Biomarkers of the Alzheimer's pathological cascade and clinical expression: role of MRI

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Objectives

- to describe, and provide evidence in support, of a dynamic biomarker based model of AD progression
- To place the role of MRI within this context
Outline

- Temporal ordering and dynamic nature of AD biomarkers ➔ graphical models
- Role of MRI
Parallels: Imaging & CSF Biomarkers; 4 classes

- **Brain Amyloidosis**
  - PET - amyloid plaque imaging
  - CSF AB 1-42

- **Neuronal dysfunction and tau mediated injury**
  - CSF t-tau and p-tau
  - FDG PET
  - Functional MRI (activation and resting state)

- **Neurodegeneration**
  - Structural MRI
  - MR Spectroscopy
  - Diffusion MRI
  - Perfusion MRI

- **Inflammation** - PET

Biomarker Reviews
- Hampel, Alzheimer’s Dement 2008
- Shaw, Nat Rev Drug Discov 2007
Model of disease staging based on PIB & MRI

Publications in 2008 and early 2009

- 11C PIB and Structural MRI Provide Complementary Information in Imaging of AD and Amnestic MCI. *Brain* 2008;131(Pt 3):665-680
- Serial PIB and MRI in normal, MCI, and AD: implications for sequence of pathological events in AD. *Brain* 2009 132(Pt 5):1355-65

- Objective: understand temporal relationships amyloid, neurodegeneration, cognition
- 11C PIB ➔ biomarker of amyloid load
- structural MRI ➔ biomarker of stage of neurodegeneration
Cross sectional group-wise comparison of global cortical PiB and hippocampal volume.

<table>
<thead>
<tr>
<th>Global cortical PiB (P &lt; 0.0016)</th>
<th>Hippocampal W score (P &lt; 0.001)</th>
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![Graph showing comparison of global cortical PiB and hippocampal volume.](image)
Cross sectional group-wise comparison global cortical PiB and hippocampal volume

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Brain 2008;131:665-680
Annual change in global PIB ratio and ventricular volume by clinical diagnosis

*Mayo plus ADNI data*

*Brain 2009 132 (Pt 5):1355-65*
Summary: Data derived from imaging consistent with model of typical late onset AD with 3 main features

- Significant plaque deposition occurs prior to neurodegeneration and clinical decline
- **Dissociation:** Change in cognition is closely coupled to rate of neurodegenerative progression, not to rate of amyloid deposition
- **Bi-phasic disease process:** Amyloid dynamic early vs. neurodegeneration dynamic mid to late stage

*Brain 2008;131(Pt 3):665-680,* and *Brain 2009 132(Pt 5):1355-65*
Proposed model relating imaging (pathology) and clinical presentation over an individual’s adult lifetime.
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Evidence of temporal ordering of biomarkers

- **Amyloid imaging** [Mintun, 2006; Aizenstein, 2008; Klunk 2004; Rowe 2007; Mormino 2009]
- **CSF Aβ42** [Peskind, 2006; Shaw, 2009; Fagan, 2007; Li, 2007; Fagan 2009; Vemuri 2009]
- **CSF tau** [Bouwman 2007; de Leon 2006; Wahlund 2003; Stefani 2006; Sluimer 2008; Hansson 2006; Sunderland 1999; Blennow 2003; Vemuri 2009]
- **FDG PET** [Minoshima, 1997; Chetelat, 2002; de Leon, 2001; Reiman, 1996; Small 1995]
- **MRI** [Fox 1997; Fox 1999; Kaye, 1997; Killiany 2000; Dickerson 2009]

**Conclusions**

- Biomarker abnormalities precede clinical symptoms
- Amyloid biomarkers become abnormal first
- Little evidence for ordering of amyloid imaging vs CSF Aβ42
- FGD PET changes before MRI [Reiman 1998]
- Little evidence for ordering of FDG PET vs CSF tau
- MRI last onset but correlates with clinical Sx longest [Vemuri, 2009]
- Non-linear functions (over long period) [Chan 2003; Carlson 2008]
Dynamic Biomarkers of the Alzheimer’s Pathological Cascade

Lancet Neurol 2010; 9: 119-28
Ab Amyloid = CSF Ab42 or amyloid PET imaging; Tau Mediated Neuron Injury and Dysfunction = CSF tau or FDG PET; Brain Structure = structural MRI
Sequence = Biomarker Dynamics Changes with Time
Simultaneously active, not start – stop, start-stop

Lancet Neurol 2010; 9: 119-28
Outline

- Temporal ordering and dynamic nature of AD biomarkers ➔ graphical model

- Role of MRI
  - How is it useful?
  - Provide evidence for useful applications
How is structural MRI not useful?

