁸F]FDG PET has proved helpful in the differential diagnosis of AD from other dementias (Fig. 2). While AD is characterized by hypometabolism involving parietotemporal and posterior cingulate cortices, FTLN is defined by prevalent CMRglc deficits in the frontal and temporal (mostly anterior) cortex, and dementia with Lewy bodies (DLB) by involvement of the parietooccipital areas. Despite some regional overlap, the typical AD pattern discriminated AD from FTLN with more than 85% sensitivity and specificity and from LBD with > 90% sensitivity and 70% specificity.²⁰

In patients with MCI, hypometabolism is seen to affect mostly the hippocampus and entorhinal cortex,^{14, 21} posterior cingulate, as well as temporoparietal cortices.¹² Reduced metabolism in AD-related regions is predictive of conversion from MCI to AD with 75–100% accuracy (about 90% sensitivity and specificity).^{22, 23}

Finally, CMRglc impairments have been observed in cognitively normal individuals at known increased risk for AD prior to symptoms onset. Hypometabolism in AD-related regions was reported in asymptomatic carriers of the ApoEε4 allele and in individuals with a maternal family history of AD, which are both risk factors for late-onset AD.^{24, 25} Furthermore, in these at-risk subjects, CMRglc reductions decline at a greater rate than in controls, possibly reflecting ongoing neurodegeneration.²⁶

PET imaging of neuropathology in AD

The deposition of Aβ protein is an early event in the pathogenesis of AD and is crucial in the amyloid cascade hypothesis.³ The best characterized amyloid PET tracer to date, [¹¹C]Pittsburgh compound B ([¹¹C]PiB),²⁶ has high sensitivity in detecting amyloid pathology *in vivo*²⁷ as it binds with high affinity to neuritic Aβ plaques but not to diffuse plaques and NFTs.²⁸ Patients with AD show high cortical [¹¹C]PiB retention, mostly involving frontal, temporal, and parietal association cortices (Fig. 3).²⁶ Low tracer uptake is observed in the pons and cerebellum,²⁶ and these regions, especially the cerebellum, are largely used as reference regions to derive semiquantitative measures of distribution volume or standardized uptake value ratios.²⁹ Cortical [¹¹C]PiB uptake is correlated with CSF levels of Aβ1–42, suggesting that PET amyloid imaging could be an early marker of prodromal AD.³⁰

Longitudinal PET studies showed no significant changes in [¹¹C]PiB retention in AD patients over time, indicating that amyloid deposition may reach a peak prior to AD diagnosis and then plateau, while CMRglc and cognition continue to worsen as AD progresses.^{31, 32}

MCI patients show a bimodal distribution of [¹¹C]PiB uptake, and are typically classified as PiB-positive (i.e., showing PiB values within the AD-range) or PiB-negative (i.e., PiB values within the normal range) patients.³³ Follow-up studies indicate that MCI converters to AD show higher [¹¹C]PiB retention at baseline than MCI nonconverters, suggesting that PiB-positive patients may be at an increased risk to decline to AD.^{33, 34}

Interestingly, high cortical [¹¹C]PiB binding has been observed in 30–50% of healthy elderly.³⁵ Longitudinal studies are needed to demonstrate whether high [¹¹C]PiB retention in normal individuals reflects a prodromal stage of AD or rather is without clinical

significance. Recent [^{11}C]PiB PET studies demonstrated higher amyloid burden in several cortical regions in cognitively normal carriers of ApoE ϵ 4 allele and normal subjects with maternal family history of AD, as compared to controls.^{36,37} These studies suggest that increased amyloid burden in healthy elderly may reflect predisposition to AD, although this remains to be verified in further longitudinal studies.

