UNSW AUSTRALIA

Annual Report 2014
Centre for Healthy Brain Ageing (CHeBA)

Never Stand Still | Medicine | School of Psychiatry

Contents

CHeBA
Healthy Brains Positive Ageing

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Postal Address:
NPI, Euroa Centre, Prince of Wales Hospital,
Barker Street, Randwick NSW 2031, Australia

Telephone 61 02 9382 3816 **Facsimile** 61 02 9382 3774
Email cheba@unsw.edu.au **Website** cheba.unsw.edu.au

Edited by: Perminder Sachdev, Henry Brodaty, Heidi Mitchell and Kate Crosbie

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Chairperson's Report: Dagmar Schmidmaier AM

2014 has been a year of remarkable findings and advancements at CHeBA.

One of the great strengths of CHeBA continues to be its multidisciplinary, comprehensive approach to brain ageing issues. This is exemplified by the 2014 achievements in broad-ranging areas such as the identification of a potential natural model for Alzheimer's disease using the Octodon degus, to the publication of the report, "Is the incidence of dementia declining?", authored by Professor Sachdev, which provides evidence that preventative health strategies could lower the risk of dementia for future generations.

In 2014, the exemplary work of Professors Sachdev and Brodaty to promote healthy ageing for all Australians, as well as positive outcomes for people with dementia and their families, was recognised by the UNSW Dean's Award for Outstanding Achievement. This is the highest award made by UNSW Medicine, and this annual report contains many examples of hope for a better future in ageing achieved under their outstanding and imaginative leadership.

Professors Sachdev and Brodaty lead a high calibre, dedicated group of researchers who bring a diverse set of skills to address research issues in brain ageing and dementia. Since its launch, CHeBA has continued to build its own unique identity as a leading research centre, with internationally competitive programs in many aspects of this field. This has been achieved with limited infrastructure and the lack of one place they can call home.

A key focus for the Advisory Committee in 2014 has been to generate new funding avenues for CHeBA to harness the talent and dedication of the researchers.

Dementia research is heavily underfunded when its prevalence is taken into account: at the last estimate, dementia funding amounted to $1 for every $7 dedicated to cancer research despite the fact that dementia is now the second leading cause of death in Australia behind heart disease. It is critical that we all, as a community of people affected by this disease and concerned about the welfare of our society, continue to talk about the need for greater funding into dementia research.

We have begun to redress this funding imbalance at CHeBA, largely thanks to the generosity of our donors, including our major donors the Thomas Foundation and The Montefiore Home. CHeBA's Marketing & Communications Officer, Heidi Mitchell, has been integral to the successful expansion of CHeBA's fundraising profile. In 2014, CHeBA raised almost $540,000 through donations and sponsorships, a 34.5% increase on 2013. However, more funding is needed if we are to make a significant impact on the burden of dementia in Australia. To this end, the Advisory Committee has worked closely with CHeBA on a new initiative to be launched in 2015: The Dementia Momentum.

On behalf of the CHeBA Advisory Committee, I would like to extend our sincere thanks to Roger Corbett AO, former Chairman (October 2012 to October 2014), who helped set the scene for the strategic direction of CHeBA. During his time as Chair, Roger played an integral part in the launch of CHeBA, and the development of a solid fundraising network including the highly successful annual ARIA corporate luncheon.

I would also like to thank my fellow Advisory Committee members for their commitment. We remain committed to assisting CHeBA create avenues to prevent or delay the onset of dementia. Our vision is to achieve, through research, healthier brain ageing and better clinical care of age-related brain diseases.

Sincerely

Dagmar Schmidmaier AM

Directors' Report

At present, the number of Australians living with dementia is expected to triple to almost 1 million over the next 35 years and spending on dementia is predicted to outstrip any other health condition by the 2060s, with a projected cost of $83 billion, or about 11 per cent of total health and residential aged-care spending.

Similarly, global projection figures are estimated to reach 135 million by 2050, with costs to grow exponentially from the current amount of $600 billion annually.

With rising figures representing an enormous social and economic burden and no available cure, dementia prevention is widely recognised as a critical area for research development. We are heartened by the World Dementia Council's statement calling on governments to adopt a risk reduction approach in public health policies and campaigns, and to increase investment for population level research into dementia risk. This aligns with our belief that dementia is at least partially preventable through strategies that will push back its onset.

