Examining Early Diagnostic and Lifestyle Intervention Strategies for Alzheimer’s disease

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www.aibl.csiro.au
What is the AIBL study?

- Large scale cohort study launched in September 2006
- 3 year prospective longitudinal study of Alzheimer's disease
- 1000+ participants (minimum age 60 years)
- Patients with AD, MCI and healthy volunteers
- Multi-disciplinary approach, 4 research streams – cognitive, imaging, biomarkers and lifestyle
- Focus on early detection, towards lifestyle interventions
AIBL is a collaborative venture

- CSIRO P-Health initiative, bringing together a “cluster” of Australian researchers and research organisations

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

*denotes signatories to the AIBL study contract

- Multidisciplinary, collaborative, brings together researchers in Perth, Adelaide, Melbourne, Canberra and Brisbane (40% subjects from WA, 60% from Vic)
Basis of AIBL

• Treatment strategies are likely to be most effective if administered early

• Development of lifestyle interventions to prevent or delay AD onset would have significant effects at the population level

• Currently no certain method of detecting whether a person is likely to develop AD.
  – *Mild cognitive impairment (MCI)*: 30 – 60% develop AD

• For treatment to be most effective we must be able to identify who is at risk of developing AD years before symptoms develop – this is what AIBL seeks to do
### 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
Volunteers

• We sought to recruit 1000+ individuals
  – At least 200 individuals with AD (McKhann et al., 1984)
  – At least 100 individuals with Mild Cognitive Impairment (MCI) (Petersen et al., 1999; Winblad et al., 2004).
  – At least 700 healthy individuals without cognitive impairment. This group included:
    • Volunteers with at least one copy of the ApoE ε4 allele,
    • Volunteers without a copy of the ApoE ε4 allele,
    • Volunteers who expressed subjective concern about their memory function
Blood taking procedure

- Fasting samples are taken and participants receive breakfast following collection

- Approx 80 ml blood is collected in 12 tubes
Clinical Pathology

ESR and FBE
Homocysteine
Serum and red cell folate
B12
Glucose
Ceruloplasmin
Ferritin/Transferrin/Iron
Insulin
Oestradiol
LH
Thyroid (TSH, FT4, FT3)
PSA (MALES ONLY)
Neuropsychology

- **Memory/learning:** California Verbal Learning Task (CVLT-II) Logical memory II (WAIS)
- **Language:** Controlled Oral Word Association (COWAT) Boston Naming Test (BNT)
- **Working memory:** Digit span task
- **Attention:** Digit Symbol (WAIS III)
- **Executive function:** Stroop
- **Spatial:** Complex figure of Rey
- **CogState battery:** [www.cogstate.com](http://www.cogstate.com)
Other clinical measures

- Hospital Anxiety and Depression Scale (HADS)
- Geriatric depression scale (GDS), 15 item version
- Clinical dementia rating (CDR)
- Wechsler Test of Adult Reading (WTAR)
- Mini-Mental State Examination (MMSE)
- Informant Questionnaire of CognitiveDecline in the Elderly (IQCode)

SUMMARY
- Comprehensive assessment, takes 2 hours
- Neuropsychologists suspend cognitive testing is participant/patient is overwhelmed (although this is rare)
- Clinical review panel meets monthly to review diagnostic classification of all AD and MCI cases and all healthy controls with any results of interest or concern
Aβ Neuroimaging

- The structure of this protein was first described by a team co-led by Professor Colin Masters (1985)

- Aβ can now be imaged in the living brain by PiB PET

- 25% of volunteers to receive PET Pittsburgh Compound B (PiB) scans
Lifestyle assessment

**Full cohort**
- Food Frequency Questionnaire (FFQ)
- Physical Activity Questionnaire (IPAQ)

**Sub-group**
- Actigraph Uni-axial Accelerometer
  - Small devices (size of matchbox), 7 days per volunteer
- Dual Energy X-Ray Absorptiometry (DEXA)
  - “Gold standard” body composition assessment, low dose radioactivity scan
Current status of study

TIMELINE

BASELINE
Clinical/cognitive data
80ml blood
Lifestyle information
PET & MRI scans

