The Australian Imaging Biomarkers and Lifestyle (AIBL) study of Ageing: what has been achieved in 5 years of collaboration?

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What is the AIBL study?

Australian Imaging Biomarkers and Lifestyle study of ageing

Launched in November 2006, largest study of its kind in Australia

Initial cohort of 1112 participants (minimum age 60 years)
- 211 Patients with Alzheimer’s disease (AD), 133 with Mild Cognitive Impairment (MCI) and 768 healthy volunteers

2 site study – 40% Perth and 60% Melbourne

Coordinator Kathryn Ellis
Study is conducted between Perth (40%) and Melbourne (60%)

- CSIRO P-Health*
- University of Melbourne*
- Neurosciences Australia Ltd (NSA)*
- Edith Cowan University (ECU)*
- Mental Health Research Institute (MHRI)*
- National Ageing Research Institute (NARI)
- Austin Health
- University of WA (UWA)
- CogState Ltd.
- Charles Gairdner Hospital radiology and nuclear medicine
- Alzheimer’s Australia
- Macquarie University

*denotes signatories to the AIBL study contract

![logos of AIBL collaborators]
Study aims

1. To improve the understanding of the pathogenesis and diagnosis of Alzheimer’s disease using neuropsychological, neuroimaging and biomarker techniques, with a focus on early diagnosis of AD

2. To examine lifestyle and diet factors that may be involved in the pathogenesis of AD, towards future lifestyle intervention

Update on imaging, biomarkers, diet and lifestyle, cognitive and other results to date
Progress

AIBL 1 – initial phase of the study
• Recruit cohort of 1000+ people (1112 by August 2008)
• Conduct thorough assessment at baseline
• Repeat assessment at 18-months

18-month assessments completed in mid-2010
Commitment from the AIBL partners and CSIRO SIEF fund to continue the study for at least 2 more timepoints (36-months and 54-months) while replenishing cohort (AIBL expansion)
3 year assessments will end by 31st July 2011
Money to enable additional imaging
AIBL active intervention study
Cohort at baseline

At Presentation/Pre-assessment

- 823 Healthy controls
- 150 MCI
- 193 AD

54 Excluded/withdrawn

Baseline Cohort (1112 participants)

- 768 Healthy controls
- 133 MCI
- 211 AD

Cohort sub-groups

- 49 Amnestic-single domain
- 77 Amnestic-multi domain
- 1 Non-amnestic-single domain
- 6 Non-amnestic-multi domain

- 372 Non Memory Complainers
- 395 Memory Complainers
- 31 NINCDS-ADRDA Possible AD
- 180 NINCDS-ADRDA Probable AD
Cohort after 18-months

Approximately 25% of MCI cases met AD criteria following 18 months.
Nearly 1/3 of NMC were SMC at 18-months.
Imaging results

- Imaging collaboration led by Chris Rowe and Victor Villemagne at Austin Health and by Nat Lenzo, Roger Price and Peter Robins in WA with strong input from CSIRO via Olivier Salvado et al.
## Imaging Cohort Baseline demographics (n=288)

<table>
<thead>
<tr>
<th></th>
<th>HC*</th>
<th>MCI</th>
<th>AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>73.6 ± 7.6</td>
<td>77.4 ± 7.5*</td>
<td>74.0 ± 8.7</td>
</tr>
<tr>
<td>MMSE</td>
<td>28.8 ± 1.2</td>
<td>27.1 ± 2.3*</td>
<td>20.5 ± 4.9*</td>
</tr>
<tr>
<td>%ApoE ε4</td>
<td>43%</td>
<td>54%</td>
<td>71%*</td>
</tr>
</tbody>
</table>

*enriched with ApoE ε4

*Significantly different from HC, p < 0.05
$^{11}$C-PIB – Image Quantification

Regions

Neocortical 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.
Baseline Imaging Findings
Aβ burden by clinical classification

Neocortical SUVR

<table>
<thead>
<tr>
<th>Group</th>
<th>SUVR ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>HC</td>
<td>1.42 ± 0.41</td>
</tr>
<tr>
<td>MCI</td>
<td>1.89 ± 0.62</td>
</tr>
<tr>
<td>AD</td>
<td>2.33 ± 0.43</td>
</tr>
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</table>