Accordingly, a major focus for CHeBA in 2014 was the leadership and expansion of a number of international consortia – COSMIC, ICC-Dementia, STROKOG and PROMOTE - examining epidemiological, genetic and psychosocial factors related to dementia. Establishing international consortia is an innovative approach which allows the pooling of data from studies across the world to generate more robust statistical models of multiple risk and protective factors, and more precise estimates for potential factors with small effect. Running large-scale statistical analyses means we are better able to identify groups at risk and implement early intervention strategies to delay, ameliorate or stop the progression of dementia. A significant achievement for our consortia in 2014 was the expansion of STROKOG, which now represents all continents, with a total sample size of more than 9000.

In 2014, CHeBA continued to consolidate its position as a leading centre of excellence in the field of brain ageing research. We outline some of our key research findings from 2014 in this report, including the development of a potential natural model for Alzheimer's progression using the Chilean rodent *Octodon degus*, results from CHeBA's Sydney Memory and Ageing Study showing the ability to metabolise glucose normally may help preserve brain structure and function, and results from the collaborative SMART trial demonstrating resistance training significantly improved global cognitive function.

We extend our congratulations to several of our researchers, whose innovative work was recognised in 2014: Honorary Associate Professor Kuldip Sidhu who was awarded the International Pioneer in Medicine award, Dr Nady Braidy who was selected to attend the prestigious Lindau Nobel Laureate Meeting and Dr Karen Mather who was awarded a Yulgilbar Post-Doctoral Excellence Award to study the biological determinants of memory loss. We also congratulate the leader of our Neuroinflammation Group, Julian Trollor, for his promotion to Professor.

CHeBA continued its strong presence in the community, largely thanks to the tireless work of Heidi Mitchell, our Marketing & Communications Officer. The first event in our *Better Brain. Better Life* public forum series, generously sponsored

"Our belief is that dementia is at least partially preventable through strategies that will push back its onset."

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by Genworth, proved highly successful with over 600 attendees and fantastic feedback; these forums will continue in 2015. 2014 heralded phenomenal growth in CHeBA's media coverage, particularly in the *Australian Financial Review* among other highly respected outlets, and fundraising profile with over $500,000 raised through donations, sponsorships and events. Due to widespread community support, CHeBA was awarded one of two $50,000 cheques given by the Dick Smith Foods Foundation in their 2014 "1 million to charity" competition. We applaud our indefatigable CHeBA Champions, who have continued to promote the message of a healthy lifestyle from a young age for positive brain ageing while raising funds for our research.

Our Advisory Committee also provided an invaluable source of knowledge and support for our community outreach and fundraising strategies. We extend a special thank you to Roger Corbett AO who stepped down as Chair, after leading the Committee since CHeBA's inception in 2012. Similarly, our Steering Committee helped drive CHeBA's strategy for this and the coming year.

Ultimately, research is a team effort and our achievements in 2014 could not have been possible without an exceptionally dedicated team of research assistants, PhD scholars, post-doctoral research associates and our collaborators, as well as our Centre Manager Angie Russell who manages finances and administration to ensure the CHeBA engine runs smoothly. Dr Sophia Dean and Kate Crosbie provided invaluable research and administrative support.

We continue with ambitious, but achievable, plans for 2015 including targeting prevention of cognitive decline. According to the latest available figures, National Health and Medical Research Council funding for Alzheimer's and other dementias is about 13 per cent of the amount of money for cancer research, while government funding overall is not proportionate to the number of people affected and the projections going ahead. To partly redress this imbalance, in 2015 we will launch **The Dementia Momentum**, a movement to bring researchers and the corporate and philanthropic community together to change the future of dementia incidence. Former CHeBA Advisory Committee member and corporate leader Mr Richard Grellman AM has been instrumental in the creation of this initiative and will continue to play an essential role as Spokesman. The Dementia Momentum seeks to raise $10 million over 5 years to advance CHeBA's research into risk and protective factors using large-scale, "big data" harnessed through international consortia. Since CHeBA has already established a number of consortia, we are in an excellent position to make a world-wide difference to prevention, earlier diagnosis, and earlier and more effective interventions.

In 2015, CHeBA plans to create a registry of people with dementia nationally. We also hope to finalise a unified space for CHeBA in 2015 through our participation with the MindGardens initiative spearheaded by a UNSW/SESLHD Health Sciences alliance.

Lastly, we wish to thank our supporters for their involvement and participation which helped make 2014 a successful year for CHeBA. We look forward to continuing to deliver outcomes to fulfil our objective of healthy brains for healthy lives in the years to come.

Sincerely

Scientia Professor Perminder Sachdev &
Scientia Professor Henry Brodaty

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About the Centre

The Centre for Healthy Brain Ageing (CHeBA) is a premier research institution in Australia, investigating brain ageing. CHeBA was established within the Faculty of Medicine at UNSW Australia in October 2012. It is headed by internationally acclaimed leaders in the field, Professor Henry Brodaty and Professor Perminder Sachdev.

