Plaque and Tangle Imaging in the Early Detection of Alzheimer’s Disease

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Disclosures

• Consulting/Speaking
  – Keiro Senior Health
  – Motion Picture and Television Fund
Overview

• Background: Alzheimer’s disease (AD) development and progression
• Early Detection of AD: Studies of Positron Emission Tomography with FDDNP
• Applications of FDDNP-PET in other cognitive disorders associated with plaque or tangle neuropathology
What is Alzheimer’s Disease?

• Progressive neurodegenerative disease
• Deterioration of memory and other cognitive functions due to neuronal cell loss
• Autopsy confirmation
  – Intracellular neurofibrillary tangles (NFT)
  – Extracellular β-amylloid senile plaques (AP)
• Gradual onset, preceded by preclinical cognitive changes (Mild Cognitive Impairment; MCI)
Amyloid Plaques and Tau Tangles in Alzheimer's Disease and Normal Aging
AD Progression

NFT

I-II Transentorhinal
Silent

III-IV Limbic
Incipient AD

V-VI Isocortical
AD

AP

A

B

C

Braak & Braak, 1991
Cognition and Aging

Normal Aging

Mild Cognitive Impairment (Pre-clinical AD)

Alzheimer’s Dementia

Cognition

Age
Early Detection of AD

- Early detection
  - Brain protection more feasible than brain repair
  - Early treatment to slow progression
  - Select candidates for clinical trials
  - Select candidates for disease modifying treatments (future)

- How Can AD be detected early?
  - Imaging biomarkers
  - Cognitive phenotypes/markers (e.g. MCI)
  - Other biomarkers (e.g. in CSF; genetics)
  - Combining biomarkers to enhance early detection
Medications for Alzheimer’s Disease

- Aricept (donepezil)
- Exelon (rivastigmine)
- Namenda (memantine)

Disease modifying

Genetic Considerations for Alzheimer’s Disease

• Rare families have a genetic mutation that causes the disease early in life in 50% of relatives
  – Presenilin genes (chromosomes 1 and 14)
  – APP gene (chromosome 21)
• Apolipoprotein E-4 is a common gene form (allele) in 20% of population that increases risk
  – Some with APOE-4 never get the disease
  – Some without APOE-4 get the disease
  – Used for research; not recommended as a predictive test
• TOMM40—linkage disequilibrium with APOE-4
• TREM2—involved in suppressing inflammatory response
Mild Cognitive Impairment

- Transitional stage between aging and AD
- Memory impairment and memory complaint
- Preservation of functional abilities
- Increased rate of progression to dementia
- Subtypes identified to improve prediction of AD
- Post-mortem
  - Many MCI look like mild AD
  - Increased NFT accumulation in medial temporal region compared to unimpaired subjects.
  - Synaptic and neuronal loss
  - Other findings, e.g. Hippocampal sclerosis

Petersen 2004; Petersen et al., 2006; Yaffe et al., 2006; Markesbery 2010; Price and Morris et al., 1999
## Imaging Techniques and the Biological Processes They Measure

<table>
<thead>
<tr>
<th>Imaging modality</th>
<th>Biological process</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT</td>
<td>Atrophy, tumors</td>
</tr>
<tr>
<td>MRI</td>
<td>Atrophy, tumors, WM hyperintensity</td>
</tr>
<tr>
<td>[F-18]FDG-PET</td>
<td>Glucose metabolism</td>
</tr>
<tr>
<td>[Tc-99m]Tc-HMPAO SPECT</td>
<td>Blood flow</td>
</tr>
<tr>
<td>[F-18]FDDNP-PET</td>
<td>Amyloid plaques and tau tangles</td>
</tr>
<tr>
<td>[C-11]PIB-PET</td>
<td>Amyloid plaques</td>
</tr>
<tr>
<td>[F-18]MPPF-PET</td>
<td>Hippocampus, 5HT1A receptors</td>
</tr>
<tr>
<td>Functional MRI</td>
<td>Blood flow, functional connectivity</td>
</tr>
<tr>
<td>DTI</td>
<td>Neuronal connectivity, WM integrity</td>
</tr>
<tr>
<td>MRS</td>
<td>Metabolite concentrations</td>
</tr>
</tbody>
</table>

PET

- Inject a radioisotope that is combined with a substance that has an affinity for certain structures or functions
- Radioisotope decays and gives off signal that is used to reconstruct images
In vitro digital autoradiogram AD brain section.

