NEWSLETTER AIBL STUDY

August 2016

THE FLOREY INSTITUTE OF NEUROSCIENCEAND MENTAL HEALTH
EDITH COWAN UNIVERSITY
AUSTIN HEALTH

AIBL Study Update from Prof. David Ames

The AIBL study is now in its tenth year and 90 month follow ups have been completed. Over its course the study has made a huge contribution to the understanding of the processes underlying Alzheimer's disease and has produced over 150 original research papers in peer reviewed journal, and numerous conference presentations (not least at the annual Alzheimer Association International meeting where AIBL presentations routinely are the most numerous from any Australian research collaboration). Our 2013 paper indicating the 30 year trajectory of amyloid protein deposition over the lifetime course of the disease process is our most important publication and this work was central to the development of a new internationally agreed definition of prodromal Alzheimer's disease, now being used to select participants for treatment studies around the globe.

The AIBL study could not have started, nor could it continue, without the dedication and enthusiasm of over 1500 volunteer participants. We salute and thank you for making possible work which we hope will improve the lot of those affected by Alzheimer's disease now and those at risk of being affected by it in the future.

Professor David Ames

BA MD BS FRCPsych FRANZCP

Professorial Fellow University of Melbourne, National Ageing Research institute and Florey Research Institute

AIBL study chairman 2006-present

Baseline	1129 HC	272 MCI	319 AD
18 month	874 HC	157 MCI	258 AD
36 month	696 HC	80 MCI	182 AD
54 month	569 HC	52 MCI	103 AD
72 month	484 HC	48 MCI	59 AD
90 month	398 HC	17 MCI	12 AD

Person contact years

December 2015	SMC	MCI	AD	Total
Years	4531	556	945	6033

Total enrollments 1776; currently enrolled 1087

"Our 2013 paper indicating the 30 year trajectory of amyloid protein deposition over the lifetime course of the disease process is our most important publication ."

aibl The Australian Imaging, Biomarkers & Lifestyle Flagship Study of Ageing

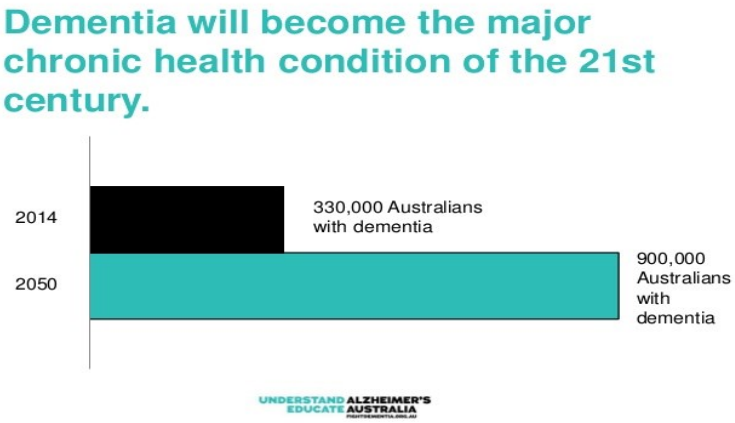
Alzheimer's Australia VIC

Alzheimer's Australia Vic share the Oak Street site where most AIBL appointments are completed.

Alzheimer's Australia represents the more than 353,800 Australians living with dementia and the estimated 1.2 million Australians involved in their care. They advocate for the needs of people living with all types of dementia, and for their families and carers, and provide support services, education and information. Alzheimer's Australia is a member of Alzheimer's Disease International, the umbrella organisation of Alzheimer's Associations around the world. Alzheimer's Australia also represents, at the national level, the interests of its federation of state and territory members on all matters relating to dementia and carer issues.

In the last financial year AAVic counselling staff assisted over 6,600, their education courses were attended by over 17,000 people and the Victorian Helpline volunteers took more than 4,300 calls. Tools in place to help include: The National Dementia Helpline – 1800 100 500; Early Intervention Services; Living with Dementia program; Counselling; Younger Onset Dementia services; Risk reduction and many more.

