The Australian Imaging Biomarkers and Lifestyle Flagship Study of Ageing

(AUSTRALIAN ADNI)

July 2012 UPDATE – Imaging
Christopher Rowe MD – Neuroimaging stream leader

October 2006

- **823 not imaged**
  - 288 imaged
    - MRI + 11C-PiB
      - Funded by CSIRO
  - 738 not imaged
  - 632 not imaged

October 2011

- **1112 participants recruited to AIBL**
- **968 participants remain in AIBL**
- **824 remain in AIBL**

- **100 Vietnam veterans AIBL-DOD**
  - MRI, CSF, F-18 PET

- **100 new participants**
  - MRI + F-18 Flutemetamol
    - Funded by GE

- **200 new participants**
  - MRI + F-18 Florbetaben
    - Funded by Bayer/Piramal

- **Replacement MCI and sMC**

- **Women’s Healthy Aging Program**

- **100 participants**
  - MRI + Flutemetamol
    - Funded by GE

- **213 participants**
  - MRI + AV-45
    - Funded anon

- **250 participants**
  - MRI and 11C-PiB
    - Funded by WA Govt

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- **100 Vietnam veterans AIBL-DOD**
  - MRI, CSF, F-18 PET

- **100 participants**
  - MRI + Flutemetamol
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- **213 participants**
  - MRI + AV-45
    - Funded anon

- **250 participants**
  - MRI and 11C-PiB
    - Funded by WA Govt

- **130 participants**
  - MRI and 11C-PiB
    - Funded by SIEF

**October 2006**

- **0 yrs**
  - 1112 participants recruited to AIBL

- **1.5 yrs**
  - 968 participants remain in AIBL

- **3 yrs**
  - 824 remain

- **4.5 yrs**
  - All to have MRI & amyloid PET

- **6 yrs**

*Diagram showing the progression of participants through different phases of the study.*
Neocortical SUVR\textsubscript{40-70} = cortical activity / cerebellar grey matter activity from 40 to 70 minutes post injection

Negative is <1.5

Follow-up PiB co-registered to baseline and saved prior ROI set used.

Single operator for all PiB scans.
2. Automatic: co-registration + MRI segmentation (GM, WM, CSF) + AAL template + PVC
## Imaging Cohort Demographics

<table>
<thead>
<tr>
<th></th>
<th>HC (n=195)</th>
<th>MCI (n=92)</th>
<th>AD (n=79)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>72</td>
<td>74</td>
<td>73</td>
</tr>
<tr>
<td>Gender (M:F)</td>
<td>47%</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>MMSE</td>
<td>29</td>
<td>27</td>
<td>21</td>
</tr>
<tr>
<td>CDR</td>
<td>0.0</td>
<td>0.5 ± 0.2</td>
<td>1.0 ± 0.5</td>
</tr>
<tr>
<td>CDR SOB</td>
<td>0.06 ± 0.2</td>
<td>1.25 ± 0.9</td>
<td>4.36 ± 1.7</td>
</tr>
<tr>
<td>% ApoE ε4</td>
<td>41%</td>
<td>61%</td>
<td>65%</td>
</tr>
<tr>
<td>Years of Education</td>
<td>13.4</td>
<td>12.5</td>
<td>12.4</td>
</tr>
</tbody>
</table>
Baseline Imaging Findings
% of Healthy who are PiB+ve

4%  12%  32%  52%

< 60 yrs data from Washington University

< 60 yrs data from Washington University

Years of age

50-59  60-69  70-79  80+

e4-  e4+
% PiB+ HC vs Age (by decade)

(PiB+ when SUVR >1.5)

Prevalence of plaques in HC

(Davies, 1988, n=110)
(Braak, 1996, n=551)
(Sugihara, 1995, n=123)

Prevalence of AD
(Tobias, 2008)

AIBL data

% PiB+ HC

ε4 corrected

15 yrs

52%
PiB neocortical SUVR in AIBL+

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean ± SD</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>HC</td>
<td>1.40 ± 0.4</td>
<td>195</td>
</tr>
<tr>
<td>MCI</td>
<td>1.91 ± 0.6</td>
<td>92</td>
</tr>
<tr>
<td>AD</td>
<td>2.30 ± 0.4</td>
<td>79</td>
</tr>
</tbody>
</table>

*Statistically significant results compared to controls (p < 0.0001)
Aβ burden vs Age

