The Australian Imaging Biomarkers and Lifestyle Flagship Study of Ageing

(aibl)

(AUSTRALIAN ADNI)

July 2011 UPDATE – Imaging
Christoher Rowe MD – Neuroimaging stream leader
$^{11}$C-PiB PET commenced at Austin Health in 2004 and expanded in 2006 through the AIBL study of aging.
1000 subjects (25% imaged with PiB PET and MRI)
A multimodality clinical study

Databases

- Cognitive functions
- Blood biomarkers
- Genomic
- Demographic and Lifestyle

PET-PiB

Amyloid beta load

Images:

- T1W: Anatomy
- T2W: CSF and structures
- SWI: Venous tree
- FLAIR: White matter lesions
- DWI: White matter connection

Methods

- 366 Participants
- Neuropsychology: CDR, MMSE, LM, CVLT-II, Rey Figure, etc
- MRI: 3D MP-RAGE, FLAIR, +/- SWI, DTI
- PET: Equilibrium imaging at 40-70 min after 300 MBq of $^{11}$C-PiB
- Image Analysis:
  - PiB PET: Standard uptake value ratios (SUVR) i.e. cortex ROIs: cerebellar grey matter
  - MRI: 3 tissue segmentation using expectation maximization probability maps
**11C-PIB – Image Quantification**

**Regions**

Neocortical $\text{SUVR}_{40-70}$

= 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</th>
<th>MCI</th>
<th>AD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=195)</td>
<td>(n=92)</td>
<td>(n=79)</td>
</tr>
<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
PiB neocortical SUVR in AIBL+

Neocortical SUVR

HC
1.40±0.4
(n = 195)

MCI
1.91±0.6
(n = 92)

AD
2.30±0.4
(n = 79)

(31%)

(68%)

(99%)

*Statistically significant results compared to controls (p < 0.0001)
### Relation between ApoE, age, and Aβ burden

#### HC

- **(n=193)**
  - Slope: 0.018 SUVR/year
  - Significance: \( p<0.0001 \)

#### HC ε4

- **(n=74)**
  - Slope: 0.029 SUVR/year
  - Significance: \( p<0.0001 \)

#### HC non-ε4

- **(n=109)**
  - Slope: 0.015 SUVR/year
  - Significance: \( p<0.0001 \)
% Healthy Elderly PiB+ve

YEARS OF AGE

60-69  70-79  80+

e4-  e4+
Aβ burden vs Age

Older AD do not have less PiB binding
### Calculated accuracy for PiB (AD vs HC)

<table>
<thead>
<tr>
<th>Age</th>
<th>Sens.</th>
<th>Specif.</th>
<th>Accuracy</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>60-69</td>
<td>95</td>
<td>88</td>
<td>92</td>
<td>89</td>
<td>95</td>
</tr>
<tr>
<td>70-79</td>
<td>95</td>
<td>68</td>
<td>84</td>
<td>75</td>
<td>93</td>
</tr>
<tr>
<td>80+</td>
<td>95</td>
<td>49</td>
<td>78</td>
<td>65</td>
<td>91</td>
</tr>
</tbody>
</table>

HC PiB+: 11% in 60’s, 32% in 70’s, 51% in 80’s  
(e4 prevalence corrected)
Aβ burden vs cognition

Neocortical SUVR

HC

MCI

AD

MMSE

Episodic Memory

$r = -0.53$ (p < 0.0001)

$r = -0.27$ (p = 0.009)

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

Females

HC

Males

Episodic Memory

PiB- PiB+ PiB- PiB+

Females

HC

Males

Episodic Memory

PiB- PiB+ PiB- PiB+

Female but not male PiB+ HC have lower memory scores

Male AD have higher PiB

AD

PiB SUVR

Females

Males

Male AD have higher PiB
Aβ burden vs hippocampal volume

HC

MCI

AD

$r = -0.16 (p = 0.04)$

$r = -0.36 (p = 0.004)$
Follow-up Data
3 year PiB PET

- **AD+ (n=15)**: 0.05 SUVR/yr
- **MCI+ (n=15)**: 0.045 SUVR/yr
- **HC+ (n=21)**
- **MCI- (n=10)**: 0.01 SUVR/yr
- **HC- (n=52)**
Note: Atrophy correction did not change shape of graphs

MCI+

- 20m follow-up (n=23)
- 38m follow-up (n=15)

AD+

- 20m follow-up (n=23)
- 38m follow-up (n=15)
5-year follow-up

- **HC+** (n=5): +6.7% 
- **HC-** (n=17): +0.0% 
- **AD+** (n=3): +0.4%

Neocortical SUVR vs. Time (months)
AD with lower MMSE have slower PiB rise
(n=40)

