PET Brain Imaging: Dementia

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3% with severe cognitive impairment in the adult population (1-year prospective prevalence, DSM-IV)

The prevalence of dementia increases with age (particularly Alzheimer’s and vascular dementia)

- 65 - 74 yrs: 2.5%
- 75 - 79 yrs: 4.0%
- 80 - 84 yrs: 11%
- 85 - 93 yrs: 24%

(Probable AD 55% of all cases) (Bachman et al., 1992)
Probable Alzheimer’s disease

- Dementia established by clinical exam and neuropsychological tests (MMSE, BDS, etc.)
- Deficits in two or more areas of cognition
- Progressive worsening of memory and other cognitive functions
- No disturbance of consciousness
- Onset between ages 40 and 90, most often after age 65
- Absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition
Dementia Clinical Workup

- Interview with patient / family member
- Physical examination
- Neurological examination
- Mental status examination (MMSE)
- Assessment for functional status
- Laboratory tests (e.g., CBC, thyroid, B12)
- Neuropsychological examination
- Neuroimaging (CT or MRI)
- EEG, lumbar puncture (when required)
- Genetic test (e.g., APOE) - not clinically accepted
Clinical Diagnostic Accuracy of AD

Clinical diagnosis with histopathology (AAN)

3 Class I articles (Holmes et al, 1999; Jobst et al, 1998 Lim et al, 1999)
10 Class II articles
DSM-IIIIR or NINCDS-ADRDA criteria (probable AD)

Overall sensitivity 81%, specificity 70%
Clinical Indication: Dementia

- **Current approval for FDG PET & SPECT**
  - Differential diagnosis

- **Future indications**
  - Early diagnosis
  - Severity, staging
  - Prognostic evaluation
  - Treatment response

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Alzheimer’s Disease vs. Frontotemporal Dementia

Onset, clinical presentation, cognitive impairment
Comprehensive clinical evaluation defined by AAN
Medical history, Physical & mental status
Laboratory test & structural imaging (CT or MRI)
Evaluation conducted by experienced physician
Inconclusive clinical evaluation
Accredited nuclear medicine facility
No prior SPECT or PET for the same indication
  Exception - changes in clinical presentation, inconclusive studies, technically inadequate SPECT - 1 year interval
PET-CT for Dementia Imaging

Advantages

- Shorter scan time
- Better image quality
- Exclusion of gross anatomic abnormality

[Images of brain scans]

Brain phantom, PET-CT
Kinahan, University of Washington

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3D-SSP Z-SCORE ANALYSIS

Ref

Normal Database

Patient (individual or group)

Z-score

3D-SSP/NEUROSTAT http://128.95.65.28/

Minoshima et al., J Nucl Med 1995
Questionable and Mild AD vs. Non-AD: ROC Analysis

Slice Presentation

3D-SSP Presentation

Burdette, Minoshima. Radiology 1996
Commercial Voxel-based Brain Software: Examples

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Examples of Dementing Disorders

- **Neurodegenerative disorders (irreversible)**
  - Alzheimer’s disease
  - Dementia with Lewy Bodies
  - Frontotemporal demenita (including Pick’s disease)
  - Other atypical neurodegenerative disorders

- **Acquired cerebral disorders (some are reversible)**
  - Vascular dementia
  - Intracranial neoplasms (frontal lobe), trauma
  - Hydrocephalus
  - Multiple sclerosis
  - Transmittable encephalopathies (e.g., Creutzfeldt-Jakob)

Modified from Berg & Morris 1990
Examples of Dementing Disorders

- **Other potentially reversible disorders**
  - **Metabolic disorder:**
    - chronic drug intoxication, alcoholism,
    - malnutrition (e.g., vitamin B12 deficiency),
  - **Infections:**
    - HIV (AIDS), neurosyphilis, tuberculous
    - or bacterial meningitis, cryptococcosis,
    - acute viral encephalitis
  - **Major depression**
Alzheimer’s Disease

First described by Alzheimer in 1907

A case of presenile dementia in 51-year-old woman

Classic neuropathological changes

- Senile plaques (amyloid deposition) and neurofibrillary tangles

Prevalence

- 1 in 10 over 65 years in the US have AD (ADEAR)
- Nearly 50% of those over 85 years in the US have AD (ADEAR)
- Most common dementia > 65 yrs old

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72 yrs female, Alzheimer’s disease (mild)
76 yrs female, Alzheimer’s disease (severe)
Clinical Diagnostic Accuracy of AD

