FUNDED BY NATIONAL INSTITUTE ON AGING
NIMH, NINR, NINDS, NCRR, and NIDA


Neil Buckholz, David Lee, Holly Soares

Industry Scientific Advisory Board (ISAB)

And Site PIs, Study Coordinators and 821 subjects enrolled in 58 Sites in US and Canada
NEEDS OF OUR FIELD

• Of course we need a treatment that works!
• Diagnose AD pathology in the brain with certainty, in subjects with symptoms or complaints
• Detect AD pathology in the brain in subjects without symptoms or complaints
• Measure change of AD in the brain
GOALS OF ADNI

• Validate biomarkers as measures of change
• Validate biomarkers as diagnostics or predictors: symptomatic and presymptomatic
• Optimize biomarker methods
• Standardize biomarker methods
• Establish a world-wide network for clinical AD studies and treatment trials
ADNI

Naturalistic study of AD progression

- 200 NORMAL 3 yrs
- 400 MCI 3 yrs
- 200 AD 2 yrs
- Visits every 6 months
- 57 sites
- Clinical, blood, LP
- Cognitive Tests
- 1.5T MRI

Some also have
- 3.0T MRI (25%)
- FDG-PET (50%)
- PiB-PET (approx 100)

All data in public database: UCLA/LONI/ADNI: No embargo of data
CONVERSION RATES

- **MCI-AD**
  - 1 YR 16%, 2 YR 40%
- **Control – MCI**
  - 1 YR 1.4%, 2 YR 3.9% (about 8 subjects)
POWER OF CLINICAL/COGNITIVE TESTS
25% CHANGE 1YR STUDY (2 ARM) :
AD (155 Subjects)

<table>
<thead>
<tr>
<th>Test</th>
<th>Sample Size</th>
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<tbody>
<tr>
<td>MMSE</td>
<td>803</td>
</tr>
<tr>
<td>RAVLT</td>
<td>607</td>
</tr>
<tr>
<td>ADAS</td>
<td>592</td>
</tr>
<tr>
<td>CDR SOB</td>
<td>449</td>
</tr>
</tbody>
</table>
AD Subjects: Hippocampal Volume (mm³)
# 1.5T MRI Comparisons - AD (n=69)

<table>
<thead>
<tr>
<th>Lab</th>
<th>Variable</th>
<th>SS/arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alexander</td>
<td>L. Hippo. Formation</td>
<td>334</td>
</tr>
<tr>
<td>Dale</td>
<td>Whole Brain</td>
<td>207</td>
</tr>
<tr>
<td>Schuff - FS</td>
<td>Hippocampus</td>
<td>201</td>
</tr>
<tr>
<td>Dale</td>
<td>Ventricle s</td>
<td>132</td>
</tr>
<tr>
<td>Dale</td>
<td>Hippocampus</td>
<td>126</td>
</tr>
<tr>
<td>Studholme</td>
<td>Temporal lobe % change</td>
<td>123</td>
</tr>
<tr>
<td>Schuff - FS</td>
<td>Ventricle s</td>
<td>119</td>
</tr>
<tr>
<td>Studhome</td>
<td>CV - % change</td>
<td>106</td>
</tr>
<tr>
<td>Fox</td>
<td>VBSI % change</td>
<td>105</td>
</tr>
<tr>
<td>Fox</td>
<td>BSI % change</td>
<td>71</td>
</tr>
<tr>
<td>Thompson</td>
<td>CV - % change</td>
<td>54</td>
</tr>
</tbody>
</table>
Normal Aging vs. Alzheimer’s Disease
FDG PET

Normal

AD
### 1.5T vs PET Comparison in AD (n=30)