Our Vision

Our vision is to achieve, through research, healthier brain ageing and better clinical care of age-related brain diseases.

Our Purpose

CHeBA is positioned as a leader in multidisciplinary research into age-related brain diseases, particularly dementia, and an international hub for collaborative engagement. Its work extends from molecular work in the Genetics and Proteomics laboratories, to tissue culture and cell-related work in the Molecular Biology & Stem Cells Group, to neuronal systems and networks in the Neuroimaging Laboratory, to clinical, epidemiological and sociological research, to research on ageing health policy using its strong links with teaching hospitals, aged care providers, state and federal governments and its established ageing cohort studies. Its work strongly emphasises implementation, capacity building and translational research.

Our Mission

Our mission is to enhance the evidence base in relation to prevention, early detection, and treatment of age-related disorders, in particular brain diseases, and improve the health care of individuals affected by these diseases.

Our Aims

The Centre aims to conduct multidisciplinary research into ageing in health and disease, and be involved in knowledge dissemination and translational research. The Centre focuses in particular on the following aims:

- Determine the pathways of normal and abnormal brain ageing in the community.
- Identify risk factors for and protective factors against abnormal brain ageing.
- Determine the prevalence of age-related neurodegenerative and cerebrovascular disorders.
- Identify biomarkers for brain disorders.
- Investigate the pathophysiology of brain diseases so that novel treatments can be discovered.
- Conduct treatment trials of novel drugs and non-pharmacological strategies.
- Conduct educational activities for a workforce involved in the care of the elderly, especially those with dementia.
- Design models of assessment and care using the latest research evidence.
- Develop research programs in special populations, e.g. young-onset dementia, dementia in intellectual disability.

Our Functions & Goals

The functions of the Centre are to:

- Build capacity and research capability for age-related research, in particular brain research.
- Support the development and sharing of infrastructure for research across different Schools and Faculties of UNSW Australia.
- Build relationships between the Centre and other similar centres in Australia and overseas.
- Build relationships between the Centre and the industry involved in the treatment and care of the elderly.

This will be achieved through:

- Strengthened collaborative research programs among staff and partners locally, nationally and internationally, supported by increased peer-reviewed grants and commissioned research.
- Development of specialised research facilities and laboratories that place the

Centre at the forefront of brain ageing research nationally and internationally, to achieve the highest quality research and advance the Centre's attractiveness to prospective researchers of excellence.

- Extensive linkages with practitioners and policy makers at local, state and national levels to improve relevance and impact of research.
- Increased numbers and quality of skilled researchers undertaking research and evaluation activities in this field.
- Enhancing numbers of post graduate research students.
- Exercising enhanced influence via dissemination and transfer of research findings through publications, presentations and forums with a focus on academic, practitioner and policy maker audiences.

Governance Structure

Centre Steering Committee

The Centre Steering Committee is the major decision making group for CHeBA. Centre Steering Committee members provide leadership across the Centre, are responsible for developing the Centre's strategy, advise on the Centre's operations and financial position, new partnership and funding opportunities. The founding Co-Directors of CHeBA are Professor Perminder Sachdev and Professor Henry Brodaty, who report to the Dean of Medicine, UNSW Australia. The Centre Steering Committee Members are:

Terry Campbell

Phillip Mitchell

- Professor Terry Campbell, Senior Associate Dean, Chair of CHeBA Steering Committee
- Professor Philip Mitchell, Head of School of Psychiatry, UNSW Australia
- Professor Henry Brodaty, Co-Director of CHeBA
- Professor Perminder Sachdev, Co-Director of CHeBA

2014 meeting date: 1 December.

CHeBA Advisory Committee

The CHeBA Advisory Committee is a group of senior academic and business leaders. Their role is to assist and guide the Directors on matters of strategy, fund-raising, policy, marketing and media, specifically to:

- Enhance the profile and community awareness of the Centre and its aims
- Facilitate the development of more effective infrastructure for the Centre, such as specialised research facilities and laboratories, IT networks, equipment and training support services
- Facilitate sponsorship for the Centre's activities, through various mechanisms for example, directly through personal networks via donation or service provision and introductions to potential high end donors, and indirectly by creating sponsorship opportunities
- Provide advice specific to areas of expertise of the Committee members, e.g. legal, government relations, business development strategy, marketing strategy and media.

The members of the CHeBA Advisory Committee are:

- Roger Corbett AO – Chairperson (until October 2014)
- Dagmar Schmidmaier AM – Chairperson (Vice-Chairperson until October 2014)
- John Gray – Deputy Chairperson
- John Thomas
- Richard Matthews AM
- Roger Layton AM
- Dr Sudarshan Sachdev

2014 meeting dates: 5 March, 24 June, 29 July, 15 September, 3 November.