PET diagnosis with histopathology

- 2 Class II articles (Silverman 2001, Minoshima 2001)
- Overall sensitivity 92%, specificity 76%
72 yrs female, slowly progressive cognitive decline
Fig. 1. Model for the progression of loss of neuronal function in neurodegenerative disorders. There is a prolonged period during which loss of neuronal function has occurred but symptoms have not yet appeared.
Mild Cognitive Impairment (MCI)


- Complaints of defective memory
- Normal activity of daily living
- Normal general cognitive function
- Absence of dementia
- Abnormal memory function for age
Heterogeneity of MCI

**Clinical presentations**
- MCI
- Amnestic
- MCI
- Multiple Domains
- MCI
- Single
- Non-memory Domain

**Possible etiologies**
- Degenerative
- Vascular
- Metabolic
- Traumatic
- Psychiatric
- Others?

**Fig. 1** Heterogeneity of the clinical presentation of mild cognitive impairment (MCI) and potential multiple aetiologies.
Metabolic Reduction in the Posterior Cingulate Cortex in Very Early Alzheimer’s Disease

Satoshi Minoshima, MD, PhD,* Bruno Giordani, PhD,† Stanley Berent, PhD,‡ Kirk A. Frey, MD, PhD,‡†
Norman L. Foster, MD,‡ and David E. Kuhl, MD*

75 yrs male, forgetfulness, normal daily living
66 yrs male, self awareness of mild memory decline
FDG-PET changes in brain glucose metabolism from normal cognition to pathologically verified Alzheimer’s disease

2001  Autopsy:  Alzheimer’s Disease:  Braak & Braak Stage IV


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Synaptic loss is a very early pathological process in AD.
# Comparison of $^{18}$F-FDG and PiB PET in Cognitive Impairment

Val J. Lowe¹, Bradley J. Kemp¹, Clifford R. Jack, Jr.¹, Matthew Senjem², Stephen Weigand³, Maria Shiung¹, Glenn Smith⁴, David Knopman⁵, Bradley Boeve⁵, Brian Mulan¹, and Ronald C. Petersen⁵

## TABLE 1. Area under the ROC Curve for Controls Versus AD Subjects

<table>
<thead>
<tr>
<th>Method</th>
<th>95% confidence interval</th>
<th>$P^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global PiB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebellum-scaled with no PVC</td>
<td>0.90 0.79, 1.00</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cerebellum-scaled with PVC</td>
<td>0.92 0.82, 1.00</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SUV-scaled with no PVC</td>
<td>0.88 0.76, 1.00</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SUV-scaled with PVC</td>
<td>0.90 0.78, 1.00</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Global $^{18}$F-FDG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pons-scaled with no PVC</td>
<td>0.89 0.78, 1.00</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pons-scaled with PVC</td>
<td>0.83 0.68, 0.98</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SUV-scaled no PVC</td>
<td>0.71 0.52, 0.89</td>
<td>0.05</td>
</tr>
<tr>
<td>SUV-scaled with PVC</td>
<td>0.68 0.49, 0.88</td>
<td>0.08</td>
</tr>
</tbody>
</table>

*Based on 2-sided Wilcoxon rank sum test.

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Proposed New Diagnostic Research Criteria for AD

- A. Early and significant episodic memory impairment
- B. Presence of medial temporal lobe atrophy (MRI)
- C. Abnormal CSF amyloid / tau biomarkers
- D. Specific pattern on PET (FDG or amyloid)
- E. Proven familial AD autosomal dominant mutation

Core diagnostic criteria: A
Supportive features: B-E
Probable AD: A + one or more of B-E
Dementia with Lewy Bodies - Distinction from AD

- 2nd most common late-onset (>65 yrs) neurodegenerative dementia
- Clinical distinction from AD difficult
- 3 core clinical features in addition to dementia
  - Parkinsonism, visual hallucination, fluctuating cognition

- Good treatment response to AChE inhibitors
- Potentially fatal adverse reaction to neuroleptics in DLB
72 yrs male, MMSE score 21, episode of visual hallucination
Autopsy-proven pure AD versus DLB

DLB Consensus Criteria 2005

Core features
- Fluctuating cognition with variations in attention and alertness
- Recurrent visual hallucinations
- Spontaneous features of parkinsonism

Suggestive features
- REM sleep behaviour disorder
- Severe neuroleptic sensitivity
- Low dopamine transporter uptake in BG by SPECT/PET imaging

Supportive features
- Relative preservation of medial temporal lobe structures on CT/MRI
- Generalised and focally reduced occipital activity on SPECT/PET
- Abnormal (low uptake) MIBG myocardial scintigraphy

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Dopamine PET Imaging: AD vs. DLB vs. PD

NC  AD  DLB  PD

Frey KA, Bohnen N, Kilbourn M, University of Michigan
### Differential Diagnosis of Dementias by Neurochemical PET