Among other amyloid imaging compounds, 2-(1-{6-[(2- ^{18}F)-fluoroethyl](methyl)amino}-2-naphthyl)ethylidene)malononitrile ([^{18}F]FDDNP) binds to NFTs as well as amyloid plaques.³⁸ [^{18}F]FDDNP PET studies reported increased tracer uptake in AD and MCI patients as compared with controls, showing a cortical uptake pattern similar to [^{11}C]PiB but also including uptake in the medial temporal lobes.³⁹ [^{18}F]FDDNP uptake yielded 100% diagnostic separation between AD and controls, and 95% between MCI and controls.³⁹ Tracer uptake showed good correlation with cognitive impairment and longitudinal changes along with progression to AD.^{40,41} Recent studies demonstrated an association between [^{18}F]FDDNP uptake and CSF tau-protein,⁴² as well as with ApoE-carrier status in nondemented individuals.⁴⁰

PET imaging of neuroinflammation in AD

A β deposition and neurodegeneration in AD are associated with local glial response and microglial activation as an inflammatory response. 1-[2-chlorophenyl]-*N*-methyl-*N*-(1-methylpropyl)-3-isoquinoline carboxamide ([^{11}C]PK11195) is a specific ligand for the peripheral benzodiazepine binding receptor site, which is expressed on activated microglia. PET with [^{11}C]PK11195 has been used to provide a quantitative *in vivo* measurement of glial activation and neuroinflammation in AD.⁴³ Increased [^{11}C]PK11195 binding was observed in patients with AD compared to healthy controls, involving the entorhinal, temporoparietal, and cingulate cortices.⁴³ Moreover, cortical [^{11}C]PK11195 binding correlated with cognition scores.⁴⁴

PET imaging of neurotransmitter systems in AD

Neurodegeneration in AD is associated with impairment of several neurotransmitter systems, including cholinergic and serotonergic innervation of the cerebral cortex.

PET imaging of the cholinergic system—Cholinergic degeneration is associated with a reduction of acetylcholinesterase (AChE) activity, which is the most important degrading enzyme for acetylcholine in the human cortex.⁴⁵ PET studies using acetylcholine analogues *N*-[^{11}C]-methylpiperidyl-4-acetate ([^{11}C]MP4A) and *N*-[^{11}C]-methyl piperidine-4-propionate ([^{11}C]MP4P), which are substrates of AChE, found a decline of cortical AChE activity in AD patients, mostly involving temporal cortex.^{46,47} AChE activity reductions have been shown in MCI patients, in particular those MCI that converted to AD at follow-up,⁴⁷ confirming the association between cholinergic degeneration and development of dementia. PET with acetylcholine analogues has also been used to measure drug-induced AChE inhibition in AD patients, which was reported to be about 30–40% for currently available AChE inhibitors, suggesting a role for PET imaging of the cholinergic system in treatment follow-up, drug dosage adjustment, and identification of likely responders.⁴⁸

PET imaging of the serotonergic system—Serotonergic system impairment plays a critical role in depression, which is often a co-occurring critical clinical issue in AD. PET studies using [^{18}F]altanserin, a tracer for serotonin (5-HT) subtypes 2A (5-HT $_2$ A) receptors, showed 40% reduction of receptor density in AD patients compared to controls, mostly involving amygdala-hippocampal complex, anterior cingulate, prefrontal, temporal, parietal, and sensorimotor cortices.⁴⁹ Moreover, AD patients showed a significant reduction of 5-HT $_1$ A receptor density in the hippocampus, as measured by [^{18}F]29-methoxyphenyl-(*N*-29-

pyridinyl)-*p*-fluoro-benzamidoethylpiperazine ([¹⁸F]MPPF) PET,⁵⁰ confirming the correlation between neuronal loss and lower receptor density in this key brain region.⁵⁰

Frontotemporal lobar degeneration

FTLD is the second most common diagnosis of dementia in individuals younger than 65 years.⁵¹ Neuropathologic alterations in FTLD are heterogeneous, including the presence of insoluble tau proteins in the form of intraneuronal NFTs or Pick bodies, or tau-negative ubiquitin-positive inclusions.^{52,53}

FTLD is clinically characterized by personality changes and cognitive disturbances, such as deficits of attention, executive functions, and language. Clinical classification of FTLD is divided into FTLD forms presenting with alterations of personal and social conduct (behavioral variant frontotemporal dementia, bvFTD, associated with bilateral involvement of the frontal lobes),⁵⁴ versus forms with prominent changes in language (semantic dementia [SD], and progressive nonfluent aphasia [PNFA], associated with impairment of temporal lobes and of left frontotemporal cortex, respectively).^{55,56} Some FTLD patients may also develop parkinsonism.⁵⁷ When behavioral and personality alterations are accompanied by clinical amyotrophic lateral sclerosis/motor neuron disease, the syndrome frontotemporal dementia with motor neuron disease emerges.⁵⁸