$[^{18}F]FDDNP$

FDDNP Flourescence Microscopy on same brain specimen shows plaque and tangle labeling.
Important Questions to Assess Imaging Probes for AD Detection and Potential Use to Test Disease Modifying Purposes

- Can it distinguish among AD-risk diagnostic groups?
- Can it predict progression?
- How does it compare to other validated imaging probes?
PET of Brain Amyloid and Tau in Mild Cognitive Impairment


• Can FDDNP distinguish among diagnostic groups?
  – Alzheimer’s disease (AD)
  – Mild cognitive impairment (MCI)
  – Healthy controls (CTL)

- All subjects received
  - NP testing (Memory, Executive, Visuospatial, Language and Attention/Speed of Information Processing)
  - FDDNP and FDG-PET and MRI Scanning

Small et al., 2006; NEJM
Regions of Interest and DVR

- Relative Distribution Volume (DVR) = ratio of tracer uptake in a region of interest compared to a region that has low uptake
  - Logan graphic method.
FDDNP Distinguishes MCI, AD and Control Subjects

- Global FDDNP binding differentiates AD from MCI and Control groups
- Highest binding in MCI in medial temporal and not different from AD subjects in that region
- Medial temporal and total binding in MCI > Controls; ns for other regions
Plaque and Tangle PET Imaging in MCI

AD  MCI  control

DV: 0.9  1.5
Neuropathological Microscopical Exam after Autopsy in AD Subject.

Increased FDDNP binding in medial temporal, parietal, and frontal areas consistent with postmortem pathology distribution in AD.

Premorbid FDDNP signal is high in areas that showed high plaque and tangle concentrations at autopsy in AD patient.

Immunohistochemical staining used to visualize B-amyloid protein and phosphorylated tau protein (both brown).
Prediction of cognitive decline by positron emission tomography of brain amyloid and tau.


Can FDDNP at baseline predict cognitive decline in people with either normal cognition or MCI over 18 months?

Arch Neurol 2012 Feb;69(2):215-22
### Subjects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MCI</th>
<th>Normal Aging</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 21)</td>
<td>(n = 22)</td>
</tr>
<tr>
<td>Mini-Mental State Examination</td>
<td>28.3 (2.0)</td>
<td>29.3 (0.8)</td>
</tr>
<tr>
<td>Age, y</td>
<td>63.5 (10.5)</td>
<td>64.6 (11.3)</td>
</tr>
<tr>
<td>Education, y</td>
<td>16.6 (3.1)</td>
<td>16.9 (3.0)</td>
</tr>
<tr>
<td>Female, No. (%)</td>
<td>12 (57.1)</td>
<td>14 (63.6)</td>
</tr>
<tr>
<td>Family history of dementia, No. (%)</td>
<td>15 (71.4)</td>
<td>16 (72.7)</td>
</tr>
<tr>
<td>Hamilton Depression Scale score</td>
<td>2.2 (2.8)</td>
<td>2.5 (3.3)</td>
</tr>
</tbody>
</table>

Small et al., 2012 Arch Neurology v 69
• For all subjects, higher global and regional baseline $[^{18}F]$FDDNP binding correlated with cognitive domain change scores.

<table>
<thead>
<tr>
<th>Cognitive Domain and Region of Interest$^a$</th>
<th>$t_{41}$</th>
<th>$r^b$</th>
<th>$P$ Value$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Executive functioning</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global</td>
<td>-2.51</td>
<td>-0.36</td>
<td>.02</td>
</tr>
<tr>
<td>Frontal</td>
<td>-1.88</td>
<td>-0.29</td>
<td>.06</td>
</tr>
<tr>
<td>Parietal</td>
<td>-2.03</td>
<td>-0.30</td>
<td>.05</td>
</tr>
<tr>
<td>Medial temporal</td>
<td>-2.65</td>
<td>-0.38</td>
<td>.01</td>
</tr>
<tr>
<td>Language</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global</td>
<td>-2.70</td>
<td>-0.39</td>
<td>.01</td>
</tr>
<tr>
<td>Parietal</td>
<td>-3.01</td>
<td>-0.42</td>
<td>.004</td>
</tr>
<tr>
<td>Medial temporal</td>
<td>-2.07</td>
<td>-0.31</td>
<td>.05</td>
</tr>
<tr>
<td>Visuospatial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global</td>
<td>-1.99</td>
<td>-0.34</td>
<td>.03</td>
</tr>
<tr>
<td>Frontal</td>
<td>-2.99</td>
<td>-0.45</td>
<td>.002</td>
</tr>
<tr>
<td>Parietal</td>
<td>-2.41</td>
<td>-0.39</td>
<td>.01</td>
</tr>
<tr>
<td>Attention and information processing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global</td>
<td>-2.52</td>
<td>-0.37</td>
<td>.01</td>
</tr>
<tr>
<td>Lateral temporal</td>
<td>-2.56</td>
<td>-0.37</td>
<td>.01</td>
</tr>
</tbody>
</table>