Older AD do not have less PiB binding
Aβ vs Memory

HC

MCI

AD

Episodic Memory

Neocortical SUVR

$r = -0.20$ ($p = 0.13$)

$r = -0.53$ ($p < 0.0001$)
Follow-up Data
LONGITUDINAL DATA
Progression over 3 years

<table>
<thead>
<tr>
<th></th>
<th>HC-</th>
<th>HC+</th>
</tr>
</thead>
<tbody>
<tr>
<td>PiB rise (SUVR/yr)</td>
<td>0.01</td>
<td>0.05 (2.5%)</td>
</tr>
<tr>
<td>Memory Decline (SD/yr)</td>
<td>-0.02</td>
<td>-0.17</td>
</tr>
</tbody>
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<table>
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<tr>
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<th>MCI+</th>
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<tr>
<td>PiB rise (SUVR/yr)</td>
<td>0.01</td>
<td>0.05</td>
</tr>
<tr>
<td>Memory Decline (SD/yr)</td>
<td>-0.04</td>
<td>-0.21</td>
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</table>
Longitudinal PiB PET
6-year follow-up

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Neocortical SUVR</th>
<th>73 yo HC female (ε3/ε3)</th>
<th>MMSE 29</th>
<th>MMSE 28 MCI</th>
<th>MMSE 30 HC</th>
<th>74 yo HC female (ε3/ε3)</th>
<th>MMSE 29</th>
<th>MMSE 30 HC</th>
<th>78 yo HC male (ε3/ε3)</th>
<th>MMSE 29</th>
<th>MMSE 30 HC</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>2.5</td>
<td>HC</td>
<td>MMSE 29</td>
<td>MMSE 29 HC</td>
<td>MMSE 29 HC</td>
<td>78 yo HC male (ε3/ε3)</td>
<td>MMSE 29</td>
<td>MMSE 30 HC</td>
<td>78 yo HC male (ε3/ε3)</td>
<td>MMSE 29</td>
<td>MMSE 30 HC</td>
</tr>
<tr>
<td>45</td>
<td>1.6</td>
<td>HC</td>
<td>MMSE 29</td>
<td>MMSE 29 HC</td>
<td>MMSE 29 HC</td>
<td>78 yo HC male (ε3/ε3)</td>
<td>MMSE 29</td>
<td>MMSE 30 HC</td>
<td>78 yo HC male (ε3/ε3)</td>
<td>MMSE 29</td>
<td>MMSE 30 HC</td>
</tr>
<tr>
<td>70</td>
<td>1.0</td>
<td>HC</td>
<td>MMSE 29</td>
<td>MMSE 29 HC</td>
<td>MMSE 29 HC</td>
<td>78 yo HC male (ε3/ε3)</td>
<td>MMSE 29</td>
<td>MMSE 30 HC</td>
<td>78 yo HC male (ε3/ε3)</td>
<td>MMSE 29</td>
<td>MMSE 30 HC</td>
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Aβ deposition over time
3-5 year follow-up
(n=158)

Neocortical SUVR$_{cb}$

Mean SUVR AD+ (2.35)

2.9%/yr
(95%CI 2.5-4.0%/yr)

19.6 yr
(95%CI 14-23 yrs)

Mean SUVR HC- (1.17)

14 yr
(95%CI 13-17 yrs)

Villemagne et al, Kinetics of Aβ deposition, AAIC, 2012
Average rate of atrophy over one year in HC PiB- vs PiB+.
Relation between baseline $\text{A}$ burden and memory decline in healthy controls
(36 months follow-up)

$r = 0.38 \ (p = 0.0005)$
Relation between rate of Aβ deposition and rate of memory decline

3-5 year follow-up

Rate of change in episodic memory

Rate of Aβ deposition

Relation between rate of Aβ deposition and rate of memory decline

HC+ (n=36)

R² = 0.22 (p = 0.041)
PiB SUVR cut-point 1.5
3 year clinical progression

HC
(n=194)

Positive Aβ
(n=60)

6% to MCI/AD

Negative Aβ
(n=134)

20% to MCI/AD

MCI
(n=92)

Positive Aβ
(n=64)

7% to AD

Negative Aβ
(n=28)

