Addressing population aging and Alzheimer’s disease through the Australian Imaging Biomarkers and Lifestyle study: Collaboration with the Alzheimer’s Disease Neuroimaging Initiative

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Abstract
The Australian Imaging Biomarkers and Lifestyle (AIBL) study is a longitudinal study of 1112 volunteers from healthy, mild cognitive impairment, and Alzheimer’s disease (AD) populations who can be assessed and followed up for prospective research into aging and AD. AIBL aims to improve understanding of the pathogenesis, early clinical manifestation, and diagnosis of AD, and identify diet and lifestyle factors that influence the development of AD. For AIBL, the magnetic resonance imaging parameters of Alzheimer’s Disease Neuroimaging Initiative (ADNI) were adopted and the Pittsburgh compound B (\textsuperscript{11}C-PiB) positron emission tomography (PET) acquisition and neuropsychological tests were designed to permit comparison and pooling with ADNI data. Differences to ADNI include assessment every 18-months, imaging in 25\% (magnetic resonance imaging, \textsuperscript{11}C-PiB PET but no fluorodeoxyglucose PET), more comprehensive neuropsychological testing, and detailed collection of diet and lifestyle data. AIBL has completed the first 18-month follow-up and is making imaging and clinical data available through the ADNI website. Cross-sectional analysis of baseline data is revealing links between cognition, brain amyloid burden, structural brain changes, biomarkers, and lifestyle.

Keywords: Alzheimer’s disease; Mild cognitive impairment; Amyloid imaging; Positron emission tomography; Magnetic resonance imaging

1. Introduction
Consistent with the worldwide increase in life expectancy, the Australian population is aging. In Australia, the number of people affected by dementia is expected to triple from the current 257,300 (1\% population) in 2010 to 1,130,700 (2.8\% of the projected total population) by 2050 [1]. Alzheimer’s disease (AD), the most common cause of dementia, currently costs the Australian health system $A3.2 billion a year in direct costs, and this is expected to be $A6 billion within 5 years. If interventions were able to delay the onset of the disease by even 5 months, there would be a 5\% reduction in the cost of AD to the Australian economy; if we could delay onset by 5 years, we would halve the costs [2].

In late 2005, Australia’s national science agency, the Commonwealth Science and Industrial Research Organization, identified the need to address this issue, and to this...
end formed a partnership with several leading Australian researchers and research institutes and universities. This partnership resulted in the Australian Imaging Biomarkers and Lifestyle (AIBL) Flagship Study of aging, which assembled a large cohort of individuals from healthy, mild cognitive impairment (MCI), and AD populations who can be assessed, compared, and then followed up over a long period to facilitate prospective research into aging and AD [3]. In this article, we overview the AIBL study and its collaboration with the Alzheimer’s Disease Neuroimaging Initiative (ADNI) worldwide effort.

2. Structure and design of the study

The primary aims that influenced the design of the study were to develop tests for earlier diagnosis of AD, to identify diet and lifestyle factors that may influence the development of AD for testing in future clinical trials, and to increase understanding of the processes that lead to the development of AD. In designing AIBL, the magnetic resonance imaging (MRI) parameters of ADNI were adopted and the Pittsburgh compound B (11C-PiB) positron emission tomography (PET) acquisition protocol and neuropsychological test battery were designed to permit comparison and pooling of data. However, distinct differences to ADNI were: imaging was funded for 25% of the cohort, and this was to take place every 18 months; the neuropsychological test battery was more comprehensive; and there was detailed collection of diet and lifestyle data. A particular strength of AIBL is that blood collection and fractionation was restricted to only two sites to ensure preparation of high quality blood samples, which are sustained by storage in liquid nitrogen.

Overseeing the study is a management committee (Fig. 1), led by Professor David Ames. The structural organization of AIBL is comparable with other ADNI programs, and comprises four streams of research (clinical and cognitive, biomarkers, lifestyle, and neuroimaging), which are each directed by a stream chair and stream leadership group. Fig 2 overviews the four streams of research that make up the AIBL program.