"It's important as a community we come to grips more than we have with the implications of a rapidly ageing population. This is not only about funding that might be necessary, it's also about commitment and hope that something can be done."
ROGER CORBETT AO

Advisory Committee Profiles

Roger Corbett AO

Director, Walmart / Fairfax Media / Reserve Bank of Australia

From January 1999 to September 2006, Roger served as CEO of Woolworths Limited. He is now a director of Wal-Mart, the Reserve Bank of Australia and Fairfax Media. Roger was appointed a Member of the Order of Australia (AM) in the 2003 Queen's Birthday Honours, for service to the retail industry, particularly as a contributor to the development of industry policy and standards, and to the community. In 2008, he was promoted to an Officer of the Order of Australia (AO) for service to business, particularly through leadership and executive roles in the retail sector and a range of allied organisations, and to the community.

John Gray

Partner HWL Ebsworth Lawyers

John is one of Australia's leading technology, media and telecommunications (TMT) practitioners, and has worked in the area of TMT for over 19 years. John has been the principal legal advisor on some of the most complex and strategically important TMT projects in the Asia Pacific region, including major system and network roll-outs, outsourcings, the procurement of cross-border IT services and innovative online transactions. He is listed on the 2012 Financial Review's Best Lawyer list.

Professor Roger Layton AM

UNSW Emeritus Professor of Marketing

Roger has published widely in the research literature and is the joint author of several books including Fundamentals of Marketing and Contemporary Hospitality Marketing – A Service Management Approach. His current research interests centre on the nature and role of marketing systems and the interplay of function and structure in the evolution of such systems.

Associate Professor Richard Matthews

MBBS AM

Director, Neuroscience Research Australia (NeuRA)

Richard is the Director of NeuRA, Nominee SESLHD, Member of the NeuRA Building Committee and was the Deputy Director-General, Strategic Development of UNSW Health; Chief Executive, Justice Health; Acting Chief Executive Officer, Corrections Health Service; Director of Clinical Services, Corrections Health Service; Director of Drug and Alcohol, Corrections Health Service. He is also on the Board of Alzheimer's Australia NSW, Chair of the Board of General Practice Education and Training (GPET), and Director of Calvary Healthcare.

Dr Sudarshan Sachdev

Ophthalmologist

Sudarshan is an ophthalmologist who has had his own private practice in Sydney for over thirty years. He has a keen interest in healthy ageing and prevention of dementia having lost his mother to Alzheimer's disease. He has supported medical researchers in various disciplines of medicine.

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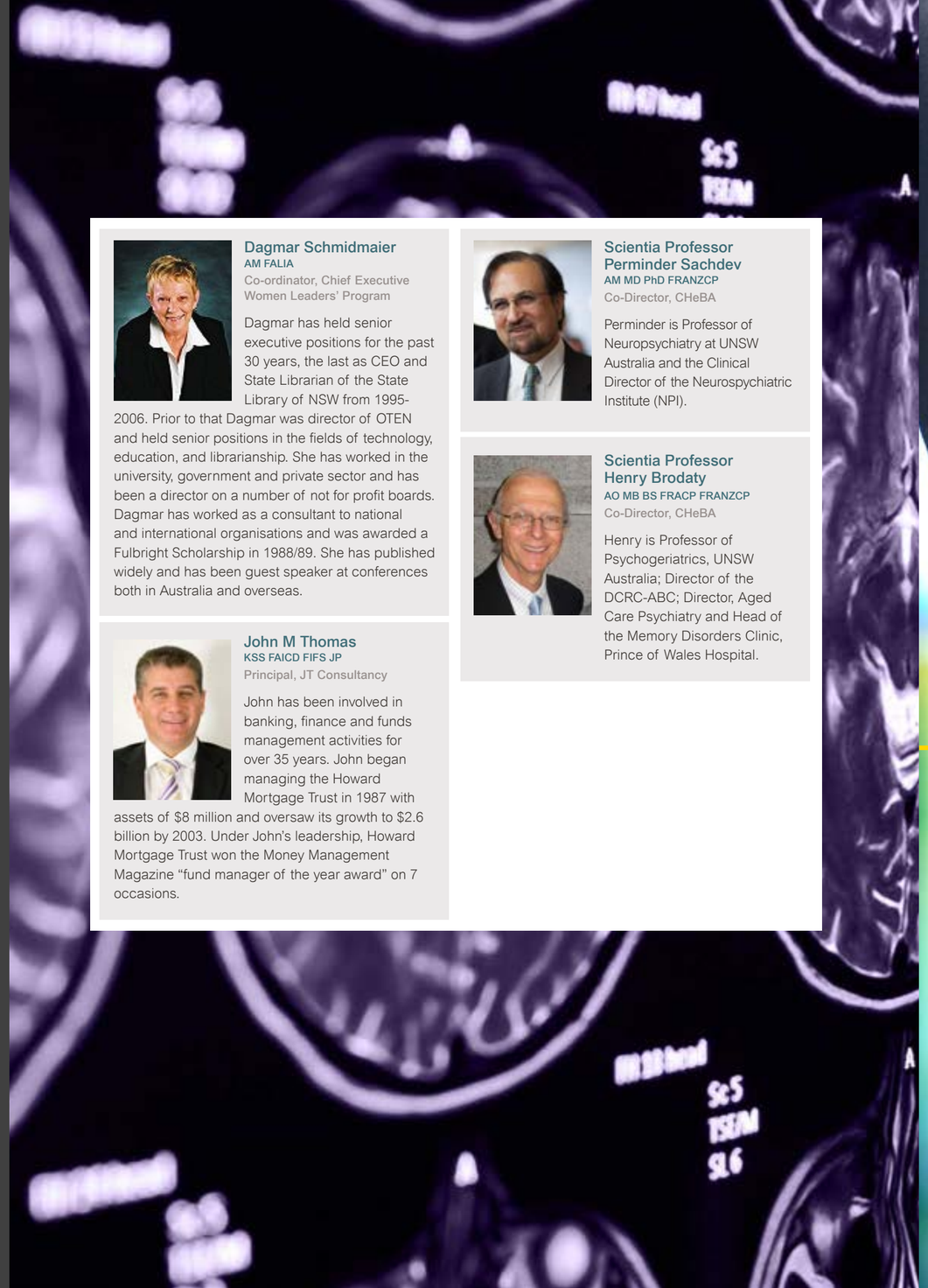

