The Australian Imaging Biomarkers and Lifestyle Flagship Study of Ageing

(AUSTRALIAN ADNI)

July 2014 UPDATE
Christopher Rowe MD – Neuroimaging stream leader
October 2006

1112 recruited

0 yrs

1.5 yrs

230 imaged

Funded by CSIRO

738 not imaged

MRI + 11C-PiB

288 imaged

Magnetic Resonance Imaging + 11C-PiB

Funded by CSIRO

823 not imaged

632 not imaged

90 new

Funded by Piramal

Florbetapir

Funded by CSIRO

142 11C-PiB

Funded by SIEF

102 Flutemetamol

Funded by GE

F-18 Flutemetamol

Funded by GE

94 Florbetapir

Funded by DCRC

F-18 Flutemetamol

Funded by GE

300 Not imaged

NAV4694

Funded by Navidea

30 11C-PiB

145 new

Funded by US DOD

F-18 Flutemetamol

Funded by GE

192 imaged

MRI and 11C-PiB

Funded by SIEF

150 Vietnam AIBL-VETS

Funded by Piramal

240 for TAU imaging (Avid and GE)

2014-15
4.5 year data release coming soon

PiB Baseline (288), 3 years (173), 4.5 yrs (141)
Plus 230 added from original cohort (flutemetamol, florbetapir or PiB at 4.5 yrs)
i.e. amyloid scan status known in 371 subjects with 4.5 yrs of follow-up.
Plus 250 new recruits (160 flute, 90 FBP)

www.adni.loni.usc.edu
- Data and Samples
- Access Data
610 research groups granted access to AIBL@LONI through ADNI website

Includes access granted to the following companies:
The natural history of Aβ deposition in sporadic AD

Neocortical SUVR

MCI +

AD

HC+


Mean SUVR AD+

(2.33)

0.043 SUVR/yr

(95%CI 0.037-0.049 SUVR/yr)

19.2 yr

(95%CI 17-23 yrs)

Mean SUVR HC-

(1.17)

12.0 yr

(95%CI 10-15 yrs)

Time (years)

3 year clinical progression rate vs PiB SUVR

Neocortical SUVR

PPV 17%
PPV 35%
PPV 44%
PPV 82%

HC (n = 183)
MCI (n = 87)
AD (n = 79)

HC to MCI or AD over 3 years  
(n=183; 13% progressed)

<table>
<thead>
<tr>
<th></th>
<th>HC positive for marker</th>
<th>OR</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>HV</td>
<td>46</td>
<td>2.2</td>
<td>0.20</td>
<td>0.90</td>
</tr>
<tr>
<td>e4</td>
<td>74</td>
<td>2.1</td>
<td>0.18</td>
<td>0.91</td>
</tr>
<tr>
<td>EM&lt;-0.5</td>
<td>22</td>
<td>4.2</td>
<td>0.32</td>
<td>0.90</td>
</tr>
<tr>
<td>PiB</td>
<td>53</td>
<td>4.8</td>
<td>0.26</td>
<td>0.93</td>
</tr>
<tr>
<td>PiB+e4</td>
<td>34</td>
<td>5.7</td>
<td>0.29</td>
<td>0.93</td>
</tr>
<tr>
<td>PiB+HV</td>
<td>17</td>
<td>10</td>
<td>0.47</td>
<td>0.92</td>
</tr>
<tr>
<td>PiB+EM</td>
<td>10</td>
<td>16</td>
<td>0.50</td>
<td>0.94</td>
</tr>
</tbody>
</table>

AIBL composite EM Z-score < -1 (n=49), OR 11, PPV 35%, NPV 96% without correction for age or education.
MCI to **AD** over 3 years (n=87; 59% progressed)

<table>
<thead>
<tr>
<th>MCI positive for marker</th>
<th>Odds Ratio</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>HV</td>
<td>4</td>
<td>0.67</td>
<td>0.65</td>
</tr>
<tr>
<td>ApoE-ε4</td>
<td>5</td>
<td>0.74</td>
<td>0.66</td>
</tr>
<tr>
<td>CVLT&lt;-1.5</td>
<td>11</td>
<td>0.80</td>
<td>0.74</td>
</tr>
<tr>
<td>PiB</td>
<td>15</td>
<td>0.77</td>
<td>0.82</td>
</tr>
<tr>
<td>PiB+ε4</td>
<td>16</td>
<td>0.79</td>
<td>0.81</td>
</tr>
<tr>
<td>PiB+HV</td>
<td>44</td>
<td>0.83</td>
<td>0.90</td>
</tr>
<tr>
<td>PiB+CVLT</td>
<td>na</td>
<td>0.86</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Initial Aβ burden is a better predictor of progression from MCI to AD than the rate of Aβ accumulation.

\[ OR = 5.4 \quad OR = 15 \]
Relation between rate of Aβ deposition and rate of episodic memory decline in HC

Accumulators

4.5-year follow-up

PiB-
(n=80)