<table>
<thead>
<tr>
<th>Lab</th>
<th>Modality</th>
<th>Variable</th>
<th>SS/arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foster</td>
<td>PET</td>
<td>hypometabolism1</td>
<td>593</td>
</tr>
<tr>
<td>Foster</td>
<td>PET</td>
<td>hypometabolism2</td>
<td>508</td>
</tr>
<tr>
<td>Jagust</td>
<td>PET</td>
<td>ROI-avg</td>
<td>396</td>
</tr>
<tr>
<td>Schuff - FS</td>
<td>MRI</td>
<td>Hippocampus</td>
<td>173</td>
</tr>
<tr>
<td>Schuff - FS</td>
<td>MRI</td>
<td>Ventricles</td>
<td>95</td>
</tr>
<tr>
<td>Reiman</td>
<td>PET</td>
<td>CV - fROI</td>
<td>91</td>
</tr>
<tr>
<td>Fox</td>
<td>MRI</td>
<td>VBSI % change</td>
<td>87</td>
</tr>
<tr>
<td>Thompson</td>
<td>MRI</td>
<td>CV - % change</td>
<td>53</td>
</tr>
<tr>
<td>Fox</td>
<td>MRI</td>
<td>BSI % change</td>
<td>50</td>
</tr>
</tbody>
</table>
1.5T MRI vs PET Comparison in MCI (n=69)

<table>
<thead>
<tr>
<th>Lab</th>
<th>Modality</th>
<th>Variable</th>
<th>SS/arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jagust</td>
<td>PET</td>
<td>ROI-avg</td>
<td>4605</td>
</tr>
<tr>
<td>Foster</td>
<td>PET</td>
<td>hypometabolism1</td>
<td>2176</td>
</tr>
<tr>
<td>Foster</td>
<td>PET</td>
<td>hypometabolism2</td>
<td>1629</td>
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<tr>
<td>Fox</td>
<td>MRI</td>
<td>VBSI % change</td>
<td>284</td>
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<tr>
<td>Schuff - FS</td>
<td>MRI</td>
<td>Ventrices</td>
<td>277</td>
</tr>
<tr>
<td>Reiman</td>
<td>PET</td>
<td>CV - fROI</td>
<td>249</td>
</tr>
<tr>
<td>Schuff - FS</td>
<td>MRI</td>
<td>Hippocampus</td>
<td>202</td>
</tr>
<tr>
<td>Fox</td>
<td>MRI</td>
<td>BSI % change</td>
<td>177</td>
</tr>
<tr>
<td>Thompson</td>
<td>MRI</td>
<td>CV - % change</td>
<td>73</td>
</tr>
</tbody>
</table>
First Conclusion

• In general atrophy, measured by MRI is a more sensitive and robust measure of rate of change
  – Hippocampus, ventricles, not that different
• With the exception of Eric Reiman’s statistically generated ROI, PET measures have less statistical power to detect a slowing of change than MRI
• BUT PET may be more sensitive to detect a treatment effect which improves function!!!
IDENTIFYING PREDICTORS

• A “predictor” is a measure which correlates with some future change

• The future change could be
  – Change of a cognitive or functional measure
  – Conversion from MCI to AD
  – Change of a biological measure

• Provides information on sequence, improves power
### BIOMARKERS

**John Trojanowski, Les Shaw, U Penn.**

<table>
<thead>
<tr>
<th></th>
<th>Tau</th>
<th>$\text{A}<em>\beta</em>{1-42}$</th>
<th>P-Tau$_{181P}$</th>
<th>Tau/$\text{A}<em>\beta</em>{1-42}$</th>
<th>P-Tau$<em>{181P}$/A$</em>\beta_{1-42}$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AD (n=102)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>122±58</td>
<td>143±41</td>
<td>42±20</td>
<td>0.9±0.5</td>
<td>0.3±0.2</td>
</tr>
<tr>
<td><strong>MCI (n=200)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>103±61</td>
<td>164±55</td>
<td>35±18</td>
<td>0.8±0.6</td>
<td>0.3±0.2</td>
</tr>
<tr>
<td><strong>NC (n=114)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>70±30</td>
<td>206±55</td>
<td>25±15</td>
<td>0.4±0.3</td>
<td>0.1±0.1</td>
</tr>
</tbody>
</table>

p<0.0001, for each of the 5 biomarker tests for AD vs NC and for MCI vs NC.

For AD vs MCI: p<0.005, Tau; p<0.01, A$_\beta_{1-42}$; p<0.01, P-Tau$_{181P}$; p<0.0005, Tau/A$_\beta_{1-42}$; p<0.005, P-Tau$_{181P}$/A$_\beta_{1-42}$. Mann-Whitney test.
**Figure 2**: Kaplan-Meier estimates of the rate of progression to Alzheimer’s disease in patients with MCI who have either normal CSF or pathological CSF at baseline.

