



Diagnostic Role of PET in Dementia **CME**

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Target Audience

This activity is intended for radiologists, nuclear medicine specialists, and neurologists who are interested in improving the early diagnosis and clinical management of dementias such as Alzheimer's disease.

Goal

The objective of this activity is to spotlight the clinical utility of positron emission tomographic (PET) scanning in the early detection and clinical management of dementias such as Alzheimer's disease; to define appropriate settings for the use of this technology; and to offer a forum for a key opinion leader in nuclear medicine and emergent PET scanning applications to highlight the value of this technology for radiologists, nuclear medicine specialists, and neurologists who are members of the Medscape audience.

Learning Objectives

Upon completion of this activity, participants will be able to:

1. Describe how PET scanning can detect subtle metabolic changes in the brain associated with Alzheimer's disease prior to the onset of symptoms.
2. Detail how PET scanning can differentiate the metabolic signs of Alzheimer's disease from other dementias, such as Lewy body dementia.
3. Discuss ways in which PET scanning is more cost-effective than clinical evaluation alone in the diagnosis of Alzheimer's disease.
4. Outline the role of PET scanning in the detection of metabolic changes in the brain linked to frontotemporal dementia.
5. Highlight the effectiveness of PET in delineating metabolic changes in the brain that may precede the development of Parkinson's disease.

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Contents of This CME Activity

1. [Diagnostic Role of PET in Dementia](#)

- Introduction
- Assessment of Alzheimer's Disease
- Delineating Frontotemporal Dementia
- The Emergent Role of Positron Emission Tomography in Parkinson's Disease
- References

Diagnostic Role of PET in Dementia

Introduction

An early application for positron emission tomography (PET) was in imaging of the brain for assessing the regional distributions of blood flow, glucose metabolism, neurotransmitters, enzymes, and receptors. Despite the early application of PET in brain research, however, the current clinical applications of PET are relatively limited to a few conditions. The intent of this program is to spotlight the clinical application of PET in the imaging work-up of dementia.

We specifically emphasize the evidence for Alzheimer's and frontotemporal dementia and highlight the differential diagnosis of these disease processes in relation to other types of dementia such as vascular dementia, dementia with Lewy bodies, Pick's disease, and the dementia associated with Parkinson's disease. The clinical role of PET in dementia is expected to grow in the near future not only in the preclinical diagnosis arena but also in the objective imaging-based prediction and evaluation of response to novel treatments in the developmental pipeline.

1. In your neurology practice, approximately how many patients do you see per month whom you suspect have Alzheimer's disease?

- 10-20
- 20-30
- 30-50
- > 50

Assessment of Alzheimer's Disease

Alzheimer's disease (AD) is the most common form of dementia and is characterized as a progressive neurodegenerative disorder associated with gradual decline in cognition and behavior. It is estimated that 8% of people older than the age of 65 years suffer from AD and the prevalence climbs with increasing age.^[1-3] The neuropathologic (neurofibrillary tangles of hyperphosphorylated tau, neuritic plaques composed of amyloid beta peptide, and neurotransmitter deficits) spread of the disease progresses from transentorhinal to the limbic and then to the neocortical brain regions.^[4,5] Association cortices are more severely involved while the primary somatosensory and motor cortices, the basal ganglia, the thalamus, and the cerebellum are relatively spared.^[6] Accurate early diagnosis of AD is important because early use of medications such as cholinesterase inhibitors may improve or delay the cognitive loss that occurs in mild-to-moderate disease.^[7] Additionally, there may be a psychosocial benefit for the individual patient if the patient becomes aware of the diagnosis before the clinical manifestation of the disease.

Normal aging of the brain is characterized by a regional decline in the cerebral glucometabolism of the prefrontal cortex.^[8] However, the hypometabolism associated with AD and its progression appears to reflect the vulnerability within the limbic-cortical network.^[8] Fluorodeoxyglucose (FDG) PET demonstrates reductions in the cerebral

glucometabolism that may occur a few years before the overt clinical manifestation of disease^[6,9-13] (Figures 1, 2).