PiB+
(n=40)

Rate of episodic memory decline

Rate of Aβ deposition (SUVR/yr)

R² = 0.07 (p = 0.54)

R² = 0.42 (p = 0.023)

R² = 0.32 (p = 0.0134)

adjusted for age, gender, education, ApoE
Relation between rate of Aβ deposition and rate of episodic memory decline

4.5-year follow-up

<table>
<thead>
<tr>
<th>Accumulators (n=120)</th>
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<table>
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<tr>
<th>THRESHOLD</th>
<th>4.5-year follow-up</th>
<th>adjusted for age, gender, yoe, ApoE</th>
<th>+adjusting baseline SUVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>PiB SUVR 1.2 (n=68)</td>
<td>R^2 = 0.19 (p = 0.0353)</td>
<td>R^2 = 0.35 (p = 0.313)</td>
<td></td>
</tr>
<tr>
<td>PiB SUVR 1.3 (n=48)</td>
<td>R^2 = 0.28 (p = 0.0162)</td>
<td>R^2 = 0.38 (p = 0.060)</td>
<td></td>
</tr>
<tr>
<td>PiB SUVR 1.4 (n=42)</td>
<td>R^2 = 0.30 (p = 0.0150)</td>
<td>R^2 = 0.39 (p = 0.028)</td>
<td></td>
</tr>
<tr>
<td>PiB SUVR 1.5 (n=40)</td>
<td>R^2 = 0.31 (p = 0.0134)</td>
<td>R^2 = 0.42 (p = 0.023)</td>
<td></td>
</tr>
<tr>
<td>PiB SUVR 1.6 (n=37)</td>
<td>R^2 = 0.31 (p = 0.0383)</td>
<td>R^2 = 0.41 (p = 0.031)</td>
<td></td>
</tr>
<tr>
<td>PiB SUVR 1.9 (n=21)</td>
<td>R^2 = 0.40 (p = 0.080)</td>
<td>R^2 = 0.48 (p = 0.067)</td>
<td></td>
</tr>
</tbody>
</table>
Optimal window for anti-Aβ intervention

Neocortical SUV_{cb}

Time (years)

Mean SUV AD+ (2.33)

Threshold cognitive effects (1.40)

Threshold AD pathology (1.20)

7.0 yr (95% CI 5-10 yrs)
Memory Test Performance over 3 years

- **CVLT-II Delayed Recall**
- **Healthy Older Persons**
- **Mild Cognitive Impairment**

### PiB -ve
- Healthy Older Persons: n = 122, SUVR = 1.16
- Mild Cognitive Impairment: n = 16, SUVR = 1.18

### PiB +ve
- Healthy Older Persons: n = 55, SUVR = 1.95
- Mild Cognitive Impairment: n = 32, SUVR = 2.21
PiB, Cerebrovascular Disease and Episodic Memory

Females

- Slope for PiB: -0.14 per year (p<0.001)
- Significant time x age interaction (p=0.008).
- Significant main effect but not time interaction for CVD (p=0.01), gender (p=0.01) and YOE (p<0.001)

Males
Executive Function

Females

- Slope for PiB+ = -0.06/year (p=0.05)
- Slope for CVD = 0.1/year (p=0.01)
- Significant main effects of gender, education, age
- Significant x time effect of CVD, trend for PiB+

Males
Episodic Memory and Educational Attainment

• Slope for PiB+ = -0.14 per year (p<0.001)

• Significant time x age interaction (p=0.008).

• Significant main effect but not time interaction for CVD (p=0.01), gender (p=0.01) and YOE (p<0.001)
PiB, CVD and Change in PiB SUVR
HA Aβ+ 54 months: Effect of APOE & BDNF

EM = AIBL Episodic Memory Composite
Conclusions and general summary

- **High Aβ**: Healthy older adults: faster cognitive decline; ↑ progression to MCI
- **Low Aβ**: Healthy older adults: no decline

- **APOE ε4**
  - High Aβ + ε4 carriage → faster cognitive decline over 54 months (Mormino et al., in press)

- **BDNF Val66Met**
  - No effect on individuals with low Aβ
  - Healthy older adults with high Aβ
    - Met carriers → ↑ memory decline/hippocampal atrophy

**High Aβ + ε4 carriage + BDNF Met → ↑↑ memory decline**
Subjective Memory Complaint

• SMC is associated with higher scores on anxiety scales but correlations with poorer cognitive performance and amyloid burden have been inconsistent - though tending towards an association.

• In the original AIBL imaging cohort of 177 HC 54% were SMC i.e. answered yes to “Do you have difficulty with your memory?” with normal psychometric test results.

• We only found higher anxiety scores and no overall increase in PiB+ve prevalence.
But there was a difference when SMC was associated with ApoE-$\varepsilon$4.
$^{18}$F-flutemetamol SUVR

*Significantly different from nMC, $p < 0.05$
Retinal amyloid fluorescence imaging

Proprietary curcumin formulation with scientifically tested and defined chemical content and high-bioavailability.