Numbers at risk are the number of patients with MCI at each time point who had not developed any type of dementia and for whom clinical follow-up was still ongoing. Cut-off values for pathological CSF were $>350$ ng/L for T-tau and $<530$ ng/L for Aβ42. The incidence of Alzheimer’s disease in patients with MCI who had pathological CSF (n=67) was 27% per year compared with 1% per year in patients with normal CSF (n=67).
PIB Imaging: Alzheimer’s Disease

FDG

PIB
Follow-Up of PIB-Positive ADNI MCI’s

<table>
<thead>
<tr>
<th>ADNI PiB MCI’s</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 65, 12 mo. follow-up</td>
<td></td>
</tr>
<tr>
<td>PiB(-)</td>
<td>18</td>
</tr>
<tr>
<td>Converters to AD</td>
<td>3</td>
</tr>
<tr>
<td>PiB(+)</td>
<td>47</td>
</tr>
<tr>
<td>Converters to AD</td>
<td>14</td>
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</tbody>
</table>
Follow-Up of ADNI PiB Controls

<table>
<thead>
<tr>
<th>ADNI PiB Ctrl’s</th>
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</thead>
<tbody>
<tr>
<td>N = 19, 12 mo. follow-up</td>
<td></td>
</tr>
<tr>
<td>PiB(-)</td>
<td>10</td>
</tr>
<tr>
<td>Converters to MCI</td>
<td>0</td>
</tr>
<tr>
<td>PiB(+)</td>
<td>9</td>
</tr>
<tr>
<td>Converters to MCI</td>
<td>2</td>
</tr>
</tbody>
</table>
PIB vs CSF Biomarkers: Aβ

Total N = 55 (11 Control, 34 MCI, 10 AD)

Mean Cortical SUVR vs CSF Aβ 1-42

Penn Autopsy Sample (56 AD, 52 Cog normal)

192 pg/ml
PREDICTING FUTURE RATE OF HIPPOCAMPAL ATROPHY

• Controls: CSF AB and tau
• MCI: APOE, CSF AB and tau, FDG PET
• AD: CSF AB and tau
Second Conclusion

• Cognitive measures, APOE, CSF, MRI are predictors
• FDG PET is also a good predictor
• But much more analysis of the ADNI data is needed with longer followup
ADNI data in support of early AD trial: proof of concept Phase II

- 2 year trial, MCI subjects with CSF $A\beta_{42} < 193$ pg/ml
- Analysis: linear mixed effects modeling, MRI covariate, CDR-SB single primary outcome
- 40% effect
- now only require 101 subjects per group
ADNI: HC atrophy and CSF Aβ

<table>
<thead>
<tr>
<th></th>
<th>Aβ&lt;sub&gt;1-42&lt;/sub&gt; &lt;192pg/mL</th>
<th>Aβ&lt;sub&gt;1-42&lt;/sub&gt; &gt;192pg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL</td>
<td>-5.6±4.7</td>
<td>-2.6±4.1</td>
</tr>
<tr>
<td>AD</td>
<td>-8.0±5.9</td>
<td>-4.2±3.5</td>
</tr>
<tr>
<td>MCI</td>
<td>-4.8±3.6</td>
<td>-2.9±3.7</td>
</tr>
<tr>
<td>NC</td>
<td>-3.6±3.2</td>
<td>-2.2±4.3</td>
</tr>
</tbody>
</table>
A prevention trial on normals could be designed with an interim analysis of hippo vol, and continue with clinical/cognitive endpoints.
ADNI Neuropathology Core

• Protocols and Support Documents Online:
  – https://adcs-adni.bbl.ucsd.edu/docs/studydocs/Neuropath%20Core

• Contact:
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  Fax. +1-314-286-2763
  Email: morrisj@abraxas.wustl.edu
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  Co-Director, Alzheimer's Disease Neuroimaging Initiative Neuropathology Core
  Tel. +1-314-362-2386
  Fax. +1-314-362-4096
  Email: cairns@wustl.edu
  – Lisa Taylor-Reinwald, BA, HTL(ASCP)
  ADNI Neuropathology Core Coordinator
### Table 1. ADNI Autopsy Rates