Dagmar Schmidmaier
AM FALIA
Co-ordinator, Chief Executive Women Leaders' Program

Dagmar has held senior executive positions for the past 30 years, the last as CEO and State Librarian of the State Library of NSW from 1995-2006. Prior to that Dagmar was director of OTEN and held senior positions in the fields of technology, education, and librarianship. She has worked in the university, government and private sector and has been a director on a number of not for profit boards. Dagmar has worked as a consultant to national and international organisations and was awarded a Fulbright Scholarship in 1988/89. She has published widely and has been guest speaker at conferences both in Australia and overseas.

John M Thomas
KSS FAICD FIFS JP
Principal, JT Consultancy

John has been involved in banking, finance and funds management activities for over 35 years. John began managing the Howard Mortgage Trust in 1987 with assets of $8 million and oversaw its growth to $2.6 billion by 2003. Under John's leadership, Howard Mortgage Trust won the Money Management Magazine "fund manager of the year award" on 7 occasions.

Scientia Professor Perminder Sachdev
AM MD PhD FRANZCP
Co-Director, CHeBA

Perminder is Professor of Neuropsychiatry at UNSW Australia and the Clinical Director of the Neurospychiatric Institute (NPI).

Scientia Professor Henry Brodaty
AO MB BS FRACP FRANZCP
Co-Director, CHeBA

Henry is Professor of Psychogeriatrics, UNSW Australia; Director of the DCRC-ABC; Director, Aged Care Psychiatry and Head of the Memory Disorders Clinic, Prince of Wales Hospital.

Significant Highlights

"Current thinking suggests it takes 25 years for symptoms of dementia to show. If we can halve the rate of that process, and build it up over 50 years, we can actually delay it showing up in our lifetime at all."

Professor Henry Brodaty

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Dean's Award for Outstanding Achievement

CHeBA's Co-Directors, Professor Henry Brodaty and Professor Perminder Sachdev, were jointly awarded the 2014 UNSW Medicine Dean's Award for Outstanding Achievement on 11 November 2014.

"The award to Perminder Sachdev and I is testimony to a wonderful, dedicated and hard-working team striving to achieve the goal of healthy brains for all of us as we age." PROFESSOR HENRY BRODATY

This is the highest award made by UNSW Medicine in recognition of outstanding contribution and significant achievements.

"The award to Perminder Sachdev and I is testimony to a wonderful, dedicated and hard-working team striving to achieve the goal of healthy brains for all of us as we age," said Professor Brodaty.

Professor Brodaty and Professor Sachdev founded the Centre for Healthy Brain Ageing in 2012, which has since established itself firmly as a pre-eminent centre in brain ageing research. Recent research breakthroughs have included the development of new diagnostic criteria for vascular cognitive disorders, findings that indicate one in four elderly people with mild cognitive impairment naturally revert to normal cognition, and world-first findings about the potential of white matter brain imaging measures as a cheaper and less invasive technique for the early diagnosis of Alzheimer's disease.