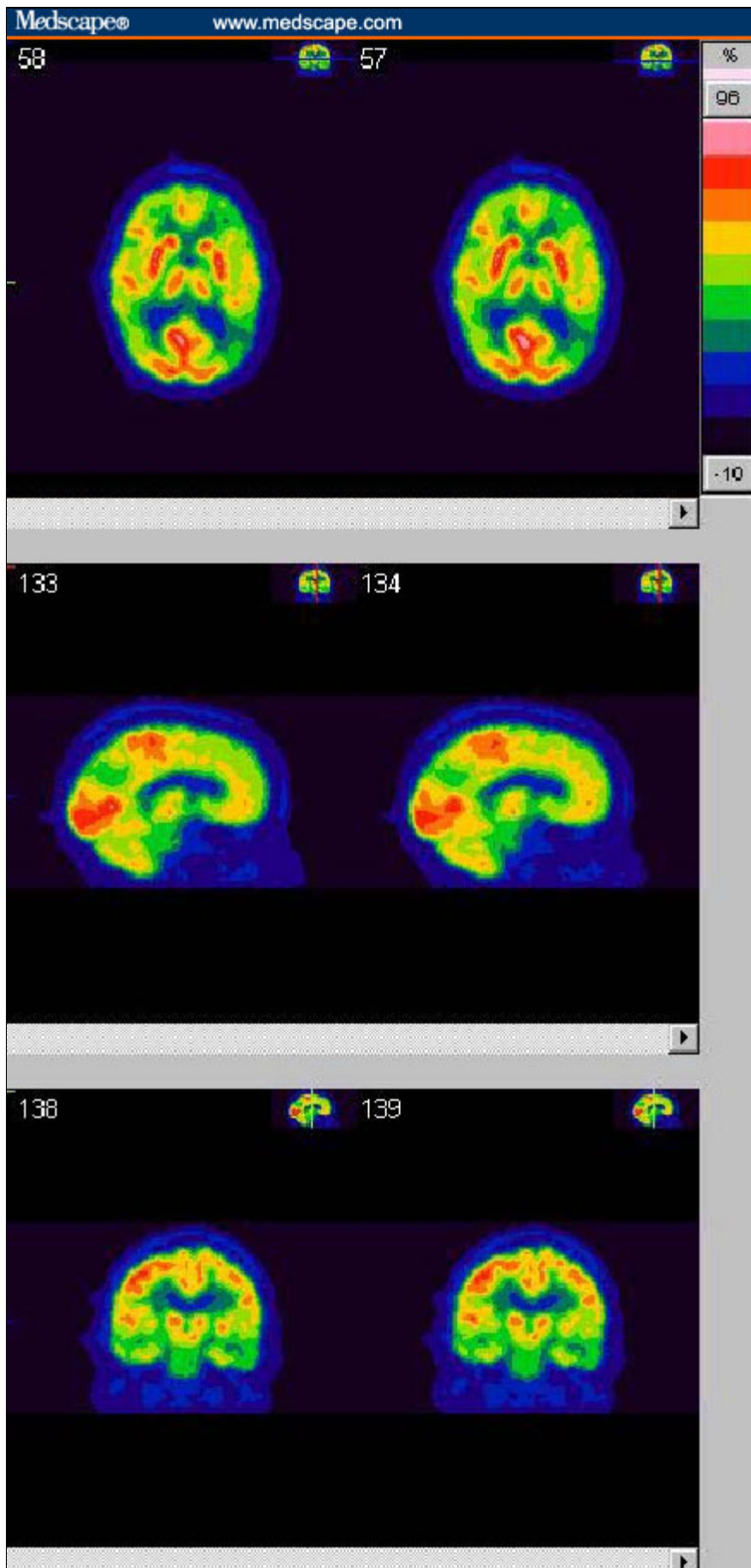


Figure 1. Coronal (top), sagittal (middle), and axial (bottom) FDG PET images of a patient with Alzheimer's disease. Note the marked relatively symmetric bilateral temporoparietal hypometabolism with sparing of the visual cortex, sensorimotor strip, and the subcortical grey matter.