Keep up-to-date by visiting their homepages fightdementia.org.au; livingwellwithdementia.org.au; or by browsing through their many researches at your next AIBL appointment.



Physical Activity & Cognition: AIBL ACTIVE update

Cognitive decline in older adults is common; with 1400 new cases of dementia diagnosed in Australia each week. The groups at risk for cognitive decline are older adults with subjective memory complaints (SMC) or Mild Cognitive Impairment (MCI).Observational studies suggest physical activity is associated with reduced rates of dementia.

Research has shown significantly greater rates of dementia in older men (aged 70+ years) who walked 0.25 to 1.0 miles per day compared to those who walked 2 miles per day. Additionally, individuals who exercised 3 times per week were less likely to develop dementia over 6 years than those who exercised infrequency. So, we asked:

Can *physical activity* slow the progression of cerebro-vascular disease in people at risk of cognitive decline who have vascular risk factors?

To answer this question, we recruited 108 AIBL participants. Half of them maintained their current level of physical activity, and half of them were given a 'physical activity intervention' of 150 min/week of moderate intensity physical activity.

We measured whether participants in the physical activity intervention group had lower levels of brain changes associated with cardiovascular risk factors, memory complaints, and cognitive impairment after 24 months compared with those who did not alter their level of physical activity.

An incredible 96% of our participants in the study retained their new level of physical activity beyond the 24mth duration of the study! Data analysis is currently underway to determine whether the intervention had any effect on the outcome measures of interest, so watch this space!

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aibl ACTIVE

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Observational studies suggest physical activity is associated with reduced rates of dementia.

The association between high amyloid and incidence of depressive symptoms in cognitively normal older adults

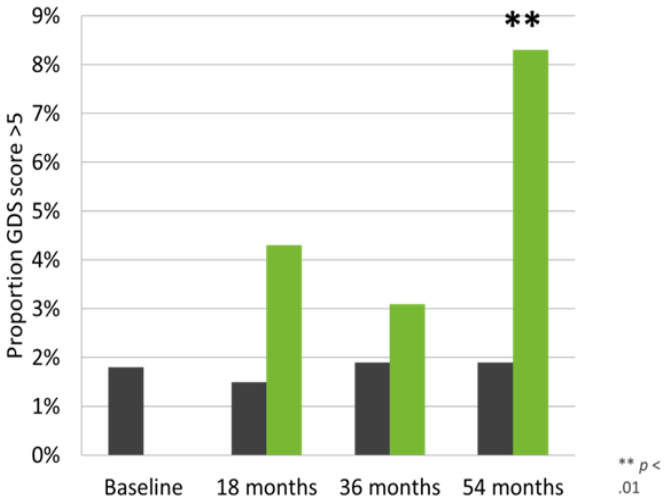
Previous studies have shown that having a history of depression increases the risk of developing Alzheimer's disease by as much as 2 to 5 times. Depression and Alzheimer's are often experienced together and share some similar symptoms such as apathy and reduced memory function. This suggests that the two conditions might be related; however the nature of the relationship between the two is not understood well.

One theory is that the two conditions share some common biological factors and even that depression occurring later in life might be an early sign of Alzheimer's disease (AD). Supporting this theory are observations from previous studies that older people with clinically diagnosed major depression often have higher levels of amyloid than those without depression. While this research supports the idea that amyloid might be involved in depression as well as AD, it's important to note that many of these prior studies were using measures of amyloid taken from the blood and were focused on people who were significantly unwell in terms of their depression. The way we measured depressive symptoms was using the Geriatric Depression Scale or GDS. Scores on those questionnaires can tell us about whether the individual is experiencing any depressive symptoms.

We look at the scores on the GDS at each of the AIBL assessment time points for those who had low amyloid and those who had high amyloid on their PET scan.

The amount of depressive symptoms reported by each of our groups didn't change much over 54 months. Also, most people scored very low on the GDS, in fact the average score was 0 for both groups at all assessments – that means that the majority of people didn't report experiencing any depressive symptoms.

We looked more closely at the people who had a high score on the GDS at any AIBL assessment regardless of whether they had high or low amyloid.