[¹⁸F]FDG PET imaging in FTLD

[¹⁸F]FDG PET studies in FTLD demonstrate the presence of metabolic impairment mainly involving frontal and anterior temporal lobes,^{59,60} with milder hypometabolism of the parietal lobes, which become more evident as the disease advances.⁵⁹ This pattern of predominantly frontal hypometabolism facilitates the differential diagnosis between AD and FTLD, although with some overlap, since frontal regions can be affected in AD and temporoparietal cortex in FTLD (Fig. 2).^{20,61}

Specific patterns of metabolic impairment have been associated with different subtypes of FTLD (Fig. 4). bvFTD patients show hypometabolism of frontal lobe regions on [¹⁸F]FDG PET, specifically involving orbitofrontal, frontopolar, medial frontal, dorsolateral, and lateral inferior frontal regions, and anterior cingulate cortices.^{62,63} Metabolic impairments spread to temporal cortex and subcortical regions in more advanced stages of bvFTD.⁶¹

Patients with SD show hypometabolism of the temporal lobes, involving particularly the anterior portion (Fig. 4).^{63,64} Metabolic reductions in SD may also involve frontal midline structures, such as gyrus rectus, cingulate, orbitofrontal, and anterior medial cortices, as well as caudate nucleus, insula, and hippocampus.⁶⁴

Finally, [¹⁸F]FDG PET studies in PNFA patients consistently reported asymmetric hypometabolism, affecting mostly frontotemporal regions of the left hemisphere, including inferior and middle frontal, dorsolateral prefrontal, frontopolar cortices, Broca's and Wernicke's areas, as well as middle and inferior temporal regions (Fig. 4).^{65,66} Some studies showed that metabolic impairment involves mainly the left insula/frontal opercular region in early stages ("pure" PNFA),⁶⁵ and extends to temporoparietal cortices in more advanced stages of disease.⁶⁶

PET imaging of neuropathology (tau pathology) in FTLD

Several types of neuropathological alterations underlie FTLD, including the presence or absence of tau and ubiquitin, while amyloid deposition is not a characteristic finding.⁵² On amyloid PET, patients with FTLD show low cortical [¹¹C]PIB retention, with uptake values close to those seen in healthy controls, confirming the lack of amyloid deposition.⁶⁷ For this

reason, [^{11}C]PIB is of great value in the differential diagnosis between FTLT and AD, especially in cases with atypical symptoms.⁶⁷

The ability of [^{18}F]FDDNP to label NFTs suggests that this tracer could be useful in PET imaging of tauopathies, such as some cases of FTLT. Patients with FTLT show high [^{18}F]FDDNP uptake in frontal and prefrontal regions compared to controls.⁶⁸ While FTLT patients show increased tracer uptake in frontal and lateral temporal regions similar to AD patients, [^{18}F]FDDNP uptake was lower than AD in parietal cortex, showing a prominent frontal/temporal signal in contrast to the typical parietal/medial temporal signal observed in AD.⁶⁸ [^{18}F]FDDNP could, therefore, provide a useful tool for evaluating the presence and extent of tau pathology *in vivo*, for differential diagnosis of FTLT from AD, and, possibly, to monitor the effect of therapies designed to prevent or slow down NFTs accumulation in both disorders.