*Significantly different from HC, p <0.05
†Significantly different from AD, p <0.05
Influence of ApoE ε4 status on PiB+ in HC

ApoE ε4-ve
- 79% PiB-ve
- 21% PiB+ve

ApoE ε4+ve
- 51% PiB-ve
- 49% PiB+ve
Age effect on AD, Plaques and PiB+

Prevalence of AD (Tobias, 2008) ~15 yrs Prevalence of PiB+ve PET in HC

Prevalence of plaques in HC
(Davies, 1988, n=110) (Braak, 1996, n=551) (Sugihara, 1995, n=123)

~15 yrs Prevalence of AD (Tobias, 2008)
Follow-up Data
PiB Change (AIBL Plus)

HC
(n=104 @ 18 mth, 60 @ 3 yr)

PiB+ 2.0%  5.5%
(18 mths) (3 yrs)

MCI
(n=48)

2.2%  4.1%

AD
(n=33)

5.7%  0.9%

Neocortical SUVR

Months

*
Average rate of atrophy over one year in HC PiB- vs PiB+. 
Follow-up PiB vs follow-up cognition by baseline diagnosis

Now we find correlation in HC and stronger in MCI!
Change in memory vs Baseline PiB: Decline >0.5 SD in HC with a 3 year follow-up (n=60)

* Significantly different from HC-, p <0.05
Change in PiB vs Change in memory
3-5 year follow-up

- HC (n=43)
- MCI (n=16)
- AD (n=11)

Change in Episodic Memory

- HC (PiB-)
- HC (PiB+)
- MCI (PiB+)
- MCI (PiB-)
- AD
## AIBL Plus

### Prediction of Conversion

(at 3 years follow-up)

<table>
<thead>
<tr>
<th></th>
<th>HC</th>
<th>MCI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=106)</td>
<td>(n=65)</td>
</tr>
<tr>
<td>PiB-veSubjects:</td>
<td>74</td>
<td>20</td>
</tr>
<tr>
<td>Converters to naMCI:</td>
<td>2 (3%)</td>
<td>Converters to AD:</td>
</tr>
<tr>
<td>Converters to MCI/AD:</td>
<td>8 (25%)</td>
<td>Converters to AD:</td>
</tr>
<tr>
<td>PiB+veSubjects:</td>
<td>32</td>
<td>Converters to D LB:</td>
</tr>
<tr>
<td>Converters to FTD:</td>
<td></td>
<td>Converters to FTD:</td>
</tr>
<tr>
<td>Converters to VaD:</td>
<td></td>
<td>Converters to VaD:</td>
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### AIBL Plus

**Prediction of Conversion MCI to AD**

**38 months**

*(n=65)*

<table>
<thead>
<tr>
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<th>Accuracy</th>
<th>NPV (CI)</th>
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<tbody>
<tr>
<td>Neocortical PiB+ve (SUVR &gt;1.5)</td>
<td>0.83</td>
<td>0.95 (CI 0.73-1.00)</td>
</tr>
<tr>
<td>ApoE ε4+</td>
<td>0.77</td>
<td>0.83 (CI 0.60-0.94)</td>
</tr>
<tr>
<td>Composite Memory (&lt;-2.0 sd)</td>
<td>0.77</td>
<td>0.79 (CI 0.59-0.91)</td>
</tr>
<tr>
<td>Hippocampal atrophy (&lt;0.76)</td>
<td>0.74</td>
<td>0.79 (CI 0.54-0.93)</td>
</tr>
<tr>
<td>Plasma Aβ_{42}/Aβ_{40} (&lt;0.17)</td>
<td>0.57</td>
<td>0.69 (CI 0.39-0.90)</td>
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</tbody>
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Summary
• Aβ deposition is slow and of similar rate in PiB+ HC and MCI (2% SUVR per year).

• A plateau in AD has not been confirmed nor denied.

• Aβ has a dose dependent role early in the development of cognitive decline and brain atrophy.

