



Neuroimaging for Dementia and Alzheimer's Disease

- **Data supports either CT or MRI under most circumstances at the time of initial dementia assessment to identify rare pathologies such as neoplasms or subdural hematomas**
- **When specific clinical criteria are met, FDG-PET can be utilized to distinguish between Alzheimer's and Pick's (fronto-temporal) disease**
- **Molecular imaging examinations that detect specific biological characteristics of Alzheimer's disease, currently used as research tools, will become clinically available in the future for early detection of disease**

There are an estimated 4.5 million people in the United States with Alzheimer's disease (AD) at this time, accounting for approximately 60-70% of all cases of dementia in the elderly. As the post World War baby boom population ages, it is anticipated that the number of Alzheimer's patients will grow dramatically, increasing the burden on both the public healthcare system as well as the caregivers of these patients. Unfortunately, treatments available at this time for AD are not effective at slowing disease progression. However, for the first time, promising disease-modifying therapies for AD are in large-scale clinical trials and it is likely that some will become available within the next few years.

The only definitive diagnosis of AD is the detection of amyloid plaques and neurofibrillary tangles at autopsy. A clinical diagnosis based on the history, physical examination, neuropsychological evaluation, and laboratory tests is usually accurate in established cases, but is more challenging in earlier, milder forms of the disease. The role of neuroimaging at present is primarily to identify potentially treatable underlying conditions that arise in patients with unusual presenting symptoms. While AD is by far the most common form of dementia (Table 1), other etiologies must be considered because prognosis and management strategies will differ. Neuroimaging is often useful for this purpose, for example, in differentiating vascular and fronto-temporal dementias from AD. The role of neuroimaging in the next few years will likely include the direct identification of early amyloid AD pathology with positron emission tomography (PET) and the detailed characterization of brain chemistry with magnetic resonance spectroscopy (MRS).

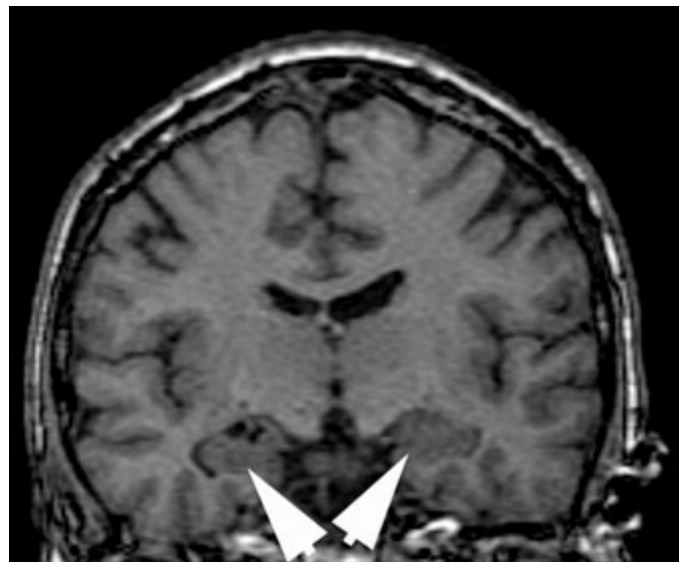


Figure 1. Coronal image of the brain, showing hippocampi (arrows). Serial imaging, which is not used in clinical practice, is necessary to demonstrate preferential shrinkage of the hippocampus that is characteristic of AD.

MRI and CT

By the time AD symptoms are clinically established, structural brain shrinkage in excess of normal aging is often evident and readily detectable with either CT or MRI. AD causes atrophy of the entire brain, although some regions such as the hippocampus are specifically affected by AD and can be assessed with quantitative volumetric methods that are usually applied to MRI (Figure 1). Up to 5% of patients presenting for initial evaluation for dementia harbor a clinically significant structural lesion that is not identified by history or

examination. Most commonly, these lesions are infarcts but occasionally neuroimaging can reveal a tumor or subdural hematoma requiring surgical evaluation. CT is usually adequate as an initial examination to look for these lesions.

Dementia on the basis of cerebrovascular disease may occur alone or in combination with AD (“mixed” dementia) and is associated with white matter abnormalities that are more evident with MRI. Vascular dementia remains a clinical diagnosis. Minimal changes on MRI, including white matter abnormality and mild brain atrophy are usually age-related and may provoke unnecessary concern. Normal pressure hydrocephalus is a very rare condition whose clinical symptoms include ataxia, incontinence, and dementia; imaging typically shows ventricular enlargement.