Other tracers in FTLT

Serotonergic neurotransmission—Selective vulnerability of the serotonergic system, which is tightly bound to behavioral modulation, has been demonstrated in FTLT by a PET study with [^{11}C]MDL100907, a selective tracer for 5-HT_{2A} receptors.⁶⁹ Patients with bvFTD showed significant reductions of 5-HT_{2A} receptor densities in frontal medial, frontopolar, cingulate cortices, and in mesencephalon compared to controls,⁶⁹ consistent with positive results of the treatment of behavioral disorders in bvFTD by selective serotonin reuptake inhibitors.⁷⁰

Neuroinflammation—Microglial cell activation has been implicated in the pathogenesis of several neurodegenerative disorders, including FTLT.⁷¹ PET studies using [^{11}C]PK11195, a marker of activated microglia, demonstrate increased binding in brains of patients with FTLT, mostly in the frontal, medial temporal, and subcortical regions.⁷² Some studies report similar findings of increased [^{11}C]PK11195 binding in AD patients. Overall, activated microglia, as reflected in increased [^{11}C]PK11195 binding, does not appear to be specific to AD or FTLT, but rather to be present in neurodegenerative disorders with diverse neuropathological substrates, thus reflecting a common neuroinflammatory reaction.

Lewy body diseases

LBD is the second most common cause of neurodegenerative dementia after AD.⁷³ Clinically, LBD is characterized by dementia, parkinsonism, fluctuating cognitive impairment, attentional disturbances, and persistent, unprovoked visual hallucinations.⁷³

At post-mortem, LBD is characterized by alpha-synuclein inclusions. Alpha-synuclein is the major component of Lewy bodies, the histopathological hallmarks of LBD, which are associated with varying degrees of AD-type pathology, including amyloid plaques and NFTs.^{74,75} LBD is also characterized by neuronal loss in the substantia nigra with consequent degeneration of nigrostriatal projections.⁷⁴

LBD includes two clinical syndromes, DLB and Parkinson's disease with dementia (PDD).⁷³ DLB is diagnosed when dementia occurs before or concurrently with parkinsonism, while PDD is characterized by onset of dementia after 12 months of parkinsonism.⁷⁴

Dementia with Lewy bodies

DLB is clinically characterized by progressive cognitive decline, accompanied by fluctuating cognition with pronounced variations in attention and alertness, impairment of visual perception including hallucinations, and parkinsonism.⁷³ Additional features are

REM sleep disorders, severe neuroleptic sensitivity, and dopaminergic system dysfunction as demonstrated by *single photon emission computed tomography* (SPECT) or PET (discussed below).⁷³ In DLB, dementia may present at the time of onset or may precede parkinsonism.⁷⁴

[¹⁸F]FDG PET imaging in DLB—[¹⁸F]FDG PET studies in DLB demonstrated widespread cortical hypometabolism, with typical marked CMRglc reductions in primary visual and occipital association areas, and less-severe reductions in parietal, frontal, and anterior cingulate cortices (Supporting Fig. S1).^{76–78} Subcortical structures and primary somatosensory cortex are relatively spared. Although this “DLB metabolic pattern” somewhat overlaps with that seen in AD because of the involvement of parietotemporal areas in both diseases,⁷⁶ the presence of occipital hypometabolism in DLB, associated with preserved metabolism in medial temporal and posterior cingulate cortices, distinguished DLB from AD with 83–90% sensitivity and 80–87% specificity (Fig. 2).^{20,76,77}

PET imaging of neuropathology in DLB—The majority of DLB patients show high [¹¹C]PiB retention, reflecting high amyloid burden, in one or more cortical regions.^{79,80} Although [¹¹C]PiB uptake levels in DLB are similar to those usually observed in AD, occipital [¹¹C]PiB retention has been shown to be higher in DLB than in AD patients.⁸⁰ DLB patients show higher cortical [¹¹C]PiB uptake as compared to PDD and Parkinson’s disease without dementia (PD), suggesting that amyloid pathology may influence, at least in part, the evolution of dementia in DLB, possibly by being associated with faster development of the full DLB clinical phenotype.^{80,81}

PET imaging of neurotransmitter systems in DLB

PET imaging of the dopaminergic system

A characteristic neuropathologic feature of DLB is the degeneration of striatal dopaminergic nerve terminals, which can be studied with [¹⁸F]DOPA PET. Reductions in [¹⁸F]DOPA uptake were reported in the striatum of DLB patients, mostly involving the putamen, at levels similar to PD.^{82,83} Dopaminergic deficits are present already at early stages of disease, when symptoms of parkinsonism are not yet evident.⁸² [¹⁸F]DOPA PET is a reliable technique to differentiate DLB and AD, with a reported sensitivity of 86% and a specificity of 100%.⁸²