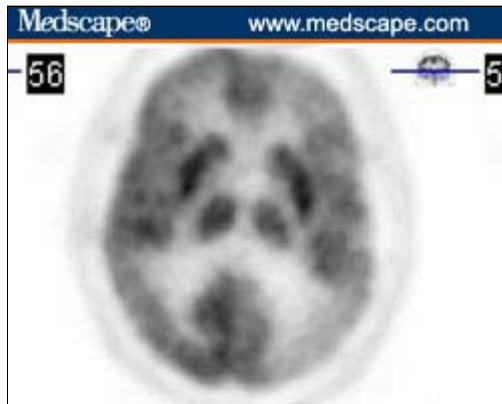


Figure 2. Lewy body dementia (DLB). Note the generalized cortical hypometabolism that also includes the occipital visual cortex.

A classic pattern is bilateral parietotemporal and posterior cingulate cortices hypometabolism, which may be asymmetric and be associated with hippocampal atrophy.^[14-19] There may also be crossed cerebellar and uncrossed basal ganglia and thalamic diaschisis.^[20] Hoffman and colleagues^[16] showed that the FDG PET demonstration of the classic metabolic abnormality associated with pathologically verified AD has a sensitivity of 93%, a specificity of 63%, and an accuracy of 82%. FDG PET is particularly useful in differentiating the Alzheimer-type glucose metabolic pattern from the pattern of the other dementias and in this sense can aid with the differential diagnosis. The sensitivity of FDG PET achieves 90%, although the specificity in differentiating AD from other dementias is lower.^[18] A group of Japanese investigators^[21] has shown that the cerebral glucose metabolism in severe AD is significantly lower than that of age-matched control subjects (5.71 ± 0.62 mg/100 g/min vs 6.85 ± 0.66 mg/100 g/min, respectively).

The exact biologic basis for the decline in the brain glucometabolism in AD is unclear. The decline in cerebral metabolic activity appears to be unrelated to neurofibrillary tangle density but seems to be associated, at least in part, with a decrease in the hexokinase activity and neuronal loss.^[22] One study^[23] has suggested that hypometabolism in AD is related to not only reduced glucose phosphorylation activity but also diminished glucose transport, particularly in the parietal and temporal cortices. Of note, other studies^[24,25] have concluded that glucose metabolism is reduced early in AD (reflecting decreased basal synaptic functioning) and is unrelated to a rate limitation in glucose delivery, abnormal glucose metabolism, or abnormal coupling between oxidation and phosphorylation. Further investigations will be needed to unravel the complexity of the observed brain hypometabolism in patients with AD.

For greater accuracy, the reduction in FDG uptake with advancing age should be corrected on the account of age-related cerebral volume loss.^[26] Additionally, it has been suggested that measurements of cerebral glucose metabolism in patients with AD may be artifactually depressed due to partial volume averaging effects in relation to the enlarged cerebral fluid space (CSF) spaces.^[27] Meltzer and colleagues^[27] studied this phenomenon by applying a magnetic resonance imaging (MRI)-based method of partial volume correction to FDG PET data. Partial volume correction of PET data resulted in 19% to 49% increases in regional activity in the patients with AD. This partial volume correction of PET data also resulted in a significant impact on the correlations between regional glucose metabolism and neurophysiologic performance and further improved interpretation of specific cognitive dysfunction in view of the functional imaging data.