In contrast to the many sites that make up US-ADNI, AIBL participants have been enrolled at one of five sites in the Australian cities of Perth and Melbourne, and imaging was performed at only one site in each city. This helps to contain costs and makes management easier.

The AIBL cohort was recruited between late 2006 and mid 2008. These participants are being followed up at 18-month intervals with the AIBL study battery [3]. We sought to recruit and characterize 1000 individuals as part of this cohort, at least 200 of whom would have a current diagnosis of AD, and at least 100 of whom would have MCI. We purposefully selected a large group of apparently healthy participants, including those who carry the apolipoprotein E e4 (APOE e4) allele, which is a risk factor for AD [4,5]. We further considered it was important to dichotomize apparently healthy individuals on the basis of whether they expressed subjective concern about their memory function, as there is disagreement in the published data as to whether such subjective memory complaints (SMC) are, or are not, predictive of future cognitive decline [6].

As reported in detail previously [3], the inception cohort comprised 1112 participants (211 with AD, 133 with MCI, and 768 healthy participants). Fig. 3 overviews the cohort. At baseline, these participants underwent a screening interview, had comprehensive cognitive testing, gave 80 mL of blood for biomarkers analysis, and completed health and lifestyle questionnaires. Approximately one quarter of the sample (287 participants) underwent amyloid PET brain imaging with 11C-PiB PET and MRI brain imaging, and a separate subgroup of 10% had ActiGraph activity monitoring and body composition scanning. The first 18-month follow-up of the AIBL cohort was completed in February 2010, and the 3-year assessments have now commenced. Subject retention at 18 months was 92%, with the largest rate of drop out in the AD group. The AD group was recruited to permit baseline comparison with healthy and MCI participants, whereas the greatest interest in these latter two groups lies in establishing predictors of their long-term cognitive outcomes.

3. The AIBL neuroimaging stream

Neuroimaging was performed in 26% of the cohort (177 healthy controls [HCs], 57 MCI, and 53 mild AD). Selection of MCI and AD for imaging was on a first come basis. In contrast, HC selection was controlled to ensure that: (1) there was a wide age spread from 60 years through to the very elderly,
(2) approximately 50% had SMC, and that (3) approximately 50% were APOE ε4 carriers. It should be noted that the HC in the imaging arm of AIBL are not representative of the general population, due to preferential inclusion of APOE ε4 allele carriers, as required to examine the relationship between this risk factor gene and beta-amyloid (Aβ) deposition. Base-

Fig 2. Overview of key outcomes from AIBL research streams. MMSE, Mini-Mental State Examination; CDR, Clinical Dementia Rating; NINCDS-ADRDA criteria, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association criteria; ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th Revision; MCI, mild cognitive impairment; LN, liquid nitrogen; MP RAGE, magnetization-prepared 180 degrees radio-frequency pulses and rapid gradient-echo; FLAIR, fluid attenuation inversion recovery; WGAs, Whole Genome Association Study.

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Fig 3. AIBL cohort at baseline. This image is reproduced with permission of the Cambridge University Press from Ellis et al, 2009 [3].
allowing AIBL to be a substantial contributor to the World Wide ADNI research effort.

3.1. Neuroimaging methodology

AIBL images are comparable to other World Wide ADNI images. MRI images were acquired using the ADNI 3D magnetization-prepared rapid gradient echo sequence, with $1 \times 1$ mm in-plane resolution and 1.2 mm slice thickness, TR/TE/T1 = 2300/2.98/900, flip angle 9°, and field of view 240 × 256 and 160 slices. T2 fast spin echo and fluid attenuation inversion recovery sequences were also obtained.