Abbreviation: $[^{18}F]$FDDNP, 2-(1-(6-[(2-fluorine 18–labeled fluoroethyl)methylamino]-2-naphthyl)ethyldene) malononitrile.

$^a$Memory domain change scores were not significantly associated with baseline global $[^{18}F]$FDDNP binding and hence were not reported in this table.

$^b$Spearman correlation coefficient and the associated 2-sided $P$ value.

• For MCI only, baseline $[^{18}F]$FDDNP signals were associated with future decreases in executive domain scores
  • global:, $r = -0.56,$
  • frontal:, $r = -0.44;$
  • parietal $r = -0.46;$
  • medial temporal $r = -0.44.$
  • $P$ value range = .01 to .05.
Cognitive Change in Subjects who are Stable versus Increased in FDDNP

Small et al., 2013 Arch Neurology v 69
Differential FDDNP-PET Patterns in Nondemented Middle-aged and Older Adults


Can we determine elevated risk of AD regardless of cognitive status (i.e. having normal cognition or MCI)?

Do Patterns of FDDNP Binding Vary Among Control and MCI Subjects?

Cluster Analysis

• Group all subjects according to their FDDNP binding patterns.

• What does this tell us about AD risk?

**TABLE 1. Subject Demographic Variables**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MCI (N = 29)</th>
<th>Control (N = 27)</th>
<th>All Subjects (N = 56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>68.6 ± 11.7</td>
<td>68.0 ± 11.6</td>
<td>68.3 ± 11.6</td>
</tr>
<tr>
<td>Education (yr)(^a)</td>
<td>16.1 ± 3.9</td>
<td>17.8 ± 2.7</td>
<td>17.0 ± 2.9</td>
</tr>
<tr>
<td>Female sex, no. (%)</td>
<td>16 (55)</td>
<td>9 (33)</td>
<td>25 (45)</td>
</tr>
<tr>
<td>AD family history, no. (%)</td>
<td>12 (41)</td>
<td>14 (52)</td>
<td>26 (46)</td>
</tr>
<tr>
<td>APOE-4 carrier, no. (%)(^b)</td>
<td>10 (38)</td>
<td>14 (52)</td>
<td>24 (45)</td>
</tr>
<tr>
<td>Mini Mental State Exam(^c)</td>
<td>27.6 ± 1.7</td>
<td>29.1 ± 1.3</td>
<td>28.3 ± 1.7</td>
</tr>
<tr>
<td>HRSD-21(^d)</td>
<td>1.9 ± 2.3</td>
<td>2.4 ± 2.4</td>
<td>2.2 ± 2.4</td>
</tr>
</tbody>
</table>

*Notes:* MCI: mild cognitive impairment; AD: Alzheimer disease; APOE-4: apolipoprotein epsilon-4; HRSD: Hamilton rating scale for depression 21-item version.

\(^a\)t(54) = 2.2, p < 0.03.

\(^b\)APOE-4 missing for three MCI subjects.

\(^c\)t(54) = 3.9, p < 0.0002.

\(^d\)HRSD-21 missing for one MCI subject.
Cluster Analysis Results

3 FDDNP Binding Types

- LG = Low Global Binding
- HT/PC = High in Temporal/Posterior Cingulate Binding
- HF/PA = High in Frontal and Parietal Binding
  - HF/PA and HT/PC do not differ in medial temporal binding levels.