Despite the resting-state brain metabolic abnormality in AD, cerebral metabolic response to passive audiovisual stimulation may reflect the integrity of synaptic function, and the potential responsiveness of brain to drug therapy.^[28] This reflects the notion of potentially reversible and irreversible stages of brain metabolic failure in AD.^[29] Pathologically, the initial functionally responsive stage of AD is accompanied by reduced synaptic energy demand of enzymes mediating mitochondrial oxidative-phosphorylation. The later irreversible stage is marked by synaptic loss, accumulation of intracellular neurofibrillary tangles, reduced general transcriptional capacity, and death of neurons.^[29] An additional interesting observation has been that delusion in patients with AD is associated with dysfunction in specific brain areas (left medial occipital region and left inferior temporal gyrus) in comparison to those without delusions.^[30] Moreover, in patients with AD and depression, there may be significant frontal lobe hypometabolism.^[31]

FDG PET has been shown to provide important prognostic information so that a negative PET scan is indicative of unlikely progression of cognitive impairment for a mean follow-up of 3 years in those patients who initially present with cognitive symptoms of dementia.^[2] In 1 study,^[32] it was found that scores less than 7 on the California Verbal Learning Test-Long Delay Free Recall test were associated with a typical AD pattern on FDG PET. Scores of 7 or above were associated with hypometabolism in the dorsolateral frontal cortex and no progression to AD. Comparison of the brain glucose pattern in early onset vs late-onset AD has shown that the overall glucose hypometabolism of early onset AD was much greater in magnitude and extent than that in the late-onset disease despite the similarity of dementia severity in both groups.^[33] The early onset group showed more severe hypometabolism in parietal, frontal, and subcortical areas and had a more rapid course in the reduction of glucose metabolism than that in the late-onset group. Another study^[34] found that age and right temporoparietal PET abnormality were the most significant predictors of subsequent global cognitive decline. A meta-analysis^[35] of 15 articles published between 1989 and 2003 demonstrated a summary sensitivity of 86% (95% confidence interval [CI]: 76%, 93%) and a summary specificity of 86% (95% CI: 72%, 93%) for FDG PET. There was, however, unexplained heterogeneity in sensitivity and specificity estimates that were unrelated to study quality. Another similar meta-analysis^[19] that involved neuroimaging results from 3511 patients with AD and 1632 normal healthy controls provided neuroimaging profiles for both early onset and longer duration patients with AD.

PET studies^[36] that have involved autopsy-confirmed cases suggest that PET diagnosis of AD is no worse or perhaps even better than the clinical diagnosis. In a study from the UCLA group, it was found that among those patients predicted by clinical criteria to have progressive dementia, 94% of them with positive PET scans did suffer a progressive decline, while only 25% of those with negative scans progressed (relative risk of 3.8). This study^[37] suggested that the evaluation of brain metabolism by PET in appropriately selected patients may improve the accuracy of prognostication. In another similar study,^[38] it was noted that FDG PET may accurately identify rapid converters from mild cognitive impairment to frank AD. Additionally, there may be metabolic differences between the sporadic and familial AD with the familial form demonstrating significantly lower cortical metabolism.^[39] In another report, MRI-guided FDG PET was used to test the hypothesis that among normal elderly, reduction of glucose metabolism in the entorhinal cortex (EC) predicts decline and the involvement of the hippocampus and the neocortex.^[40] It was found that at baseline, metabolic reduction in the EC predicted longitudinal memory and temporal neocortex metabolic reductions. Among those who declined, apolipoprotein E E4 carriers showed marked longitudinal metabolic reduction of the temporal neocortex. The investigators concluded that initial metabolic decline in EC in otherwise normal elderly predicted future cognitive and brain metabolism reductions and that progressive E4-related hypometabolism might underlie the known increased susceptibility for dementia.

Although most investigations have concentrated on the metabolic abnormalities of the grey matter in patients with AD, there are reports that indicate potential other superimposed pathology of the white matter in the brain. DeCarli and colleagues^[41] examined the cerebral metabolism, cognitive performance, and brain volumes in healthy controls and 2 groups of patients with probable Alzheimer's disease, 1 group with severe abnormalities of the white matter and the other group with either none or minimal white matter abnormalities. They found that while in patients without white matter abnormalities, there was a correlation between the association neocortex metabolism and the neuropsychological performance, such correlation was not evident in the group of AD patients with abnormal white matter. This was postulated to probably reflect the disruption of the long corticocortical pathways that are induced by the superimposed white matter abnormalities.

