Presymptomatic Tests for AD: the Search for Mechanism

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Barcelona, Spain

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NYU School of Medicine
AD phenotype

Aβ and Tau

Oxidative stress and inflammation

Cellular response

Primary etiology

Phenomena and Pathology Targets

Mechanistic Targets
Objective of Early Diagnosis

Brain Health

Age

Preclinical

MCI

AD

Time
Objective of Early Diagnosis

- **Preclinical**
- **MCI**
- **AD**

Brain Health vs. Time

Age

MCI

AD
Percentage Cases

AD (n = 203)

MCI (n = 72)

NL (n = 130)

Automated MRI Regional Boundary Shift
6-year prediction of Normal to MCI

Prediction of MCI

Accuracy
SS/SP (n=13,32)

MESH MODELING

Thompson et al, Neuroimage 2004
3-year MRI hippocampal atrophy rate

ANATOMY

superior

inferior

NL-NL
n=10

NL-decline
n=7

Annual tissue loss %
Atrophy and Metabolism

10-Year decline from NL to AD

NL 1993

MCI 1997

AD 2003

de Leon et al PNAS 2001
Automated Hippocampus Sampling
7-year advanced prediction of Normal to MCI and AD

Prediction of MCI

Accuracy
SS/SP (n=25,47) 76%
82/79%

FDG-PET for Prediction and Progression: NL Aging

- Estimated Earliest Detection: -11 yrs
- Baseline Prediction: 76%
- Longitudinal Prediction: 74%

- NL-NL (47)
- NL-MCI (19)
- NL-AD (6)

Years from Baseline vs. Hip metabolism
Typical vs. Robust Normal Reference Databases

AD \( n=33 \)

MCI \( n=37 \)

Effect Size

Typical DB
Robust DB

IPL L, IPL R, LTL L, LRL R, PCC L, PCC R

C

D

Typical DB (\( n=55 \), top) and Robust DB (\( n=55 \), bottom)

**NL-AD (1993-2003) Post-mortem validated AD**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Year</th>
<th>Image</th>
<th>Z score</th>
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<tbody>
<tr>
<td>NL</td>
<td>1993</td>
<td><img src="image1.png" alt="Image" /></td>
<td>4</td>
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<tr>
<td>MCI</td>
<td>1995</td>
<td><img src="image2.png" alt="Image" /></td>
<td>3</td>
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<tr>
<td>Mild AD</td>
<td>1996</td>
<td><img src="image3.png" alt="Image" /></td>
<td>2</td>
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<tr>
<td>Mod AD</td>
<td>2000</td>
<td><img src="image4.png" alt="Image" /></td>
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**Path: AD 2003 CERAD definite, Braak stage C-VI**


Best Paper of the Year European Journal of Nuclear Medicine 2009
PIB and FDG

65 year old male

AD

71 years old male

Best Paper of the Year European Journal of Nuclear Medicine 2008

<table>
<thead>
<tr>
<th></th>
<th>AD vs NL</th>
<th>MCI vs NL</th>
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<tbody>
<tr>
<td><strong>FDG</strong></td>
<td>92</td>
<td>85</td>
</tr>
<tr>
<td>Accuracy (%)</td>
<td></td>
<td></td>
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<tr>
<td><strong>PIB</strong></td>
<td>96</td>
<td>75</td>
</tr>
<tr>
<td>Accuracy (%)</td>
<td></td>
<td></td>
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<tr>
<td>% Agreement</td>
<td>94</td>
<td>54</td>
</tr>
</tbody>
</table>

CSF Analytes in Normal Aging n=78

Longitudinal memory by high and low P-tau231 in 57 NL

Black = Low P-tau231
Red = high P-tau231

P<.05
Longitudinal MTL-GM by high and low P-tau231 in 57 NL

Black = Low P-tau231
Red = high P-tau231

P<.05

Glodzik, de Leon et al Neurobiol. Aging 2010
The Search for Mechanism
$^{15}\text{H}_2\text{O}-\text{PET}$  
EPI-ASL  
True-FISP-ASL
MRI True-FISP Hippocampal Perfusion Imaging
MRI with rebreathing apparatus
Vasoreactivity to CO₂ challenge

~2% CBF change/mmHg change in CO₂
Hippocampal Vasoreactivity and Cardiovascular Risk

Glodzik, Rusinek… de Leon et al. JCBF 2010
Cortical Vasoreactivity and Cardiovascular Risk

Glodzik, Rusinek ... de Leon et al. JCBF 2010
Parental History of AD in NL

- No Hx 59%
- Maternal 27%
- Paternal 10%
- Maternal and Paternal 4%
- Neither 10%

Normal cognition, MMSE 28-30
Age 48-80 yrs
Education > 11 yrs
FDG-PET in individual cases
Longitudinal change in NL with AD mothers

Mosconi et al, Neurology 2008
CSF Biomarkers and AD Maternal History in NL

- AB42/40
- IsoP
- P-tau231
- T-tau

FH-22, FHp-14, FHm-23
Parietal PIB-PET Uptake in NL with Maternal History of AD

Mosconi, de Leon et al PNAS et al 2010
AD phenotype

Aβ and Tau

Oxidative stress and inflammation

Cellular response

Phenomena and Pathology Targets

Mechanistic Targets
Conclusions

• PET and MR imaged hippocampal pathology appears early and is progression sensitive.

• The pathology specific P-tau231 and Ab also appear early but are not progression sensitive.

• Imaging and biomarkers may have a role in identifying mechanisms of AD-progression by considering energetics and vascular function.
Collaborating Scientists

• **NYU**
  – Lidia Glodzik
  – Lisa Mosconi
  – Henry Rusinek
  – Wai Tsui
  – Elizabeth Pirraglia
  – Yi Li

• **Institute Basic Research**
  – Pankaj Mehta

• **Cornell University**
  - Shankar Vallabhajosula
  - Stanley Goldsmith

• **Temple University**
  – Domenico Pratico

• **Einstein College of Medicine**
  – Peter Davies

• **University of California L.A.**
  – Liana Apostolova
  – Paul Thompson

• **Applied Neurosolutions**
  – Ray Zinkowski

• **Turku U. Finland**
  – Juha Rinne

• **Sahlgrenska U. Goteborg**
  – Kaj Blennow
  – Henryk Zetterberg
  – Anders Wallin