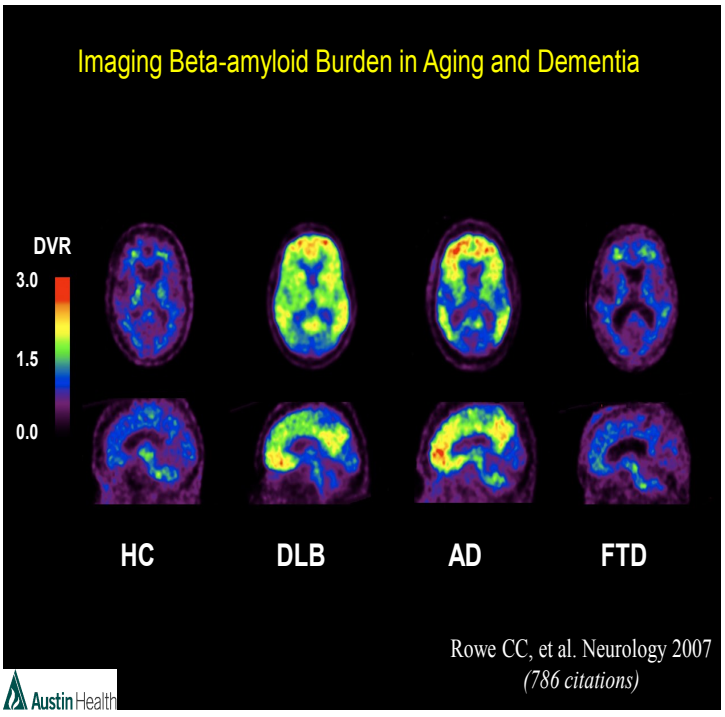
Summary

High amyloid is not associated with a general increase in depressive symptoms in healthy older adults, but high amyloid is associated with increased incidence of clinically significant depression over 54 months in healthy older adults. Also, high amyloid and depression together are associated with progression to MCI/AD. The next step will be to investigate specific depressive symptoms associated with high amyloid to differentiate amyloid-associated depression from other depression.

Karra Harrington
PhD Candidate

The Florey Institute of Neuroscience and Mental Health

Imaging Update from Prof. Christopher Rowe



AIBL has been a world leader in using brain scans called positron emission tomography (PET) to detect the characteristic pathological findings of Alzheimer's disease. These are amyloid plaques and tau tangles. Both are microscopic clumps of abnormal protein that slowly build up and eventually damage brain cells leading to memory loss and other features of Alzheimer's disease.

AIBL has shown from repeated amyloid PET scans over many years in AIBL volunteers that it takes 30 years for the amyloid plaque to build to the level found in mild Alzheimer's dementia and that PET scanning can detect it at low levels up to 15 years before any symptoms develop. This breakthrough discovery has enabled drug trials in older persons with amyloid that start treatment with anti-amyloid drugs before symptoms in the hope of stopping memory decline and later dementia.

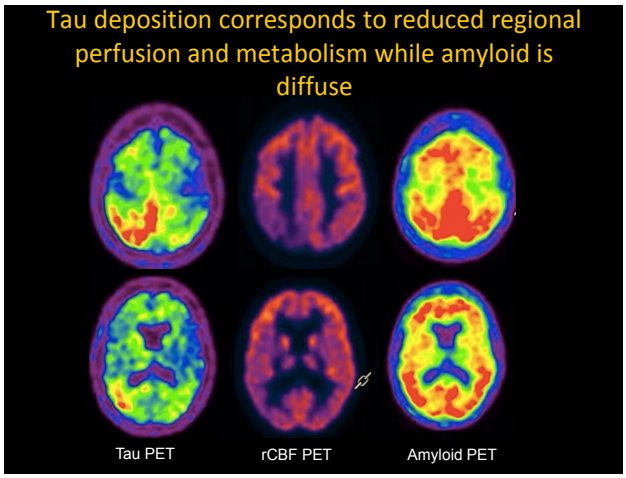
Being able to measure amyloid has enabled AIBL researchers to find lifestyle and genetic factors that

change the rate of amyloid build-up and the rate of damage to memory. High education, exercise and good diet protect to some degree from the damaging effects of amyloid on memory while certain genes accelerate the damage.