In addition to founding and leading CHeBA, both Professors have a long and distinguished history of academic and professional contribution in the fields of mental health, neuropsychiatry, geriatrics, health care policy and community involvement.

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Dr Nady Braidy

Attended 2014 Lindau Nobel Laureate Meeting

Dr Nady Braidy was one of 15 young Australian scientists selected by the Australian Academy of Science to attend the 2014 Nobel Laureate meeting in Lindau, Germany to meet with Nobel Prize winners in the fields of physiology and medicine.

The 64th Lindau Nobel Laureates Meeting (29 June – 4 July 2014) brought together 600 young researchers from 80 different countries to interact with giants in these fields and build networks with other researchers. Overall 20,000 researchers applied worldwide. The 15 Australians chosen went through a rigorous selection process to be put forward by the Australian Academy of Science.

Dr Braidy is a National Health and Medical Research Council early career postdoctoral fellow at CHeBA. His work investigates the pathobiology of Alzheimer's disease and is the first to link the decline of one of the longevity genes, NAD+, with ageing. Next, he hopes to show that NAD+ levels can be increased in animal models, possibly leading to a reversal of age-related brain diseases.

Dr Braidy said he was "honoured and flabbergasted" to be selected, and he made the most of the Nobel Laureate opportunity to forge new collaborations.

"We're already working with one of the leading neuroscientists in South America," he told *The Australian* newspaper. The approach is paying dividends, with several research publications already in the pipeline.

Dr Karen Mather

Awarded Yulgilbar Post-Doctoral Excellence Award

Leader of CHeBA's Genetics and Genomics Group, researcher **Dr Karen Mather**, received a $20,000 post-doctoral excellence award from the Yulgilbar Foundation in 2014, as part of a $10 million philanthropic initiative to find a cure Alzheimer's disease.

Dr Mather's research project is investigating the biological determinants of an early symptom of Alzheimer's disease, memory loss. Using identical twins from CHeBA's Older Australian Twins Study, this research aims to identify RNA differences between co-twins who differ in their performance on memory tests. RNA is one of the three major macromolecules (along with DNA and proteins) that are essential for life. RNA carries information from DNA, the genetic blueprint, to form proteins and perform other functions in the cell and the body, and is therefore a very important but less well understood part of the puzzle in understanding memory impairment and dementia. This study has the potential to increase understanding of the early development of late-onset Alzheimer's disease and ultimately may suggest novel diagnostic, prognostic and treatment strategies.

The Yulgilbar Foundation, established by Sarah and Baillieu Myer through the Myer Family Company, provides funding to find a cure for Alzheimer's disease and, to date, has awarded five post-doctoral excellence awards to top-up the salaries of young researchers who are working to cure, prevent or slow down the advancement of Alzheimer's.

The Yulgilbar Foundation has called for donations from other philanthropists, pledging to match any donations received. "We think that this is a great opportunity for private philanthropy to value-add to the government program by bringing the innovation and young minds into the mix," said Baillieu Myer.

Professors Sachdev and Brodaty expressed their gratitude to Yulgilbar Foundation for their generous support of Dr Mather.

"With funding for dementia research grossly underfunded when its prevalence and disease burden are taken into account, it is extremely promising to see such a push for philanthropic funding in this area by the Myer Family Company. We hope it encourages other philanthropists to recognise the importance of supporting CHeBA's research into age-related cognitive disorders," said Professor Sachdev.

Honorary Associate Professor Kuldip Sidhu

Receives International Pioneer in Medicine Award

Co-Leader of CHeBA's Molecular Biology & Stem Cells Group, **Honorary Associate Professor Kuldip Sidhu** was awarded the "International Pioneer in Medicine Award" at the World Congress of the Society of Brain Mapping and Therapeutics (SBMT) in Sydney, held on 17-19 March 2014.

> "This award is also recognition of an important area of research that is destined to bring a paradigm change in human medicine."
> HON. ASSOCIATE PROFESSOR KULDIP SIDHU

The International Pioneer in Medicine Award is presented to individuals who have significantly contributed to scientific advancement in the fields of medicine and image guided therapy through a multidisciplinary approach. Their ground breaking work has made development of state-of-the-art technology and scientific discovery a reality.