Ercoli et al., 2009
FDDNP in MCI and Normal Cognition

Ercoli et al., 2009
### FDDNP Cluster Membership According to Cognitive Status

<table>
<thead>
<tr>
<th>Diagnostic Group</th>
<th>FDDNP Signal Clusters No. of Subjects per Cluster</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LG</td>
</tr>
<tr>
<td>Normal cognition</td>
<td>19</td>
</tr>
<tr>
<td>MCI</td>
<td>5</td>
</tr>
<tr>
<td>MCI-A</td>
<td>4</td>
</tr>
<tr>
<td>MCI-A+</td>
<td>1</td>
</tr>
</tbody>
</table>

Ercoli et al., 2009
Neuropsychological Domains and FDDNP Cluster Membership

- Being in any high FDDNP binding cluster is associated with poorer cognition in at least one domain compared to LG
- Being in HF/PA appears to have highest risk for poor cognition in all domains compared to LG

<table>
<thead>
<tr>
<th>Cognitive Domain</th>
<th>LG</th>
<th>HF/PA, HT/PC &lt; LG;</th>
<th>HF/PA vs HT/PC ns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Executive</td>
<td></td>
<td>HF/PA &lt; LG;</td>
<td>HF/PA and HT/PC ns; LG vs HT/PC ns</td>
</tr>
<tr>
<td>Visuospatial</td>
<td></td>
<td>HF/PA, HT/PC &lt; LG;</td>
<td>HF/PA vs HT/PC ns</td>
</tr>
<tr>
<td>Language</td>
<td></td>
<td>HF/PA &lt; LG;</td>
<td>HT/PC &lt; LG (p = .07); HF/PA vs HT/PC ns</td>
</tr>
<tr>
<td>Psychomotor</td>
<td></td>
<td>HF/PA &lt; LG;</td>
<td>HF/PA vs HT/PC (p = .08); HT/PC vs LG ns</td>
</tr>
</tbody>
</table>
Assessment of dementia risk in aging adults using both FDG-PET and FDDNP-PET imaging.


- Are FDDNP patterns associated with dementia risk according to FDG-PET scans performed in the same subjects?
- FDG-PET scans of subjects in the three FDDNP-PET clusters were analyzed using visual ratings and SPM analysis.

Silverman et al., 2001; Ercoli et al., 2012 Int J Geriatr Psychiatry. 2012;27
CMRGlc Alterations in Dementia

- Normal
- Alzheimer's
- Pick's Disease

- Normal
- Multiple Infarct Dementia
- Mild Cognitive Impairment
### RESULTS: Visual Ratings

Table 2. Number and percent of Alzheimer's disease like and non-Alzheimer's disease-like FDG-PET scan visual ratings in each of the FDDNP-PET subgroups.

<table>
<thead>
<tr>
<th>Visual Rating of FDG-PET Pattern</th>
<th>FDDNP-PET Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LG</td>
</tr>
<tr>
<td>N = 23</td>
<td>N = 7</td>
</tr>
<tr>
<td>AD-like (N/percent)</td>
<td>5/21.7</td>
</tr>
<tr>
<td>Non-AD-like (N/percent)</td>
<td>18/78.3</td>
</tr>
</tbody>
</table>
The color scale shows cortical voxels in which significant hypometabolism ($p < 0.01$) on FDG PET scans:

**Peak areas of significance in HF/PA vs LG:**
- Higher Perisylvian $p_{\text{voxel corrected}} = 0.03$
- Left mid-temporal gyrus $p < 0.0005$
- Left inferior parietal/Posterior Temporal $p_{\text{cluster corrected}} = 0.001$
- Bilateral Posterior cingulate cortex (right greater than left)
- Left dorsolateral prefrontal cortex, $p_{\text{cluster corrected}} = 0.01$

HF/PA appears AD-like according to FDG PET standards.
SPM of FDG-PET images comparing High Temporal/Posterior Cingulate (HT/PC) with the Low Global (LG) FDDNP binding subjects

The color scale highlights cortical voxels in which significant hypometabolism (p < 0.01).

P values for peak areas of significance shown for:
- Bilateral parahippocampal gyrus (left > right) $p_{\text{cluster corrected}} = 0.003$;
- Left mid frontal – inferior frontal gyrus $p < 0.005$;
- Anterior middle temporal gyrus $p = 0.001$;
- Bilateral posterior cingulate $p = 0.001$.