PET with $^{11}$C-PiB using a Phillips Allegro PET camera was performed at both AIBL sites to quantify in vivo brain $\beta$. Participants received $\sim 370$ MBq $^{11}$C-PiB IV over 1 minute. A 30-minute acquisition in 3D mode (consisting of six frames each of 5 minutes) was performed starting 40 minutes after injection of PiB, following a transmission scan performed for attenuation correction purposes. PET images were reconstructed using a 3D RAMLA algorithm. PET data was corrected for partial volume effects using a three-compartment model as previously described [7]. The acquisition in 5-minute frames allows reconstruction of the 50–70-minute postinjection data to match the ADNI protocol.

3.2. Neuroimaging stream findings

The key aim of the neuroimaging stream of AIBL was to evaluate the degree and pattern of $^{11}$C-PiB retention in a well-characterized cohort of HC, MCI, and AD participants. We also aimed to correlate $\beta$ burden with clinical and cognitive measures, evaluate the relationship between $\beta$ burden and $APOE$ genetic status, establish the prevalence of $\beta$ deposition in asymptomatic HC and in HC with SMC, and examine the relationship of grey and white matter atrophy to $\beta$ deposition. Furthermore, we aim to exploit the prospective longitudinal design to evaluate the rate and pattern of $^{11}$C-PiB retention in a well-described [7]. The acquisition in 5-minute frames allows reconstruction of the 50–70-minute postinjection data to match the ADNI protocol.

A focus of our analyses has been to use advanced analysis techniques to tackle this dataset [7–9]. Similar to atrophy patterns, $^{11}$C-PiB retention patterns can be computed, allowing a quantitative estimation of $\beta$ amyloid deposition at the pixel or regional level. Recent improvement of those techniques has revealed differences between grey matter atrophy and $\beta$ amyloid deposition patterns [7]. Furthermore, both pixel-wise and regional correlation between PiB binding, atrophy, and other clinical measurements (e.g., cognitive scores) have generated new findings and therefore hypotheses. For example, we have shown that hippocampal atrophy is regionally correlated only to PiB retention in the inferior temporal lobe, and only at the earliest stages of the disease in healthy, asymptomatic individuals with high PiB signal [7,9]. Such results reveal a new theory that the increased accumulation of $\beta$ amyloid in the temporal inferior cortex disrupts connections with the hippocampus [7].

A key advantage of the imaging subgroup has been to have a “gold-standard” comparison (brain $\beta$ levels) from which to compare other putative biomarkers. This has been particularly beneficial to our biomarker stream, as discussed later in the text.

3.3. ADNI data sharing

A key aim of the ADNI is to make data available to researchers around the world. Through the support of the Alzheimer’s Association and ADNI statistics core personnel, the AIBL neuroimaging stream data (and accompanying clinical and cognitive data) are available through the ADNI data website (http://www.loni.ucla.edu/ADNI/) or through the AIBL website (www.aibl.csiro.au).

4. Biomarkers stream

There is strong interest in developing techniques for the diagnosis and monitoring the progress of AD through the use of blood biomarkers, as this is less invasive than cerebrospinal fluid collection and relatively low cost [10]. In line with other ADNI studies, AIBL collects fasting blood samples from all volunteers to examine a range of potential markers of disease. This has allowed the AIBL study to investigate many putative biomarkers in blood, including plasma $\beta$ levels. Blood plasma $\beta$ is an attractive biomarker because the most accepted theory of the cause of AD suggests that it results from excessive $\beta$ in the brain (which is caused by either increased production or impaired clearance of $\beta$ oligomers that then aggregate to form extracellular plaques and vascular wall deposits) [11].

Although there is now a large body of evidence to suggest that cerebrospinal fluid $\beta$ levels are altered in AD patients, compared with cognitively healthy individuals, the same is not the case for plasma $\beta$ levels. Numerous studies have investigated $\beta$ levels in plasma; however, a range of confounding factors have resulted in inconclusive findings [12,13]. Most studies have employed relatively small sample sizes. AIBL and other ADNI projects provide an opportunity to examine this in large and well-characterized cohorts. In addition, the design of AIBL allows for blood samples to be fractionated and stored within 2.5 hours (as collection occurs on site) ensuring sample integrity.