These PET scans also provide more accurate diagnosis of Alzheimer's disease and allow diagnosis when symptoms are mild. For this reason, amyloid scans are now approved in the USA and Europe to help diagnosis but the scans are very expensive costing up to $US 4000. As yet, they are not approved in Australia.

More recently, AIBL researchers have helped develop PET scans for measuring tau tangles and AIBL participants are now being asked to also have these scans. To reduce the demand on AIBL volunteers the interval between amyloid PET scans has been extended. Tau tangles develop later than amyloid plaques and are more toxic to brain cells. Learning more about them is vital as treatments for tau may be needed on top of treatment for amyloid to stop development of dementia from Alzheimer's disease.

The imaging discoveries from AIBL have been presented around the world and published in the top neuroscience journals such as Lancet Neurology, Brain, Annals of Neurology, and have won prizes from the US Alzheimer's Association for most important imaging publications in the field of dementia two years in a row. AIBL images after de-identification, are made available to researchers across the globe and there have been over 1000 requests for access to this data from universities such as Harvard and Oxford and international pharmaceutical companies working on cures for Alzheimer's disease.



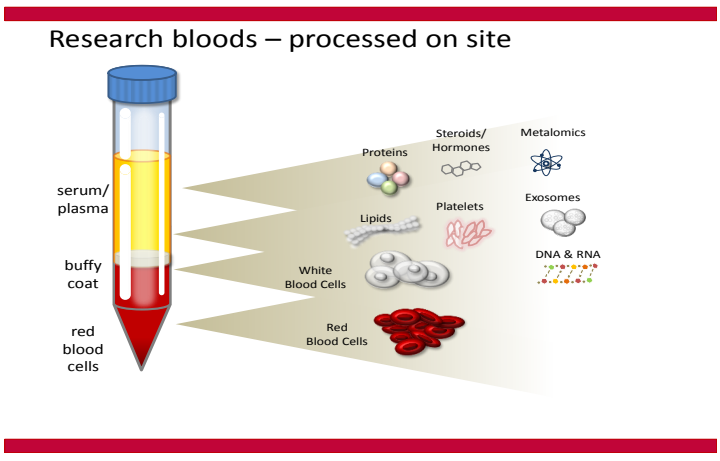
Prof. Rowe FRACP MD is Director of Molecular Imaging Research and a consultant neurologist to the Memory Disorders Clinic at the Austin Hospital, Melbourne.

Austin Health

Blood Biomarker Update

A milestone reached, the AIBL study has processed over 500,000 aliquots of blood for storage in our liquid nitrogen facilities in Melbourne and Perth. This material is in high demand from researchers both within Australia and internationally for research into the biology of Alzheimer's disease and for the identification of biomarkers (a quantifiable biological entity that can measure disease severity and progression).

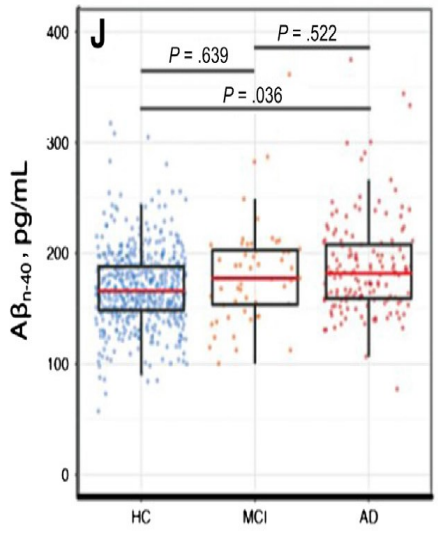
Notable achievements include the profiling of metal content in blood, focusing on a perturbation



in the efficiency of copper and iron trafficking transport proteins in Alzheimer's disease. Also an extensive profiling of the lipid content of blood over 8 years of follow-up visits is underway with the Baker IDI. A panel of blood analytes, currently undergoing patent filing in conjunction with CSIRO, has proved useful for distinguishing AD from cognitively normal participants in >80% of cases; this work will now be validated against other dementia disease types. Despite earlier investigations of blood abeta not correlating with PET-abeta load, current work with Araclon, a Spanish company, is showing more promising results, as their proprietary assay measures a class of blood abeta that was previously undetectable in earlier experiments, and which correlates strongly with PET-amyloid deposition rates. Likewise, mass spectrometry approaches, conducted by both Australian and international researchers, are measuring rarer forms of blood abeta that are providing strong correlations with brain-amyloid deposition.