• At later stages the correlation is lost.
Over Three Years

- 25% of PiB+ HC develop MCI/AD (c.f. 3% of PiB-)

- 71% PiB+ MCI develop AD (c.f. 5% of PiB- but 20% of these develop other dementias)

- Combination of biomarkers provides better prediction (e.g. if PiB+ and hippocampal atrophy is present the 2 year progression from MCI to AD is 95%)
• Biomarkers results
- Perth, Melbourne and Brisbane teams working together on a “panel” of biomarkers

- 151 protein analyte levels were measured

- A group of less than 10 classify AD with 80% sensitivity and specificity and approximately 90% accuracy

- Currently subject of a patent application
• Diet and lifestyle
• AIBL sub-set - n=227 (healthy controls only)
• Worn for seven consecutive days on front of hip
• Output includes
  – Total counts (average activity over 7 days)
  – Peak counts (average highest intensity reached over 7 days)
Both total physical activity and higher intensity physical activity is associated with:

- Lower insulin (Regensteiner, 1991)
- Lower triglycerides (Lehtonen, 2009)
- Higher levels of HDL (Lehtonen, 2009)

Higher levels of intense physical activity is associated with better performance in assessments targeting:

- Working memory
- Attention
- Verbal & Spatial Learning and Recall
- Executive Functioning
• Establishment of Australian norms of a wide range of neuropsychological tests on 768 healthy elderly people
• Paper by Koftopoulos et al. now in preparation.
672 HC and 64 MCI completed a subjective memory questionnaire at 18 month follow up.

MMSE, CVLT, RCFT, BNT, GDS, HADS, group membership and APOE ε4 status were used to determine predictors of SMC scores.

Group membership explained 20% of variance. Adding affective measures explained 27%. Only group membership and HADS were significant individual predictors.

SMCs reflect mood rather than objectively measured cognitive performance.

Predictors of rapid decline in AD

• Alessandro Sona, Ping Zhang et al. (submitted to Int Psychogeriatrics)
• 211 AD at baseline – 156 followed at 18 months
• 33% (51) rapid decliners (lost 6+ MMSE points in 18 months)
• Higher CDR and CDR box score plus baseline prescription of a Chel predicted faster decline (OR 3.4 univariate)
Other results

- Data on diet and affective symptoms (GDS and HADS) now in preparation (Berk et al.)
- Relationship between GDS and HADS scores under investigation by C. Bryant et al.
- Anticholinergic drug consumption linked to subtle cognitive difficulty in HCs (paper in press)
Achievements

AIBL has provided significant knowledge in the imaging area

- $A\beta$ plaque build up is very slow – 1-2% per year
- $A\beta$ plaque formation occurs before brain atrophy.
- The prevalence of a positive PiB amyloid PET scan parallels the prevalence of Alzheimer’s disease (AD) 15 years later
- A positive PiB scan is the strongest predictive test for AD in persons with mild memory impairment
- Has this brought forward the detection of AD by at least 18 months?
Achievements

- 17 peer reviewed papers published to date
- 4 papers under review at peer reviewed journals
• A highly motivated and well-characterized cohort who represent a unique resource for the study of AD in Australia

• Cross-sectional analysis of the AIBL dataset have already demonstrated links between cognition, brain beta-amyloid burden and blood biomarkers

• 36-month follow-up data is underway (due for completion late 2011)

• Follow-up of this cohort will allow the significance of candidate risk factors associated with cognitive decline and early diagnostic indicators of AD to be examined.
Continuation, add-on and complimentary studies

36 month follow ups commenced and will continue at 54 months too while allowing replenishment of cohort

ADNI data uploads

Cerebro-spinal fluid

Australian Brain Bank Network

New Study: AIBL Rate of Change Substudy

3 NHMRC grants for 2011 (blood work, imaging and intervention)

Initial carer strain study now completed

AIBL active about to commence
Financial Supporters

- CSIRO (AUS)
- National Health and Medical Research Council (NHMRC) (AUS)
- Alzheimer’s Association (USA)
- Alzheimer’s Drug Discovery Foundation (USA)
- An Anonymous Foundation (USA)
- Pfizer
- GE Healthcare
- Astra Zeneca
The AIBL management team

* AIBL management committee

  Prof. David Ames
  Prof. Richard Head
  Dr. Kathryn Ellis
  Dr. Lance Macauley
  Prof. Ralph Martins
  Prof. Colin Masters
  Dr. Andrew Milner
  Dr. Tim O’Meara
  Dr. Stephanie Rainey-Smith
  Prof. Christopher Rowe
  Dr. Cassandra Szoeke
  Dr. Kevin Taddei

* The AIBL study team comprises 80+ scientists (see www.aibl.csiro.au)
AIBL study team

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