FIRST FOLLOW UP (18mth)
Clinical/cognitive data
80ml blood
Lifestyle information
PET & MRI scans
Cohort at baseline

At Presentation/Pre-assessment

- **823 Healthy controls**
  - 745
  - 46
  - 7
- **150 MCI**
  - 20
  - 79
  - 33
- **193 AD**
  - 3
  - 8
  - 171

Excluded/withdrawn: 54

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**

Memory Complainers:
- **372 Non Memory Complainers**
- **395 Memory Complainers**

Probable AD:
- **31 NINCDS-ADRDA Possible AD**
- **180 NINCDS-ADRDA Probable AD**
Cohort characteristics

<table>
<thead>
<tr>
<th></th>
<th>HC</th>
<th>MCI</th>
<th>AD</th>
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<tbody>
<tr>
<td>N</td>
<td>768</td>
<td>133</td>
<td>211</td>
</tr>
<tr>
<td>Age</td>
<td>70.5 (7.0)</td>
<td>76.2 (7.6)</td>
<td>78.5 (8.6)</td>
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<tr>
<td>MMSE</td>
<td>28.9</td>
<td>26.2</td>
<td>19.1</td>
</tr>
<tr>
<td>CDR</td>
<td>0.0</td>
<td>0.5</td>
<td>0.9</td>
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<tr>
<td>ApoEε4 carriers (%)</td>
<td>26.8</td>
<td>47.5</td>
<td>64.4</td>
</tr>
<tr>
<td>Sex (%m/ f)</td>
<td>43 / 57</td>
<td>44 / 56</td>
<td>39 / 61</td>
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</table>
Memory measures

Fig 1: CVLT II learning

CVLT-II learning T-scores

- HC
- MCI
- AD

Fig 2: CVLT II recall

CVLT-II recall following short (left) and long (right) delay, displayed as Z scores
Other cognitive tasks

**WAIS-III Digit Span and Digit Span Coding Age Scaled Scores**

**Verbal Fluency**

**Letter and Category Fluency Age Scaled Scores**
• Participants (n=287)
  • 177 Healthy elderly controls (HC)
    81 Non-memory complainers (49% ApoE ε4+ve)
    96 Memory complainer (40% ApoE ε4+ve)
  • 57 MCI participants
  • 53 AD participants

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<th>AD</th>
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<tr>
<td>Age</td>
<td>73.6 ± 7.6</td>
<td>77.4 ± 7.5</td>
<td>74.0 ± 8.7</td>
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<tr>
<td>MMSE</td>
<td>28.8 ± 1.2</td>
<td>27.1 ± 2.3</td>
<td>20.5 ± 4.9</td>
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<td>Sex (M/F)</td>
<td>87/90</td>
<td>29/29</td>
<td>24/30</td>
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<tr>
<td>% ApoE ε4</td>
<td>43%</td>
<td>52%</td>
<td>74%</td>
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Representative images

**SUVR**

**AD**

**HC**
In the HC subgroup, 49% of HC ApoE ε4+ were PIB+ve, compared to 21% of the HC ApoE ε4-ve group.
Predicting conversion (pre-AIBL data)

Healthy volunteers

- 23 PiB -ve subjects scanned, only 1 converted to MCI (4%)
- 10 PiB +ve subjects scanned, 3 converted to MCI/AD (30%)

MCI patients

- 14 PiB-ve subjects scanned, 5 converted to dementia (36%)
- 15 PiB+ve subjects scanned, 12 converted to AD (80%)

Rowe & Villemagne 2009
Exercise and Blood plasma Aβ

• 553 Healthy Volunteers (57% female, mean age 70 ± 8.5) completed the IPAQ (International Physical Activity Scale)

• IPAQ scores were correlated with plasma Aβ levels (ratio Aβ42/ Aβ40)

Brown et al. 2009
MEASURE OF FOOD INTAKE
- Cancer Council of Victoria Food frequency questionnaire (CCVFFQ)
  - Total consumption of foods and nutrients
  - Consumption of fish (Omega 3, DHA)

CLINICAL/NEUROPSYCHOLOGICAL MEASURES
- Mini-mental state exam (MMSE)
  - The most widely used brief measure of cognitive function.
- CVLT II
  - Primary memory measure
  - Consists 16 word list (read 5 times)
  - Measures learning, short recall and long recall