Alzheimer’s Disease	60-70%
Vascular dementia	20%
Mixed etiology	6%
Fronto-temporal dementia	5-10%
Dementia with Lewy bodies	25%
Normal pressure hydrocephalus	1%
Depression	1%
Tumor	1%

Note: Patients may have more than one cause of dementia

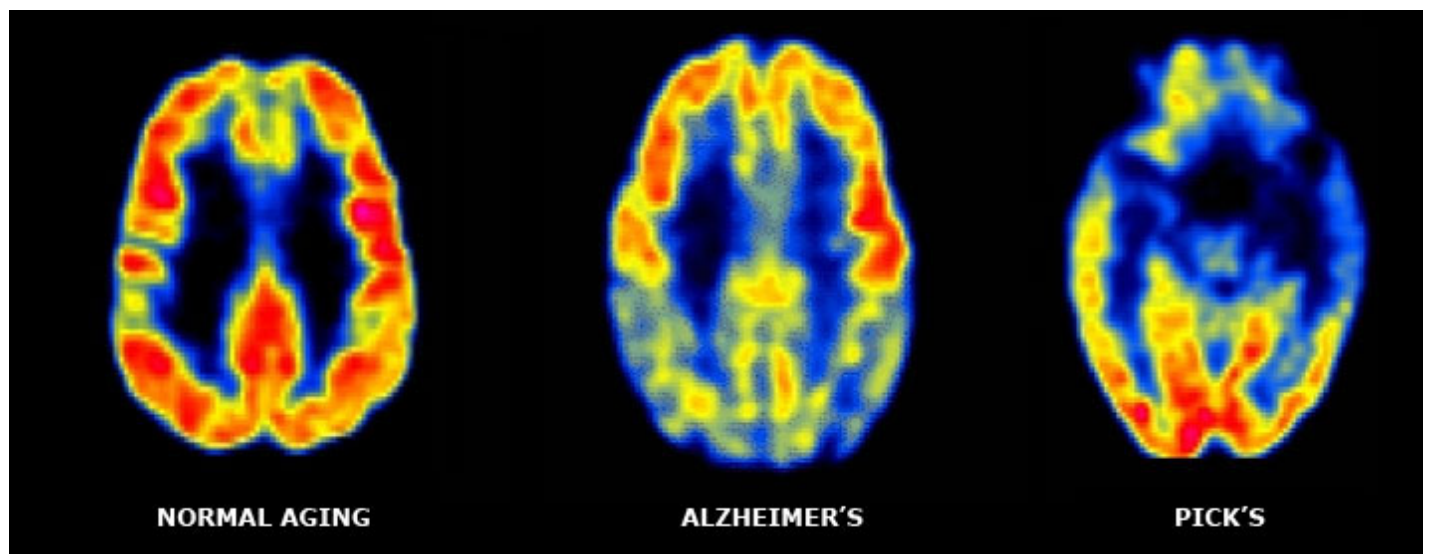


Figure 2. FDG PET images showing patterns of metabolic activity that are characteristic of patients with Alzheimer’s disease, Pick’s disease (fronto-temporal dementia) and elderly individuals with no dementia. Red, high FDG uptake, Blue, low FDG uptake.

FDG-PET Imaging

FDG-PET is useful for distinguishing between Alzheimer’s and fronto-temporal (Pick’s) dementias and is now Medicare reimbursable for this purpose. Before FDG-PET can be ordered, a [scheduling worksheet](#) must be completed that documents the justification for and potential benefit of FDG-PET for clinical management of the patient (Table 2).

FDG-PET images show the regional distribution of the rate of glucose metabolism. Because active neurons have a very high metabolic rate, FDG uptake is high in brains of healthy subjects, especially in the cortex. In contrast, FDG uptake in AD is greatly diminished, especially in the temporal and parietal regions of the brain. The characteristic pattern of FDG uptake seen in Alzheimer’s patients is very different from that seen in

fronto-temporal dementia (Figure 2), allowing the differential diagnoses of these diseases.