The cerebral blood flow in patients with AD dementia shows similar reductions in the bilateral temporoparietal cortex despite the observation that similar flow pattern may also be seen with other types of dementia.^[42] The differential hemodynamic aspects of AD in comparison to vascular dementia have been investigated.^[43] PET was used to obtain information on the distribution patterns of perfusion, energy metabolism, vascular transit time, vascular reactivity, and oxygen extraction fraction. It was noted that from the hemodynamic point of view, the preservation of vascular reserve with AD might be a unique difference between AD and vascular dementia. Moreover, this study suggested the integrity of the vascular hemodynamics at the level of the arterioles in AD. Another study^[44] arrived at a similar conclusion that perfusion changes were not clearly either primary or limiting in AD, although another study^[45] using PET with O-15 labeled water showed a decline in the posterior cingulate perfusion in mild AD. The PET studies of cerebral perfusion in vascular dementia have suggested a state of misery perfusion that may involve the whole cerebral cortex.^[46] Moreover, Mielke and colleagues^[47] have noted a different pattern in the glucose metabolism with vascular dementia which consisted of scattered areas of metabolic reduction involving both cortical and subcortical structures.

Kantarci and Jack^[48] reviewed the evidence for the imaging-based evaluation of AD. They attest that although the current clinical criteria for the diagnosis of AD are reliable, these criteria remained to be validated by clinicians of varying levels of expertise at different clinical settings. They indicate that the diagnostic accuracy of PET for

distinguishing patients with AD from healthy elderly individuals is comparable to the accuracy of a pathologically confirmed clinical diagnosis. Additionally, they submit that the sensitivity of PET for distinguishing patients with dementia with Lewy bodies from AD is higher than that with clinical evaluation.

The cost-effectiveness of FDG PET in the diagnosis of AD has been investigated.^[49,50] A decision-analytic model was used to compare the costs and quality-adjusted life years (QALYs) associated with strategies involving SPECT, MRI, and PET as functional imaging adjuncts to the standard clinical work-up. In this study, although PET resulted in some benefit but this was at a high cost in comparison to the standard diagnostic regimen for AD. Another study, however, found PET to be cost-effective in this clinical setting. Silverman and colleagues^[7] performed a decision analysis to compare the relative value of a conventional approach (based on clinical criteria for the presence of dementia and excluding non-AD etiologies that could contribute to patient's symptoms) vs a PET strategy. The PET strategy was found to result in a reduction of false-negative and false-positive findings in comparison to the conventional clinical approach (3.1% vs 82% and 12% vs 23%, respectively, at a prevalence rate of 51.6% in the group). There was cost-savings of \$1138 per correct diagnosis and a lower cost per unit benefit that was maintained over a wide range of tested values for sensitivity, specificity, cost of PET, and long-term care. It was concluded that use of PET in the work-up of early dementia in elderly patients can contribute significantly and economically to the evaluation and more appropriate treatment of these patients.