- HT/PC appears to be a mixed group re: etiology (mixed dementia, FTD, atypical AD)
Conclusion

• The FDG-PET data provided independent validation that different patterns of FDDNP-PET binding in non-demented individuals may be associated with differential dementia risk.
Objective: Identify MCI-N subjects with early AD-like patterns of plaque and tangle accumulations

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Hi-G</th>
<th>Hi-MTL</th>
<th>Low-MTL</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD</td>
<td>17</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>MCI-N</td>
<td>10</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>MCI-A</td>
<td>9</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>CTL</td>
<td>3</td>
<td>10</td>
<td>16</td>
</tr>
</tbody>
</table>

Ercoli et al., (in preparation);
Non-Amnestic MCI and AD risk
Summary and Significance of FDDNP Studies

- FDDNP can distinguish among people with normal cognition, MCI and AD.
- FDDNP has potential for predicting cognitive decline in both cognitively intact and at-risk people.
- FDDNP correlates with both memory and non-memory functions.
  - The ability to track multiple cognitive domains may assist in differential diagnosis of AD vs. other dementias.
  - Implications: monitoring for progression
- FDDNP may identify ‘asymptomatic’ people or atypical cognitive presentations to flag people for clinical monitoring.
- FDDNP patterns are consistent with FDG-PET indicators of dementia risk.
Other Applications of FDDNP

Down Syndrome
Down Syndrome:

- Objectives:
  - Compare FDDNP-PET binding values among controls, AD and DS subjects
  - In patients with DS, determine whether FDDNP-PET binding is related to age and clinical measures consistent with dementia:
    - Behavior, Emotional functioning, Language ability
### Subject Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CTL (n=10)</th>
<th>AD (n=10)</th>
<th>DS (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>44±7</td>
<td>67±6</td>
<td>38±11</td>
</tr>
<tr>
<td>Education (y)</td>
<td>16±2</td>
<td>16±3</td>
<td>12±3</td>
</tr>
<tr>
<td>Female (%)</td>
<td>6 (60)</td>
<td>5 (50)</td>
<td>12 (60)</td>
</tr>
<tr>
<td>MMSE</td>
<td>29.8±0.4</td>
<td>18.7±6.8</td>
<td>*</td>
</tr>
</tbody>
</table>

*Mean ± SD WASI Full Scale IQ score = 57±5; Dementia Questionnaire for Mentally retarded persons = 12 ± 9; Total score, 6 ± 4 Cognitive scale, 6 ± 7 Social scale.
Results

Mean global FDDNP values in DS significantly higher compared to healthy controls, but comparable to AD (DS vs. Controls: $t(df) = 9.8(2P < 0.001)$

Within the DS group, age was significantly correlated with increased FDDNP binding in several regions: Medial temporal ($r = .72, p = .0003$), Parietal ($r = .57, p = .009$), Frontal ($r = .46, p = .04$), Lateral temporal ($r = .43, p = .05$)
Parametric FDDNP PET Images of Control, Young DS, Older DS and AD subject

Nelson et al., 2011 Arch Neurol v68
Conclusions

• FDDNP binding is increased in DS, compared to levels observed in AD

• In people with DS, FDDNP binding levels correlate with
  – Age
  – Language and behavioral disturbances

• Brain amyloid and tau deposition in DS may manifest behavioral abnormalities that are more likely to occur with increasing age

• FDDNP binding values may eventually be helpful as early predictors of future cognitive decline in DS
Future Studies

• Disease modifying clinical trials
• Healthy aging interventions
• Use FDDNP in combination with other biomarkers (e.g. CSF biomarkers, other genes)
• Other disorders of amyloid or tau neuropathology
Chronic Traumatic Encephalopathy

• Recruited retired NFL players aged 45 to 73 years who had histories of mood and cognitive problems
• Performed clinical evaluations and FDDNP PET scans to determine tau and amyloid deposition
• Compared results to those of non-athletes matched for age, educational achievement, family history of dementia, and BMI
FDDNP-PET Binding Levels vs. Number of Concussions
Collaborators

- **Semel Institute for Neuroscience & Human Behavior**
  - Gary Small, Susan Bookheimer, Alison Burggren, Helen Lavretsky, Karen Miller, Prabha Siddarth, Linda Nelson

- **Department of Pathology**
  - Harry Vinters

- **Department of Molecular & Medical Pharmacology**
  - Jorge Barrio, Henry Huang, Vladimir Kepe, Mike Phelps, S. Satyamurthy, Dan Silverman

- **Department of Neurology**
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