66% to AD

Hazard Ratio 3.6 (OR 4)
*(p= 0.016)
Corrected for age, gender, education

Hazard Ratio 11 (OR 25)
*(p< 0.0001)
Prediction of Progression: HC to MCI/AD (at 36 months follow-up)  
n=194

<table>
<thead>
<tr>
<th>Conditions</th>
<th>ACCURACY</th>
<th>PPV</th>
<th>NPV</th>
<th>Odds Ratio</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hippocampal atrophy</td>
<td>0.54</td>
<td>0.16</td>
<td>0.92</td>
<td>2</td>
<td>0.8-6</td>
</tr>
<tr>
<td>PiB+ve (SUVR &gt;1.5)</td>
<td>0.57</td>
<td>0.2</td>
<td>0.94</td>
<td>4</td>
<td>4-10</td>
</tr>
<tr>
<td>PiB + Hipp Vol (n=118, ++ vs --)</td>
<td>0.63</td>
<td>0.32</td>
<td>0.94</td>
<td>7</td>
<td>2-26</td>
</tr>
<tr>
<td>Composite Memory (&lt; -1.0 SD)</td>
<td>0.64</td>
<td>0.3</td>
<td>0.97</td>
<td>14</td>
<td>4-43</td>
</tr>
<tr>
<td>Memory + Hipp Vol (n=123, ++ vs --)</td>
<td>0.65</td>
<td>0.32</td>
<td>0.98</td>
<td>23</td>
<td>4-129</td>
</tr>
<tr>
<td>PiB + Memory (n=126, ++ vs --)</td>
<td>0.73</td>
<td>0.48</td>
<td>0.97</td>
<td>31</td>
<td>7-125</td>
</tr>
</tbody>
</table>
Prediction of Progression: MCI to AD  
(at 36 months follow-up)  
n=92

<table>
<thead>
<tr>
<th>Condition</th>
<th>ACCURACY</th>
<th>PPV</th>
<th>NPV</th>
<th>Odds Ratio</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hippocampal atrophy</td>
<td>0.68</td>
<td>0.61</td>
<td>0.75</td>
<td>5</td>
<td>2-14</td>
</tr>
<tr>
<td>Composite Memory (&lt;-2.0 SD)</td>
<td>0.70</td>
<td>0.59</td>
<td>0.81</td>
<td>6</td>
<td>2-18</td>
</tr>
<tr>
<td>ApoE ε4+</td>
<td>0.76</td>
<td>0.71</td>
<td>0.80</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>PiB+ve (SUVR &gt;1.5)</td>
<td>0.80</td>
<td>0.66</td>
<td>0.93</td>
<td>25</td>
<td>5-114</td>
</tr>
<tr>
<td>PiB+ve MRI-ve (n=6/13+ vs 0/11--)</td>
<td>0.75</td>
<td>0.46</td>
<td>1.00</td>
<td>&gt;100</td>
<td>n/a</td>
</tr>
<tr>
<td>PiB-ve MRI+ve (n=1/12+- vs 0/11--)</td>
<td>0.54</td>
<td>0.08</td>
<td>1.00</td>
<td>&lt;1</td>
<td></td>
</tr>
<tr>
<td>PiB + Hipp Vol (n=29/37++ vs 0/11--)</td>
<td>0.89</td>
<td>0.78</td>
<td>1.00</td>
<td>&gt;100</td>
<td>n/a</td>
</tr>
</tbody>
</table>
Summary

- Aβ deposition is slow and of similar rate in PiB+ HC and MCI (3% SUVR per year).
- A plateau occurs with advancing dementia.
- Aβ is common in older HC
  - 11% if 60-69
  - 32% if 70-79
  - 51% if 80+ years

and strongly related to genetics i.e. ApoE-ε4 status (risk 2-3X)
Over 3 Years

- Aβ in HC is associated with faster cognitive decline and grey matter atrophy.
- 20% of PiB+ HC develop MCI/AD (c.f. 6% of PiB-)
- 74% PiB+ MCI develop AD c.f. 16% of PiB-Odds Ratio = 25 (but 20% PiB- develop other dementias)
- Combination of biomarkers provides better prediction (e.g. if PiB+ and hippocampal atrophy = 86% accuracy, PPV 78%).
Baseline and 18 mth MRI, PiB scans and corresponding clinical data are available from www.loni.ucla.edu/ADNI/Data/ (look for the AIBL button in the ADNI data site)

36 month data coming soon!