FDG PET may be used for the differential diagnosis of dementia. A cerebral metabolic pattern other than that for classic AD pattern may occur in 10% to 20% of patients suffering from clinically probable AD.^[51] Most patients with possible but atypical Alzheimer's-type dementia may show metabolic patterns such as isolated bilateral frontal involvement. This metabolic pattern is suggested to correspond to other disease processes such as Pick's disease, frontal lobe dementia or progressive subcortical gliosis.^[51,52] The differences in the pattern of glucose metabolism between AD and that for dementia with Lewy bodies (DLB) have also been studied.^[53-56] The reduction in the occipital (visual association cortex) glucometabolism in DLB can differentiate DLB from AD with a sensitivity of 86% and a specificity of 91%.^[56] In another study, the relative utility of neuropsychological testing and FDG PET were compared for differentiating AD from DLB. The DLB group was significantly more limited than the AD group in visual discrimination task. PET studies also showed significantly lower metabolism in the visual cortex (Brodmann areas 17, 18, 19) in the DLB than in the AD group, but no major differences in the other areas typically affected in AD. This study suggested that both AD and DLB demonstrate a similar profile of cerebral hypometabolism except for the visual cortex where the DLB group shows markedly lower glucose metabolism than the AD group.^[57] Similar findings of distinctive diminished glucose metabolism of the occipital region in DLB have been reported by other investigators.^[58]

Other PET radiotracers directed toward imaging the cholinergic system, the neurofibrillary tangles, the beta-amyloid deposits, and oxygen metabolism may also prove useful in the future imaging diagnosis of AD.^[59-68] The Japanese investigators compared the perfusion, oxygen metabolism, and oxygen extraction fraction of the medial temporal lobe in patients with probable mild-to-moderate AD and normal controls.^[59] The decline in the oxygen consumption of the medial temporal lobe was found to be the distinctive feature of AD and correlated with some of the nonverbal memory test scores and cognitive impairment scales. Kuhl and colleagues^[60] mapped the cerebral acetylcholinesterase (AChE) activity in patients with AD and in normal controls. AChE activity is diminished in postmortem AD brain. Such mapping with PET allows for possibility of imaging-based monitoring of cholinesterase inhibitor therapy in AD. Intravenous N-[11C]methylpiperidin-4-yl propionate ([11C]PMP) served as the in vivo AChE substrate. The use of PET with this tracer was found to provide valid measures of cerebral AChE in normal subjects and AD patients, facilitating imaging-based confirmation of central inhibition by inhibition therapy and identification of responders. PET imaging of the cholinergic system may also provide additional evidence for the support of the cholinergic hypothesis in AD as well as insight into the functional mechanisms of novel drug therapies directed to the cholinergic system.^[61,62,66,68]

There have also been strides in developing specific radiotracers for PET imaging of the neurofibrillary tangles and beta-amyloid senile plaques in the brains of living AD patients. One such tracer, 2-(1-(6-[(2-[18F]fluoroethyl)(methyl)amino]-2-naphthyl)ethylidene)malononitrile ([18F]FDDNP), was observed to have greater accumulation and slower clearance in neurofibrillary tangle and beta-amyloid plaque-dense brain areas and correlated with lower memory performance scores.^[63] Other compounds with similar functionality have also been reported.^[64,65,67] Such PET-based compounds are expected to allow monitoring of anti-amyloid treatments in AD and potentially detect plaque formation in asymptomatic individuals at risk for development of clinical AD.

In summary, the role of PET in the diagnostic work-up of patients with AD is expected to grow as the overwhelming current evidence suggests that the insertion of PET into the diagnostic algorithm of patients with dementia will allow cost-effective diagnosis of AD at an early stage and facilitate evaluation of novel drug therapies in this increasingly incident disease in the setting of aging population.^[69]

2. In your practice, approximately how many PET scans do you order per month in patients who exhibit the signs and symptoms of Alzheimer's disease?

- 5-10
- 10-20
- 20-30
- > 30

Delineating Frontotemporal Dementia

FDG PET may be valuable in the clinical recognition of frontotemporal dementia (FTD)^[70] (Figure 3). A recent study^[71] reported on the pattern of the progression of decline of glucose metabolism in FTD. These investigators performed FDG PET imaging in 22 patients with mild FTD and followed them for an average of 19.5 months. The scans were compared to scans from 15 healthy age-matched control subjects on a voxel-by-voxel basis using Statistical Parametric Mapping (SPM) analysis. Patients with FTD showed significant symmetrical hypometabolism of the frontal lobes sparing the motor cortex, caudate, insula, and the thalami. In early stages of FTD, the hypometabolism was limited to the frontal and anterior temporal lobes but during progression of disease, the pathological changes spread into the parietal and temporal cortices.^[71,72]