AIBL is in a position now to undertake longitudinal investigations, due to the extensive collection of material and data which in some cases spans 10 years. Considering that we believe AD to have a 20 year development phase, only now are certain aspects of the disease coming to light.

Targeted: Blood Abeta



Rembach et al 2014

- Dr Christopher Fowler
AIBL Melbourne coordinator

aibl The Australian Imaging, Biomarkers & Lifestyle Flagship Study of Ageing

Do you know someone who can help?

New volunteers are needed for a number of current and upcoming projects. We are looking for people who are:

Aged 65 to 85 with no diagnosed memory impairment (such as MCI or dementia) and would like to be in a drug trial – call Alex Barac about the A4 study on (03) 9389 2904

Aged 50 or older with a diagnosed memory impairment (e.g. Mild Cognitive Impairment or Alzheimer's disease dementia) and would like to be in a drug trial – call Cheryl Donohue about the Brain Imaging Study on (03) 9389 2938

Aged 50+ and do not want to be in a drug trial, but happy to be involved in brain imaging research – call Denise El-Sheikh on (03) 9496 3326

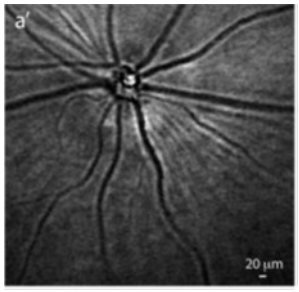
Aged over 50, have been diagnosed with a terminal illness, and are interested in becoming a brain donor – call David Baxendale on (03) 9496 5952

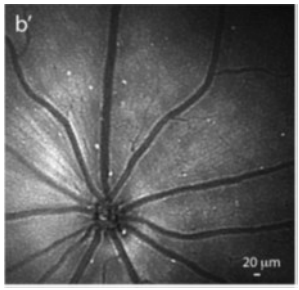
AIBL retinal imaging project

Over the next year many existing AIBL participants will be contacted in regards to a new component of the study which involves retinal imaging. Eye testing will be performed at the Oak St facility with a new generation eye camera, sourced from the USA in collaboration with NeuroVision and CSIRO.

The tests will analyse the eye vasculature as well as look for deposits of abeta-amyloid. The aim is to investigate the health of the eye and the relationship between amyloid in the eye with PET-amyloid

brain imagining results. If a significant relationship is established, compared to PET imaging, retinal imaging could be a less invasive, faster and cheaper test to measure amyloid accumulation, permitting a wider proportion of the population to be screened to identify people at risk of developing Alzheimer's disease. Preliminary results from the Perth side of the AIBL study has shown a significant relationship between eye-amyloid and PET-scan results, however an increased study size is needed to further validate the findings.





Non-invasive optical image of Aβ plaques in transgenic mice. Representative images from (a) control mouse; (b) AD-transgenic mouse with observed Aβ plaques (spots).
- Image taken from Koronyo-Hamaoui, M. et al., Neuroimage 2011 S204-217.

AIBL at AAIC

Many AIBL researchers attended the Alzheimer's Association International Conference (AAIC) in July, which is the largest Alzheimer's disease conference in the world. The AIBL study was very well represented at this meeting, with over 25 presentations on AIBL data.

RIP Alan Rembach

On a sad note, our colleague Dr. Alan Rembach, the Victorian coordinator of the AIBL study from 2012-2014 died suddenly in November 2014 before reaching the age of 40. He is survived by his wife Bonnie and daughter Tali (pictured), as well as his son Ezra, who was born September 2015. I would like to acknowledge Alan's enormous contribution to the success of the AIBL study and note how much we, his friends and colleagues, miss him every day.