Koronyo-Hamaoui et al. NeuroImage 2011;
Masuda et al. Bioorg Med Chem. 2011

NeuroVision Imaging
Los Angeles, CA
Retinal amyloid index correlates with Neocortical SUVR

Retinal amyloid fluorescence imaging | Shaun Frost
Exosomes as biomarkers for AD

- Exosomes = Extracellular membrane vesicles, 50-130nm in diameter
- Secreted by a variety of mammalian cells
- Isolated from a variety of biological fluids
  - serum, plasma, CSF, milk, urine, saliva, etc...
- Contain protein and RNA (including miRNA)

- Source of circulating biomarkers
- Contain many proteins involved in neurodegenerative diseases

Current Study:
- AIM: to identify AD miRNA profile in blood derived exosomes
- APPROACH: isolated exosomes from blood of healthy aged controls and AD patients
  - Profile the exosomal miRNA using next gen sequencing
  - validate the miRNA profile using qPCR
Differentially expressed exosomal miRNA in AD patients

- 17 miRNA were found to be significantly deregulated ($p$ (AD Vs HC) $\leq 0.05$)
- There are two major clusters:
  - Cluster 1 contains 15 miRNA which were found to be up-regulated.
  - Cluster 2 contains 3 miRNA which were found to be down-regulated.
- Validation in 15 AD and 35 Healthy Controls blind to diagnosis using qPCR:
  - 13/15 AD correctly identified (Sensitivity of 87%) (2 patients high Aβ / APOε4 negative)
  - 27/35 HC correctly identified (Specificity of 77%) (5 subjects high Aβ / 3 APOε4 positive)
Correlation of Imaged and Blood-Based Estimates of Neocortical Amyloid Burden (NAB)

$$\beta=0.23$$
$$p<0.001$$

$$\beta=0.54$$
$$p<0.0001$$

Burnham et al  Predicting AD from a blood based biomarker profile
Jul 14 4-5:30pm O2-13-06 Hall A1
### Bivariate correlates of progression to Alzheimer’s disease over 54 Months

<table>
<thead>
<tr>
<th></th>
<th>No (n)</th>
<th>Yes (n)</th>
<th>Odds</th>
<th>$\chi^2$</th>
<th>$p$</th>
<th>Odds ratio (95%CI)</th>
<th>PPV (95%CI)</th>
<th>NPV (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HC Progressed to MCI/AD</strong></td>
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<tr>
<td>Predicted PiB Negative</td>
<td>304 (95.30%)</td>
<td>15 (4.70%)</td>
<td>0.05</td>
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<tr>
<td>Predicted PiB Positive</td>
<td>240 (90.37%)</td>
<td>26 (9.63%)</td>
<td>0.11</td>
<td>4.75</td>
<td>0.003</td>
<td>2.16 (1.12-4.17)</td>
<td>9.90% (8.18%-11.95%)</td>
<td>95.16% (93.30%-96.52%)</td>
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<tr>
<td><strong>MCI Progressed to AD</strong></td>
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</tr>
<tr>
<td>Predicted PiB Negative</td>
<td>10 (71.43%)</td>
<td>4 (28.57%)</td>
<td>0.40</td>
<td></td>
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</tr>
<tr>
<td>Predicted PiB Positive</td>
<td>7 (20.00%)</td>
<td>28 (80.00%)</td>
<td>4.00</td>
<td>9.51</td>
<td>0.002</td>
<td>10.00 (2.41-41.58)</td>
<td>71.62% (60.74%-80.45%)</td>
<td>79.85% (63.14%-90.16%)</td>
</tr>
</tbody>
</table>
*APOE* genotype-dependent effects of diet and physical activity on cognition and Alzheimer's-related pathology: Data from the AIBL Study of Ageing

Rainey-Smith *et al.*, Jul 14 2014, 2:15PM - 3:45PM, Hall A3, O2-02-05

Linear mixed models (LMM) analyses: $p < 0.01$. Controlling for age, gender, years of education, country of birth, body mass index, energy intake.

*Gardener, Rainey-Smith et al, 2014, Molecular Psychiatry (In press).*
Significant interaction of the BDNF Val66Met variant with physical activity was observed for hippocampal and temporal lobe volumes (volumes corrected for intracranial volume).
This association did not exist in BDNF Met carriers.
Future Directions for AIBL Imaging

- Further refine prognostic value and comparative effectiveness of imaging and blood biomarkers
- Examine genetic and environmental influences on rate of decline in Aβ+ve HC
- Add Tau imaging
- Create a new pool of amyloid scan positive HC and MCI for early intervention trials
- Use AIBL infrastructure to support the A4 and DIAN therapy trials
AIBL is a large collaborative study and a complete list of contributors and the management committee can be found at www.aibl.csiro.au

This research was funded in part by the Science and Industry Endowment Fund and CSIRO.

We thank all who took part in the study.