<table>
<thead>
<tr>
<th></th>
<th>AD</th>
<th>FTD</th>
<th>DLB</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDG PET</td>
<td>Posterior</td>
<td>Anterior</td>
<td>Posterior+VC</td>
</tr>
<tr>
<td>Dopamine PET</td>
<td>-</td>
<td>Variable</td>
<td>Decrease</td>
</tr>
<tr>
<td>Amyloid PET</td>
<td>Increase</td>
<td>-</td>
<td>Increase</td>
</tr>
<tr>
<td>I-123 MIBG (heart)</td>
<td>-</td>
<td>(-)</td>
<td>Decrease</td>
</tr>
</tbody>
</table>

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Frontotemporal Dementia (FTD)

Clinical features
Heterogeneous group
Male and female equally affected, early-onset (avg < 60 yrs)
20-40% family history
Behavioral changes, language dysfunction
Relationship with ALS (motor neuron disease)
Chromosome 17 mutation in 10-15% hereditary FTD

Early referral to neurologist / psychiatrist
Behavioral management
Anti-psychotics, anti-depressants helpful in some cases
No significant effects by cholinesterase inhibitors

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59 yrs male, progressive cognitive decline, agitation
61 yrs female, progressive cognitive decline, language problem
57 yrs female, impaired word comprehension, agnosia
Imaging of amyloid plaques and cerebral glucose metabolism in semantic dementia and Alzheimer’s disease


Glucose metabolism $[^{18}F]$FDG PET

Amyloid plaque load $[^{11}C]$PIB PET

Neuroimage 2008;39:619-633

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Frontal Hypoperfusion / Hypometabolism

- Findings may not be specific:
  - Advanced aging
  - Frontotemporal dementia
  - Ischemia
  - Depression
  - Alcoholism
  - Schizophrenia
  - Brain trauma
  - Substance exposure
  - Others
<table>
<thead>
<tr>
<th>Rank</th>
<th>Cause of Death</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Heart disease</td>
<td>652,486</td>
</tr>
<tr>
<td>2.</td>
<td>Cancer</td>
<td>553,888</td>
</tr>
<tr>
<td>3.</td>
<td>Stroke (cerebrovascular diseases)</td>
<td>150,074</td>
</tr>
<tr>
<td>4.</td>
<td>Chronic lower respiratory diseases</td>
<td>121,987</td>
</tr>
<tr>
<td>5.</td>
<td>Accidents (unintentional injuries)</td>
<td>112,012</td>
</tr>
<tr>
<td>6.</td>
<td>Diabetes</td>
<td>73,138</td>
</tr>
<tr>
<td>7.</td>
<td>Alzheimer's disease</td>
<td>65,965</td>
</tr>
<tr>
<td>8.</td>
<td>Influenza/Pneumonia</td>
<td>59,664</td>
</tr>
<tr>
<td>9.</td>
<td>Renal diseases</td>
<td>42,480</td>
</tr>
<tr>
<td>10.</td>
<td>Septicemia</td>
<td>33,373</td>
</tr>
</tbody>
</table>

Source: CDC Deaths: Final Data for 2004, Table 12
Figure 5. Age-Adjusted death rates for selected leading cause of death: United States, 1958–2004

1Circled numbers indicate ranking of conditions as leading causes of death in 2004.
NOTE: Age-adjusted rates per 100,000 U.S. standard population, see “Technical Notes.”
# Drug Treatments for Alzheimer’s Disease

<table>
<thead>
<tr>
<th>Class</th>
<th>Target</th>
<th>Since initial idea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-cholinergic</td>
<td>transmitter</td>
<td>30 years</td>
</tr>
<tr>
<td>Estrogen</td>
<td>trophic?</td>
<td>25 years</td>
</tr>
<tr>
<td>Anti-glutamatergic</td>
<td>transmitter</td>
<td>20 years</td>
</tr>
<tr>
<td>Anti-oxidant</td>
<td>oxidation</td>
<td>20 years</td>
</tr>
<tr>
<td>Anti-inflammatory</td>
<td>immune</td>
<td>15 years</td>
</tr>
<tr>
<td>Chelating</td>
<td>amyloid</td>
<td>15 years</td>
</tr>
<tr>
<td>Amyloid Vaccine</td>
<td>amyloid</td>
<td>&lt;10 years</td>
</tr>
<tr>
<td>Secretase inhibitor</td>
<td>amyloid</td>
<td>&lt;10 years</td>
</tr>
</tbody>
</table>
The New Drug Development Process