**09-01-2005 to 03-29-2010**

<table>
<thead>
<tr>
<th>ADNI Funding Period</th>
<th>ADNI-NPC</th>
<th>Deaths</th>
<th>Autopsies</th>
<th>Autopsy Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>09-01-2005 to 08-31-2007</td>
<td>NO</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>09-01-2007 to 08-31-2008</td>
<td>YES</td>
<td>10</td>
<td>4</td>
<td>40.0</td>
</tr>
<tr>
<td>09-01-2008 to 08-31-2009</td>
<td>YES</td>
<td>9</td>
<td>5</td>
<td>55.5</td>
</tr>
<tr>
<td>09-01-2009 to 03-01-2010</td>
<td>YES</td>
<td>3</td>
<td>1</td>
<td>33.3</td>
</tr>
<tr>
<td>Total (2005-2009)</td>
<td>-</td>
<td>28</td>
<td>10</td>
<td>35.7</td>
</tr>
<tr>
<td>Total since NPC established</td>
<td>-</td>
<td>21</td>
<td>10</td>
<td>47.6</td>
</tr>
</tbody>
</table>

Note: The ADNI-NPC was established on 9/1/2007. During the initial stage of ADNI1 the NPC had not been established and no autopsies were performed on the 6 ADNI participants who expired during 2007 and the first half of 2008.

Autopsy rate = number of brain autopsies/total number of ADNI participants who died.
Table 2. Clinical and Neuropathologic Diagnoses at Expiration

<table>
<thead>
<tr>
<th>Clinical diagnosis</th>
<th>Neuropathologic diagnosis [N (%)]</th>
<th>TOTAL (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AD</td>
<td>AD + DLB</td>
</tr>
<tr>
<td>DAT</td>
<td>2 (20)</td>
<td>3 (30)</td>
</tr>
<tr>
<td>MCI</td>
<td>2 (20)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Normal</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>TOTAL (%)</td>
<td>4 (40)</td>
<td>3 (30)</td>
</tr>
</tbody>
</table>

Note: N, number of ADNI cases. AD, Alzheimer’s disease; AGD, argyrophilic grain disease; DAT, dementia of the Alzheimer type; DLB, dementia with Lewy bodies; MCI, mild cognitive impairment; TDP-43, TDP-43 proteinopathy in the medial temporal lobe.

Mild small vessel disease (arteriolosclerosis and cerebral amyloid angiopathy) was a feature of all cases but none had infarcts.
SCOPE OF ADNI2

• If renewed ($69 million), ADNI2 will:
• Continue to follow more than 400 controls and MCI from ADNI1 for 5 more years
• Enroll:
  – 100 additional EMCI (supplements 200 from GO
  – 150 new controls, LMCI, and AD
• MRI at 3, 6, months and annually
• F18 amyloid (AV-45)/FDG baseline and Yr2
• LP on 100% of subjects at enrollment
• Genetics
F-AV-45 Scans
Spectrum of Pathology

AVID
ADNI Industry Scientific Advisory Board

New members Abbott, Genentech, Roche, Bayer

PIB/PET Supplement: Alzheimer’s Association and GE Healthcare
Cerebrospinal Fluid Extension: Alzheimer’s Association, AstraZeneca, Cure Alzheimer’s Fund, Merck, Pfizer and an anonymous foundation

Genome-Wide Genotyping: Gene Network Sciences, Merck, Pfizer and an anonymous foundation

Genome-Wide Genotyping Genetic Analysis: NIBIB, Merck, Pfizer and an anonymous foundation
Publications


127) Friedman L et al. Circadian Clock Gene Polymorphisms and Sleep/Wake Disturbance in...
140) Apostolova L et al. 3D PIB and CSF biomarker associations with hippocampal atrophy in ADNI. Submitted, 2010.
143) Murphy E et al. Six-Month Neuroanatomical Change in MTL Structures is Associated with Subsequent Memory Decline in Elderly Controls. Submitted, 2010.
146) McDonald M et al. ABCA7 and BIN1 are susceptibility genes for Alzheimer’s disease. Submitted, 2010.
Abstracts


21) Lee W, Langbaum JBS, Chen K, Roschke C, Bandy D, Alexander GE, Foster NL, Weiner,


35) Nikelski J, Evans A, Chertkow H. Assessment of Structural Differences in Normal Aging and...


These slides and much more at ADNI-INFO.ORG

All data at www.loni.ucla.edu/ADNI/