At least 6 months of progressive dementia
Completed comprehensive neurological examination conducted by physician experienced in diagnosis and assessment of dementia
Meet diagnostic criteria for Alzheimer’s disease and fronto-temporal dementia
No clinical diagnosis for dementia symptoms
No previous brain SPECT or FDG PET for same indication

Future Imaging Examinations for Dementia

Proton magnetic resonance spectroscopic imaging (MRS) can be performed as an add-on examination after conventional MRI. Proton MRS imaging assesses several characteristic hydrogen-containing biochemicals in an array of voxels, each about 2-7 cm³, which are displayed as a spectrum for each voxel of tissue. One of the principle peaks in the spectrum of a healthy brain is that of the neuronal marker, n-acetyl aspartate (NAA), while other major peaks include choline, creatinine, and myo-inositol. Even before the development of overt dementia due to AD, there is a decrease in the ratio of NAA: creatinine in the temporal lobe, which is not seen in patients whose memory loss and cognitive declines were attributed to other causes of dementia.

Several highly specific PET imaging agents have been developed which bind to the characteristic β -amyloid plaque found in AD. Currently, the most sensitive and specific of these, known as Pittsburgh Compound B (PIB), rapidly crosses the blood brain barrier and is retained by β -amyloid fibrils but not in normal brain tissue. In Alzheimer's patients, the high contrast images show marked retention of PIB in areas where β -amyloid is characteristically found, such as the parietal and frontal cortices. In contrast, patients with fronto-temporal dementia have normal-appearing PIB images.

Interestingly, PIB binding is seen in approximately 20% of apparently normal older subjects, and whether this is an indication of antecedent AD is a topic of intense investigation. PIB-PET also has applications in drug development because it can be used to demonstrate whether drugs that are designed to act on β -amyloid, which are currently in development, reduce or stabilize the burden of β -amyloid plaque.

At this time, both proton MRS and PIB-PET are research tools. However, with the recent dramatic advances in understanding the biology of AD and the expectation that drugs will become available to treat it, these neuroimaging tools will likely be brought into the clinical mainstream for early diagnosis and intervention.

Scheduling

MRI or CT for evaluation of patients with dementia may be ordered through ROE for appointments at the MGH Main Campus, Mass General West Imaging Waltham, and Mass General Imaging Chelsea or by telephone at 617-724-XRAY (9729) for all locations.

FDG PET may be ordered by telephone at 617-724-7212 after the completion of a [scheduling worksheet](#) documenting the diagnosis evidence for AD and fronto-temporal dementia and the potential benefits of FDG PET imaging.

Further Information

For further questions, please contact [Ramon Gilberto Gonzalez, M.D., Ph.D.](#), Chief of the Division of Neuroradiology, MGH Department of Radiology at 617-726-8628.

We would like to thank Dr. Gonzalez and Keith Johnson, M.D., Neurologist and Radiologist, Nuclear Medicine Division, MGH Department of Radiology, for their assistance and advice for this issue.

References

- Clarfield, A. (2003) *The decreasing prevalence of reversible dementias: an updated meta-analysis*. Arch Intern Med **163**: 2219-29.
- Frederick, BD, Lyoo, IK, Satlin, A, Ahn, KH, Kim, MJ, Yurgelun-Todd, DA, Cohen, BM and Renshaw, PF. (2004) *In vivo proton magnetic resonance spectroscopy of the temporal lobe in Alzheimer's disease*. Prog Neuropsychopharmacol Biol Psychiatry. **28**: 1313-22
- Kantarci, K and Jack, CR, Jr. (2003) *Neuroimaging in Alzheimer disease: an evidence-based review*. Neuroimaging Clin N Am. **13**: 197-209
- Klunk, WE, Engler, H, Nordberg, A, Bacskai, BJ, Wang, Y, Price, JC, Bergstrom, M, Hyman, BT, Langstrom, B and Mathis, CA. (2003) *Imaging the pathology of Alzheimer's disease: amyloid-imaging with positron emission tomography*. Neuroimaging Clin N Am. **13**: 781-9
- Knopman DS, DeKosky ST, Cummings JL, Chui H, Corey-Bloom J, Relkin N, Small GW, Miller B, Stevens JC. Practice parameter: diagnosis of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2001 May 8;56(9):1143-53.
- McMahon, PM, Araki, SS, Sandberg, EA, Neumann, PJ and Gazelle, GS. (2003) *Cost-effectiveness of PET in the diagnosis of Alzheimer disease*. Radiology. **228**: 515-22

©2006 MGH Department of Radiology

Janet Cochrane Miller, D. Phil., Author

Susanna I. Lee, M.D., Ph.D., Editor