We have conducted a comprehensive study to determine the clinical value of plasma $\beta$ as an AD biomarker, comparing directly a sandwich enzyme-linked immunosorbent assay and the Innogenetics commercial kit [10]. Plasma $\beta$ levels were also compared, in a subset of participants, against $\beta$ load obtained through $^{11}$C-PiB neuroimaging. $\beta_{1–42}$ and $\beta_{1–42}$ were found to be significantly lower in AD patients and inversely correlated with $\beta$ load in the PiB-PET subset, but differences were small and there was large overlap between groups. Although further investigation is required, these findings suggest that plasma $\beta$ levels, measured under these conditions, are not sufficient per se to diagnose AD in individual cases [10], but may be a useful component for a biomarker panel.
Further hypothesis-driven research is occurring in our laboratories, investigating the blood levels of different metals, a proteomics approach to candidate analytes, and of both APOE genotype and ApoE levels, as well as sex hormones, on plasma Aβ levels and brain Aβ load with promising preliminary results.

The ability to compare the blood biomarker findings with other AIBL markers, in addition to the potential of pooling these findings with other ADNI studies, suggests the yield will be significant.

5. Why a lifestyle research stream?

AIBL differs from other ADNI programs by focusing a research stream on specifically understanding diet and exercise patterns in the AIBL cohort. The AIBL study was founded on the proposition that a lifestyle-related intervention would have significant effects at the population level on the development of AD.

Therefore, a key aim of the AIBL study is to better ascertain which health and lifestyle factors protect against or contribute to the development of AD. The extent to which these factors confer an increased or decreased risk requires further investigation to clarify how much variance in the incidence of AD can be attributed to genetic endowment and how much to other factors, and how different causative and protective factors interact. Importantly, identification of such factors might permit early treatment and modification of risk factors to delay or defer the onset of cognitive decline.

We have subsequently collected detailed information on the exercise levels of the cohort using the International Physical Activity Questionnaire [14]. In addition, a subgroup of the Perth cohort had their physical activity recorded for 7 days by a computerized ActiGraph monitor. This allows for comparability of the subjective and objective measures of physical activity, in addition to comparison of these outcomes with biomarker, cognitive, and imaging data collected as part of the study. In addition, all participants provided detailed information about their dietary intake through completion of the Food Frequency Questionnaire [15]. A subgroup of Perth participants received low dose radioactive scans to assess body composition (including fluid, bone, and adipose tissue). We have found that greater physical activity is associated with reduced cardiovascular risk factors such as plasma insulin, glucose, and total cholesterol, as well as a reduction in the blood levels of Aβ.

The wealth of data on physical and dietary aspects of the cohort examined in correlation with longitudinal biomarker, cognitive and imaging data, will allow prospective examination of diet and lifestyle factors on clinical progression.

6. The future of AIBL

The AIBL study has now completed its first 18-month follow-up and has commenced the 3-year reassessments. Baseline data from the study has generated five peer-reviewed papers to date [3,7–10], with six currently under review and more in preparation. The AIBL study has grown to include over 80 scientists from varying research and clinical disciplines, which resulted in 22 abstracts submitted to the 2010 International Conference of Alzheimer’s Disease.

In the short term, the aim of AIBL is to further explore the cross-sectional data of the baseline cohort. These cross-sectional analyses will continue to reveal links between cognition, brain Aβ burden, structural brain changes, biomarkers, and lifestyle. The first 18-month follow-up will be analyzed to reveal risk factors associated with cognitive decline and identify early diagnostic indicators of AD. However, the long-term goal of AIBL is to identify predictors of successful cognitive aging and incipient MCI and AD, and identify lifestyle factors, which may mediate pathological processes leading to AD.

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References


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