Striatal presynaptic dopaminergic innervation has also been assessed with [¹¹C]DTBZ, which binds to type-2 presynaptic vesicular monoaminergic transporters. As with [¹⁸F]DOPA, striatal [¹¹C]DTBZ binding values are severely reduced in DLB,⁸⁴ and [¹¹C]DTBZ PET accurately distinguishes DLB from AD.⁸⁴

PET imaging of the cholinergic system

PET studies using [¹¹C]MP4A to measure AChE activity have shown that DLB is characterized by severe cholinergic deafferentation of the neocortex, particularly in posterior cortical regions.^{83,85} DLB patients show more widespread and profound cortical [¹¹C]MP4A uptake reductions as compared to PD, and no differences compared to PDD patients,⁸⁵ suggesting that DLB and PDD may share a common pathological background in terms of brain cholinergic dysfunction. Moreover, widespread cortical cholinergic impairment may contribute to explain the favorable response to treatment with cholinesterase inhibitors in both DLB and PDD patients.⁷³

Parkinson's disease with dementia

Many patients with PD develop dementia, with a reported average prevalence of 40%.⁸⁶ This condition is referred to as PDD.

[¹⁸F]FDG PET imaging in PDD—On [¹⁸F]FDG PET, patients with PDD show metabolic reductions involving predominantly the occipital cortex, similar to DLB (Supporting Fig. S1). In addition, cortical hypometabolism may affect parietal, frontal, and lateral temporal regions.⁷⁸ PDD patients showed less extensive metabolic deficit in lateral temporal areas as compared to DLB patients, and, more severe hypometabolism in parietal and frontal regions compared to PD patients.⁷⁸ These data suggest that the development of dementia in PD may be associated with the progression of metabolic deficits to fronto-parietal, rather than occipital, areas. Overall, the pattern of hypometabolism observed in PDD patients shows close similarities to those described in DLB, confirming that the two pathologies have similar underlying neurobiological characteristics and are both part of the LBD spectrum.

PET imaging of neuropathology in PDD—Imaging studies using [¹¹C]PiB PET, a marker of brain amyloid deposition, demonstrated that the majority of PDD patients have no [¹¹C]PiB cortical uptake,⁸⁷ with tracer retention significantly lower than both AD and DLB patients, and comparable to PD and normal subjects.^{79,80} Detailed examinations of the morphology of A β pathology suggest that the lack of [¹¹C]PiB retention in PDD may be due to absence of core-dense amyloid plaques.⁸⁸

PET imaging of neurotransmitter systems in PDD

PET imaging of the dopaminergic system

Patients with PDD show significant reductions of striatal [¹⁸F]DOPA uptake compared to controls, with lower uptake values in the putamen, particularly in the posterior part, in the hemisphere contralateral to the most affected body side.⁸³ The level and pattern of striatal decreased [¹⁸F]DOPA uptake are comparable to those observed both in PD without dementia and in DLB.⁸³

PET imaging of the cholinergic system

PET with [¹¹C]MP4A and [¹¹C]MP4P demonstrates a widespread impairment of AChE activity in cerebral cortex in PDD, especially in the posterior cortical regions,^{83,89} similar to findings in DLB patients. Cortical [¹¹C]MP4A reductions in PDD correlate with striatal dopaminergic impairment, pointing toward an interdependent degeneration in dopaminergic and cholinergic neurons.⁸⁹

Summary and conclusions

Brain PET using [¹⁸F]FDG is a firmly established imaging technique in the early detection and differential diagnosis of dementia. Overall, AD is characterized by early and progressive regional CM-Rglc impairment of parietotemporal and posterior cingulate areas, DLB by metabolic impairment of the primary and association visual occipital cortex, and FTLT by impairment of the frontal and anterior temporal regions, with different patterns of hypometabolism observed in different subtypes of FTLT and DLB.