$r = 0.42 \ (p = 0.008)$
Average rate of atrophy over one year in HC PiB- vs PiB+. 
Change in memory vs Baseline PiB: Decline $>0.5$ SD in HC with a 3 year follow-up ($n=80$)
Relation between baseline Aβ 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

**HC ε4+**
(n=20)

**HC ε4-**
(n=50)

Rate of change in episodic memory vs. Rate of Aβ deposition

*Effect of ApoE status*
Relation between rate of Aβ deposition and rate of memory decline

3-5 year follow-up

Relation between rate of Aβ deposition and rate of memory decline

MCI ε4+
(n=11)

MCI ε4-
(n=12)

Rate of change in episodic memory

stable Aβ burden

increase Aβ burden

Rate of Aβ deposition

R² = 0.74 (p = 0.04)

R² = 0.40 (p = 0.28)

effect of ApoE status
Prediction of Progression: HC to MCI/AD

20 months
n=195

PiB-ve Subjects: 135
Converters to MCI/AD 3 (2%)

PiB+ve Subjects: 60
Converters to MCI/AD 6 (10%)

36 months
n=178

PiB-ve Subjects: 124
Converters to MCI/AD 8 (6%)

PiB+ve Subjects: 54
Converters to MCI/AD 9 (17%)
## Prediction of Progression: HC to MCI/AD

### 20 months

<table>
<thead>
<tr>
<th>Condition</th>
<th>Accuracy</th>
<th>NPV</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neocortical PiB+ve (SUVR &gt;1.5)</td>
<td>0.54</td>
<td>0.98 (CI 0.93-0.99)</td>
<td>4.9</td>
</tr>
</tbody>
</table>

### 36 months

<table>
<thead>
<tr>
<th>Condition</th>
<th>Accuracy</th>
<th>NPV</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neocortical PiB+ve (SUVR &gt;1.5)</td>
<td>0.56</td>
<td>0.94 (CI 0.87-0.97)</td>
<td>3.0</td>
</tr>
</tbody>
</table>
Prediction of Progression: MCI to Dementia

<table>
<thead>
<tr>
<th></th>
<th>20 Months</th>
<th></th>
<th>36 Months</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>n=92</td>
<td></td>
<td>n=72</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PiB -ve:</strong></td>
<td>29</td>
<td></td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Converters to AD</td>
<td>2 (7%)</td>
<td>Converters to AD</td>
<td>3 (16%)</td>
<td></td>
</tr>
<tr>
<td>DLB</td>
<td>1 (3%)</td>
<td>DLB</td>
<td>1 (5%)</td>
<td></td>
</tr>
<tr>
<td>FTD</td>
<td>2 (7%)</td>
<td>FTD</td>
<td>2 (10%)</td>
<td></td>
</tr>
<tr>
<td>VaD</td>
<td>1 (3%)</td>
<td>VaD</td>
<td>1 (5%)</td>
<td></td>
</tr>
<tr>
<td><strong>PiB +ve:</strong></td>
<td>63</td>
<td></td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>Converters to AD</td>
<td>32 (51%)</td>
<td>Converters to AD</td>
<td>39 (74%)</td>
<td></td>
</tr>
</tbody>
</table>
Prediction of Progression: MCI to Dementia  
(at 36 months follow-up)

<table>
<thead>
<tr>
<th></th>
<th>ACCURACY</th>
<th>Odds Ratio</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>PiB+ve (SUVR &gt;1.5)</td>
<td>0.79</td>
<td>15</td>
<td>0.83 (CI 0.58-0.96)</td>
</tr>
<tr>
<td>ApoE ε4+</td>
<td>0.78</td>
<td>11</td>
<td>0.77 (CI 0.50-0.92)</td>
</tr>
<tr>
<td>Composite Memory (&lt;2.0)</td>
<td>0.68</td>
<td>5</td>
<td>0.64 (CI 0.36-0.86)</td>
</tr>
<tr>
<td>Hippocampal atrophy (&lt;0.0021)</td>
<td>0.60</td>
<td>2</td>
<td>0.57 (CI 0.34-0.77)</td>
</tr>
<tr>
<td>PiB + Hipp Vol (n=30, ++ vs --)</td>
<td>0.86</td>
<td>&gt;20</td>
<td>1.00 (CI 0.52-1.00)</td>
</tr>
</tbody>
</table>
Summary
AIBL+ Findings

- Aβ deposition is slow and of similar rate in PiB+ HC and MCI (2% 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)
• Aβ in HC is associated with faster cognitive decline and grey matter atrophy.

• 17% of PiB+ HC develop MCI/AD (c.f. 6% of PiB-)

• 74% PiB+ MCI develop AD c.f. 16% of PiB-
  Odds Ratio = 12 (but 20% PiB- develop other dementias)

• Combination of biomarkers provides better prediction (e.g. if PiB+ and hippocampal atrophy = 86% accuracy)