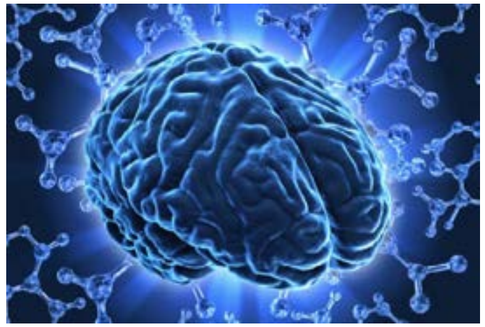
Hon. Associate Professor Sidhu received the award for his landmark contributions to stem cell research, including spearheading the building of a unique global consortium for study of patient-derived stem cells, known as induced pluripotent stem cells (iPSC). He co-authored the findings with 2012 Nobel Prize winner Dr Shinya Yamanaka.

"This is also recognition of an important area of research that is destined to bring a paradigm change in human medicine," said Hon. Associate Professor Sidhu.

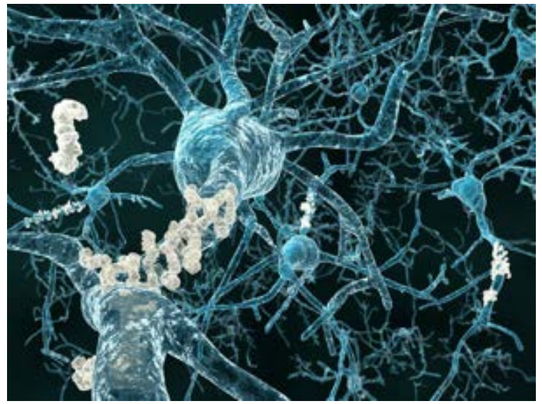
"The awards committee has been impressed with the pioneering work of Hon. Associate Professor Sidhu. His ground breaking consortium approach is a great example of how the Brain Mapping Foundation would like to plan and execute its global alliance for NanoBioElectronic," said Dr Shouleh Nikzad, President of SBMT (2014-2015).

Hon. Associate Professor Sidhu presented a paper "Brain in the Petri dish – disease modelling" with CHeBA's Professor Sachdev and Dr Henry Chung. The paper covered patient-derived stem cell technology (iPSC), which allows a brain disease process to be modelled in the Petri dish with cells derived from patients, which could ultimately allow for personalised treatments.

"This was an exciting opportunity for researchers from all over the world to hear about the most cutting-edge research and hopefully it will lead to further collaborations down the track," said Hon. Associate Professor Sidhu, who was the Co-Convener of the event and President of the SBMT (2013-2014).



NHMRC Grant Success – World First Study



As part of the 2014 National Health and Medical Research Council (NHMRC) grant round, Professor Sachdev was awarded $625,000 to better understand how amyloid plaques in the brain affect cognitive function.

'Plaques' on the brain are one of the hallmark indicators of Alzheimer's disease, but it is still not fully understood how they grow or how they are linked to cognitive decline. Professor Sachdev and his team will conduct the world's first study using PET scans with amyloid imaging of 100 sets of twins aged 65+ to study the relationship between plaques and cognitive function, and to shed light on how genes and environments contribute to the development of the plaques.

Modern imaging techniques, like PET scans, have revolutionised research into normal and pathological brain ageing. Many people develop plaques made of the protein amyloid as well as neurofibrillary tangles – both believed to be primary culprits for dementia. However, their presence does not mean cognitive decline is certain.

"People with Alzheimer's disease all have amyloid, but if brain scans are taken of people in their 70s and 80s you see it's possible to have amyloid but not dementia," explained Professor Sachdev.

Appointments

Professor Perminder Sachdev

Appointed Chief Medical Advisor to Alzheimer's Australia

Professor Sachdev was appointed Chief Medical Advisor to Alzheimer's Australia in 2014. The role involves providing advice and feedback to Alzheimer's Australia on their policies as well as new developments in dementia and Alzheimer's research generally. Professor Brodaty continues as Chief Medical Advisor to Alzheimer's Australia NSW.

"With funding for dementia research grossly underfunded when its prevalence and disease burden are taken into account, it is extremely promising to see such a push for philanthropic funding in this area."
PROFESSOR PERMINDER SACHDEV

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Is the Incidence of Dementia Declining? Report

A report released on 9 April 2014 by Alzheimer's Australia and CHeBA, *Is the Incidence of Dementia Declining?*, suggested that action on preventative health could lower the risk of dementia for future generations.

Author of the report, Professor Sachdev, said "There is evidence from recent studies in Europe that the age-specific rates of dementia may be modifiable. It is possible that environmental and lifestyle factors, such as diet and exercise, could make a significant contribution to reducing the risk of developing dementia.

"A recent study in the UK in 2011 found that the expected prevalence of dementia in people aged 65 years and older was estimated to be 8.1 per cent but the actual prevalence was found to be 6.5 per cent – a decrease of about 20 per cent from what was expected."