New perspectives are offered by tracers for amyloid imaging, which appear to be sensitive for detecting pathology at the preclinical stages of AD and may contribute to the differential diagnosis of amyloid-positive diseases (AD and DLB) from tauopathies (FTLT).

Tracers for local AChE activity as well as other receptors shed light on neurotransmitter deficits in dementing disorders. PET tracers for the presynaptic dopaminergic system are accurate markers of the impairment of dopamine synthesis characteristic of LBD.

In conclusion, PET imaging with different tracers offers reliable biomarkers in dementia, which can assist clinicians in the diagnosis of different dementing disorders, especially in the presence of overlapping phenotypes. Additionally, due to its capacity to correlate with disease progression, PET imaging can support physicians in giving patients more accurate information regarding prognosis, management, and treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. [^{18}F]FDG PET scan of a representative patient with AD. From left to right: axial sections showing reduced tracer uptake in (A) inferior parietal lobules, bilaterally, where a slight asymmetry is noticeable (left < right); (B) superior temporal gyri, bilaterally, with the left hemisphere being more affected than the right; (C) bilateral medial temporal lobes and inferior temporal cortex; and (D) a coronal section showing hypometabolism of the hippocampi.

Figure 2.

Representative cortical [^{18}F]FDG PET patterns in NL, AD, DLB, and FTD. 3D-surface projection (3D-SSP) maps and corresponding Z scores showing CMRglc reductions in clinical groups as compared with a NL database are displayed on a color-coded scale ranging from 0 (black) to 10 (red). From left to right: 3D-SSP maps are shown on the right and left lateral, superior, and inferior, anterior and posterior, right and left middle views of a standardized brain image.

Figure 3. ^{18}F FDG and ^{11}C PiB PET scans of a representative normal subject (left side of figure) and a patient with AD (right side). For both scans, standardized uptake value ratios to the cerebellum are displayed using a color-coded scale (range: 1–2.5).

Figure 4. [18F]FDG PET in different forms of FTLD, showing three representative cases with bvFTD (top), PNFA (middle), and SD (bottom).

Table 1

PET tracers used to investigate functional activity, neuropathological processes, and neurotransmitter activity in dementia

Tracer	Targets
[¹⁸ F]FDG	Functional activity, glucose use
[¹¹ C]PiB	Amyloid plaques
[¹⁸ F]FDDNP	Tau-protein
[¹¹ C]PK11195	Microglial activation
[¹¹ C]MP4A, [¹¹ C]MP4P, [¹¹ C]PMP	Cholinergic neurons, AChE activity
[¹¹ C]nicotine, [¹⁸ F]A85380	Cholinergic neurons, nicotinic receptors
[¹⁸ F]DOPA	Dopaminergic neurons, dopa decarboxylation, and vesicular storage
[¹¹ C]DTBZ	Dopaminergic neurons, monoamine transporters
[¹¹ C]WAY-100635, [¹⁸ F]MPPF	Serotonergic neurons, 5HT1A receptors
[¹⁸ F]/[¹¹ C]altanserin, [¹¹ C]MDL-100907	Serotonergic neurons, 5HT2A receptors

Table 2

Major findings in dementia for PET tracers mainly used in clinical practice

Disease	[¹⁸ F]FDG	[¹¹ C]PiB/[¹⁸ F]FDDNP	Dopaminergic system tracers
AD	Parietotemporal, posterior cingulate, medial temporal hypometabolism, accompanied by frontal hypometabolism in advanced disease	high cortical uptake, mostly in frontal, parietal, and temporal association cortices	Normal
FTLD	bv FTD: frontal lobe hypometabolism, accompanied by temporal and subcortical hypometabolism in advanced stages; SD: temporal hypometabolism, associated with frontal hypometabolism; PNFA: left frontotemporal hypometabolism	Low cortical [¹¹ C]PiB retention; high [¹⁸ F]FDDNP uptake in frontal and prefrontal regions	Normal
LBD	Widespread hypometabolism with marked metabolic reductions in occipital cortex	DLB: high cortical [¹¹ C]PiB retention; PDD: low cortical [¹¹ C]PiB retention	Marked reduction in striatum, more prominent in putamen