ANALYSIS
- Healthy controls (639 volunteers)
- Partial correlations were performed between nutritional & cognitive variables
Greater fish consumption was associated with higher cognition in healthy controls

<table>
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<tr>
<th>NEUROPSYCHOLOGICAL MEASURE (RAW)</th>
<th>Total Fish</th>
<th>Total Omega 3</th>
<th>Omega 3/6 ratio</th>
<th>DHA</th>
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<tbody>
<tr>
<td>MMSE</td>
<td>P=0.012*</td>
<td>0.013*</td>
<td>0.047*</td>
<td>0.013*</td>
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<tr>
<td>Learning (T score)</td>
<td>0.001**</td>
<td>0.000**</td>
<td>0.046*</td>
<td>0.000**</td>
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<tr>
<td>Short term recall/ Retention</td>
<td>0.031*</td>
<td>0.035*</td>
<td>0.070</td>
<td>0.033*</td>
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<td>Delayed recall</td>
<td>0.009**</td>
<td>0.010**</td>
<td>0.076</td>
<td>0.010**</td>
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<tr>
<td>Recognition</td>
<td>0.030*</td>
<td>0.046*</td>
<td>0.016*</td>
<td>0.050*</td>
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*Correlation is significant at the 0.05 level (2-tailed); **Correlation is significant at the 0.01 level (2-tailed).
n=639 Healthy controls (memory complainers + non-memory complainers). Omega 3 = ALA + DHA + EPA. Controlled for sex, years of education, genotype, BMI and age.

Follow-up (18mth): Progress to date

- 50% of follow-ups completed. On track for full completion by December 2009

- Follow-up classifications for 432 people have been confirmed

<table>
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<tr>
<th>Baseline classification</th>
<th>Number retested</th>
<th>Unchanged from baseline</th>
<th>Reclassified HC</th>
<th>Reclassified MCI</th>
<th>Reclassified AD</th>
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<tr>
<td>HC</td>
<td>387</td>
<td>377</td>
<td>N/A</td>
<td>8</td>
<td>2</td>
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<tr>
<td>MCI</td>
<td>28</td>
<td>22</td>
<td>2</td>
<td>N/A</td>
<td>4</td>
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<tr>
<td>AD</td>
<td>17</td>
<td>17</td>
<td>0</td>
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Summary

• The baseline characteristics demonstrate a highly motivated, well balanced cohort.

• Neuropsychological findings reveal HC>MCI>AD on performance, as expected

• Brain imaging:
  — AD showed marked cortical and striatal PiB retention with relative sparing of occipital and sensorimotor cortex.
  — 67% of MCI participants showed significant cortical PiB retention, similar to AD.
  — 36% of HC volunteers showed significant cortical PiB retention, though lower than in AD.
  — Greater PiB burden in ApoE ε4+ volunteers than ApoE ε4- volunteers
• Levels of exercise correlate with blood amyloid levels

• Higher intake of fish is correlated with better cognition

• First follow-up is 50% complete

• These data will assist development of techniques for early detection of AD and provide a cohort suitable for targeted early intervention studies
Acknowledgements and thanks

• The AIBL volunteers and their families

• The staff of our collaborating organisations

- Austin Hospital, Melbourne
- WA PET Centre, Perth
- Sir Charles Gairdner Hospital, Perth
- Edith Cowan University
- CSIRO ICT Centre, Brisbane
- University of Melbourne
- Mental Health Research Institute
- Neurosciences Australia Ltd
- National Ageing Research Institute
- University of WA (UWA)
- CogState Ltd.
Management committee

Prof. David Ames (NARI)
Mr. Lindsay Bevege (NSV)
Dr. Kathryn Ellis (Uni of Melb.)
Prof. Peter Hudson (NSV)
Prof. Ralph Martins (ECU)
Prof. Colin Masters (MHRI)
Dr. Andrew Milner (NSV)
Prof. Chris Rowe (ARMC)
Dr. Cassandra Szoeke (CSIRO)
AIBL study team

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<td>Jane Khoo</td>
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