**Basic Research**
- 1 Year

**Pre-clinical Testing**
- 3.5 Years
  - Target Discovery
  - Planning
  - Market Size/Needs
  - Screening
  - Animal Testing
    - Mice, Rat, Dog, and Monkey
  - Biological Activity
  - ADME
  - Short-Term
    - TOX
  - Long-Term
    - Institutional Review Boards
    - GLP
    - mdPET
    - Translation Study

**Clinical Trials**
- 1 Year
  - Phase 1
    - 20-80 Healthy Volunteers
  - Phase 2
    - 100-300 Patient Volunteers
  - Phase 3
    - 1000-3000 Patient Volunteers
    - Treatment IND
    - Parallel Track
  - Phase 4
    - Safety/Effectiveness

**FDA Review**
- 2.5 Years

**Post Marketing Testing**
- 5,000 Compounds Evaluated
- IND Submitted
- GCP
- NDA Submitted
- Questions & Answers
- 5 Enter Trials
- 1 Approved
Fig 1. Conceptual model of the relationship of biomarkers, surrogate endpoints, and the process of evaluating therapeutic interventions.
## ADNI: Alzheimer’s Disease Neuroimaging Initiative

### Study Overview

<table>
<thead>
<tr>
<th>Current Status:</th>
<th>Recruiting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purpose:</td>
<td>The purpose of this study is to examine how brain imaging technology can be used with other tests to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). This information will aid future clinical trials by providing a standard assessment tool to measure the effects of treatments being studied.</td>
</tr>
</tbody>
</table>
| Sponsor(s):    | National Institute on Aging (NIA)  
                 National Institute for Biomedical Imaging and Bioengineering (NIBIB)  
                 Foundation for the National Institutes of Health  
                 Institute for the Study of Aging (ISOA)  
                 Alzheimer's Association |
| Official Title:| Alzheimer's Disease Neuroimaging Initiative |
| Principal Investigator(s): | Ronald Petersen MD, PhD, Mayo Clinic - Rochester, MN  
                              Michael Weiner MD, University of California, San Francisco  
                              Leon Thal MD, University of California, San Diego |
Associations between cognitive, functional, and FDG-PET measures of decline in AD and MCI

Susan M. Landau\textsuperscript{a,\#}, Danielle Harvey\textsuperscript{b}, Cindee M. Madison\textsuperscript{a}, Robert A. Koepp\textsuperscript{e}, Eric M. Reiman\textsuperscript{d}, Norman L. Foster\textsuperscript{e}, Michael W. Weiner\textsuperscript{f}, William J. Jagust\textsuperscript{a,g}, the Alzheimer’s Disease Neuroimaging Initiative\textsuperscript{1}

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Reducing between scanner differences in multi-center PET studies

Aniket Joshi\textsuperscript{a,c}, Robert A. Koepp\textsuperscript{a,*}, Jeffrey A. Fessler\textsuperscript{b,c}

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Radiotracers for PET & SPECT in Dementia

- **Glucose Metabolism:** $^{18}\text{F-FDG}$
- **Oxygen Metabolism:** $^{15}\text{O-O}_2$
- **Blood Flow:** $^{15}\text{O-water}, ^{123}\text{I-IMP}, ^{99}\text{mTc-HMPAO}, ^{99}\text{mTc-ECD}$
- **Cholinergic System:** $^{11}\text{C-scopolamine}, ^{11}\text{C-TRB}, ^{11}\text{C-NMPB}, ^{123}\text{I-IBVM}, ^{123}\text{I-QNB}, ^{11}\text{C-PMP}, ^{11}\text{C-BMP}$
- **Dopaminergic System:** $^{18}\text{F-dopa}, ^{11}\text{C-nomifensine}, ^{11}\text{C-raclopride}, ^{11}\text{C-DTBZ}, ^{123}\text{I-IBZP}, ^{123}\text{I-IBF}, ^{123}\text{I-IBZM}$
- **Serotonergic System:** $^{18}\text{F-setoperone}, ^{18}\text{F-altanserin}$
- **Benzodiazepine Receptors:** $^{11}\text{C-FMZ}, ^{123}\text{I-IMZ}, ^{11}\text{C-PK11195}$
- **Amyloid:** $^{11}\text{C-PIB}, ^{11}\text{C-SB13}, ^{18}\text{F-AV45}, ^{18}\text{F-FDDNP}$
Summary

- Clinical dementia workup
- Fluorodeoxyglucose (FDG) PET imaging
- Voxel-based brain software for better diagnosis
- Alzheimer’s disease (AD)
- Mild cognitive impairment (MCI)
- Dementia with Lewy bodies (DLB)
- Frontotemporal dementia (FTD)
- Drug developments and brain PET in clinical trials
- Neurochemical PET imaging