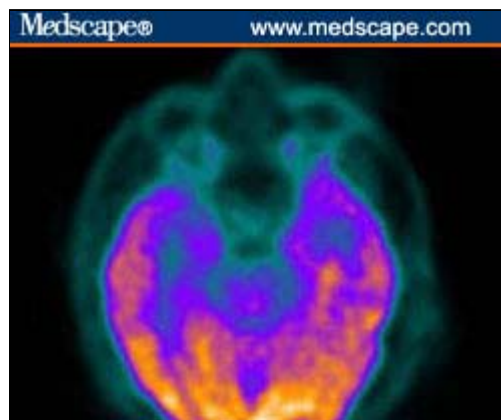
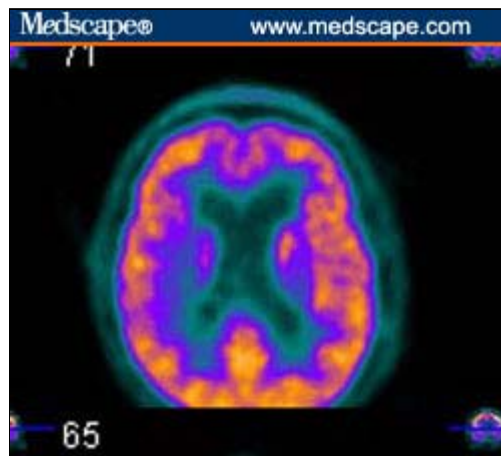


Figure 3 (A, B). Frontotemporal dementia. Note the relatively symmetric metabolic decline of the frontal and temporal lobes.

Another investigation involving 29 patients with FTD and 11 healthy subjects showed that FTD is associated with hypometabolism involving extensive areas of the brain including the frontal and anterior temporal cortices, the cingulate gyri, uncus, insula, and basal ganglia (putamen and globus pallidus) and medial thalamic regions and more frequently lateralized to the left.^[73] A German study compared the metabolic pattern of brain in AD and FTD using SPM analysis. It was noted that in FTD, there was greater decline in the glucose metabolism of the left insula/left inferior frontal gyrus (Brodmann areas 13, 45, 47) and in the medial frontal gyrus bilaterally. In AD, however, there was significant decrease in the glucose metabolism of the right middle temporal gyrus (Brodmann area 39). The authors concluded that PET is a promising tool for discriminating FTD from AD.^[74] In another relatively similar study, a voxel-to-voxel group comparison identified metabolic impairment in the bilateral ventromedial frontal area, the left anterior insula, and the inferior frontal cortex in both groups although there was more activity in the right middle temporal gyrus with FTD in comparison to early onset AD. All the cortical structures involved were considered critical for the phenotypic observation of altered social behavior and aphasia in FTD and impaired linguistic and visuo-constructive abilities in early onset AD.^[75,76]

3. What percentage of patients that you manage in your practice have Parkinson's disease?

- 5%-10%
- 10%-15%
- 15%-20%
- > 20%

The Emergent Role of Positron Emission Tomography in Parkinson's Disease

Parkinson disease (PD) may also be associated with dementia. In 1 study, FDG PET was performed in 8 nondemented PD patients, 6 of them were receiving dopaminergic medications, and 8 age-matched control subjects.^[77] On average, in PD patients, the regional glucose metabolism was 25% below control values for all brain regions with the greatest differences seen in the posterior brain areas (visual association cortex, primary visual cortex, and parietal cortex) and thalamus. This study suggested that in PD patients without dementia, the cortical hypometabolism primarily may affect the posterior brain areas. A recent study^[78] found that while nondemented patients with PD had a moderate cholinergic dysfunction, demented PD patients presented with severe cholinergic deficit in various cortical regions.

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