- **Not an indicator of an AD-specific pathology or molecular pathway** – AB amyloid biomarkers
- **Not the earliest biomarker of disease** – AB amyloid
- **Not the earliest biomarker of neuronal pathology/injury** – FDG PET or CSF tau
Effect of APOE 4 on biomarkers

- AB chaperone

Vemuri et al, Annals of Neurology, April 2010
How is structural MRI useful?

- Measure of downstream pathological event – not necessarily bad
- Measure of pathologic process that is closely linked with cognitive impairment – i.e. neurodegeneration
- Clinical usefulness hinges on MRI being accurate measure of stage of neurodegenerative pathology
  - cross sectional ➔ stage
  - longitudinal ➔ change in stage
Antemortem MRI based Structural Abnormality Index (STAND)-Scores Correlate with Postmortem Braak Neurofibrilllary Tangle Stage

Vemuri, NeuroImage 2008
Role of MRI – clinical utility

- Biomarker evidence in support of a diagnosis of AD
- Predict future cognitive course = early diagnosis
  - In MCI
  - in pre symptomatic subjects
- Measure disease progression
Aid in clinical diagnosis

- 2 ways this can be operationalized
STAND algorithm for Individual Diagnosis

Main Component of the STAND-Algorithm
Large library of (AD and CN) MRI scans from which regions differentiating AD from CN are detected and used to score new incoming cases.

Vemuri et al
NeuroImage 2008; 39: 1186-1197
“Automated” AD Diagnosis*

- Kloppel et al 2008
- Driscoll et al 2009
- Davatzikos et al 2009
- Fennema-Notestine et al 2009
- Vemuri et al 2008
Prediction

- MCI to AD
  - Apostolova, 2006
  - Visser, 1999
  - Devanand, 2007
  - Stoub, 2005
  - Convit, 2000
  - Killiany, 2000
  - Dickerson, 2001
  - Risacher, 2009 #6500

- Pre symptomatic subjects
Baseline adjusted hippocampal volume: relationship to progression from MCI to AD

Stable (\%) - 100, 80, 60, 40, 20, 0

Years - 0, 1, 2, 3, 4, 5, 6

Baseline adjusted  hippocampal volume: relationship to progression from MCI to AD

Neurology, 1999;52:1397-1403
CSF AB and decreased brain volume in cognitively normal elderly (CDR 0) 
Fagan et al Annals 2009
Cortical Thickness in PIB + vs – control elderly
Dickerson et al Cereb Cortex 2009
Measure of Disease Progression
ADNI: sample size per arm to detect a 25% reduction in rate (0-12 months) of decline in AD

MRI, FDG PET, cognitive tests, in AD, n=30

<table>
<thead>
<tr>
<th>Lab</th>
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<th>Variable</th>
<th>SS/arm</th>
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<td>Reiman</td>
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<tr>
<td>Thompson</td>
<td>MRI</td>
<td>CV % change</td>
<td>53</td>
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<tr>
<td>Fox</td>
<td>MRI</td>
<td>BSI% change</td>
<td>50</td>
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Summary: Biomarker-based disease staging

- Modeling provides a framework for hypothesis testing that relates temporal changes in AD biomarkers with clinical disease stage and with each other
- Specific details of model will undoubtedly change
- However, certain principles will stand up
  - Biomarkers measure specific aspects of AD path
  - Temporally ordered: amyloid => neuronal path => cognition
  - Temporal ordering: both onset and ceiling
  - Non linear function of time
  - Combination of biomarkers needed for comprehensive staging
Structural MRI: diagnosis, prediction, measure progression

Ab Amyloid = CSF Ab42 or amyloid PET imaging; Tau Mediated Neuron Injury and Dysfunction = CSF tau or FDG PET; Brain Structure = structural MRI

Lancet Neurol 2010; 9: 119-28
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Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade


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Michael W. Weiner
Ronald C. Petersen
John Q. Trojanowski