Alzheimer's Australia's National President, Ita Buttrose, said that the report highlights the importance of changing the way Australians think about dementia.

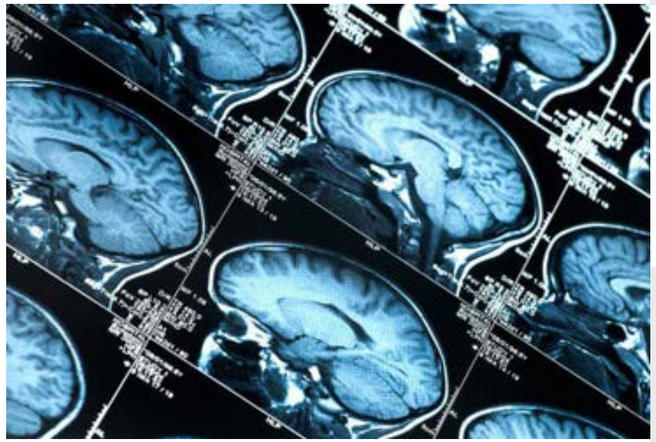
"The changes in the brain that lead to dementia begin up to 20 years before symptoms first appear. People of all ages can make simple lifestyle changes that may reduce their risk of dementia, such as increasing physical activity and controlling blood pressure and cholesterol," Ms Buttrose said.

The report also cautions that the total numbers of people with dementia will continue to rise, even with changes in age-specific prevalence, because of the increasing numbers of older people in Australia.

Many Australians remain unaware of the connections between dementia and other major chronic diseases

Role of Glucose in Preserving Brain Structure and Function

Results from CHeBA's Sydney Memory and Ageing Study have shown that the ability to metabolise glucose normally may help preserve brain structure and function.



The findings were published in the January 2014 edition of the journal, *Age*. As part of the study, researchers assessed the brain function of 880 people aged between 70-90 years of age (and without dementia) with a variety of memory tests and brain scans.

"Knowing that poor control of glucose can harm the brain means that doing all we can to keep glucose levels healthy with the right food and exercise gives us a better chance of avoiding dementia." PROFESSOR PERMINDER SACHDEV

The researchers found that those participants who developed new glucose disorders such as diabetes or pre-diabetes (glucose levels higher than normal but not high enough to be considered diabetes) during the course of the study, had an accelerated decline in brain volume and cognition over the two year period. In people with impaired fasting glucose - meaning their blood glucose levels are edging towards diabetes - some had signs of two problems caused by rising blood glucose: oxidative stress and inflammation.

"Both these processes can damage brain cells and increase the risk of cognitive decline," said Professor Sachdev.

However, those who had pre-diabetes at the beginning of the study but maintained stable glucose levels over the two years did not show these same effects.

Studies of longevity indicate that choosing carbohydrates wisely, eating a vegetable-rich diet with fish, olive oil and small amounts of lean meat, exercising and maintaining a healthy weight are all beneficial, said Professor Sachdev.

The authors of the study believe that one way of reducing the risk of dementia is also by reducing diabetes, particularly in the elderly.

"Prevention of diabetes is also a strategy for the prevention of dementia," said Professor Sachdev.

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Professor Lynn Chenoweth

Professor Lynn Chenoweth, who was appointed a half-time professor position at CHeBA in 2013, brings a wealth of experience in aged care nursing, care models and healthy ageing and has strengthened CHeBA's collaborative relationships with a number of universities and industry care providers. In 2014, Professor Chenoweth worked on a wide range of projects in her role with CHeBA.

1. The iHome Project Undertaking research in nursing homes requires managers, nurses, residents and their families to participate and is logistically difficult. By contrast, doing experiments in virtual space could reduce costs and simplify research. Professor Chenoweth and colleagues have been developing an iHome computer model (a virtual residential aged care facility) using existing data sets to populate the model. The team makes adjustments to the characteristics of residents, staff and care environment, to reflect the diversity in aged care facility design, in order to run virtual experiments. The aim is to identify best practice in the real world setting to produce quality outcomes for people with dementia. The iHome base model care systems, care environment, and participant activity models have been completed. Further developments are contingent on funding.

2. Evaluating the Benefits of Smart Technology in In-Home Care Practice This project aims to develop and evaluate assistive technologies to support navigation, localization and shadowing for older people living in the community and in residential care. Navigation technology has the capacity to take a device or a person to a desired destination, for example the dining room, while safely negotiating doorways, corridors and inclines. Localization is a technique to determine the position of people or devices. This enables carers to know the whereabouts of a person or a device. Shadowing technology enables a device to safely follow a user, allowing the user to move efficiently from task to task.To date, first-level construction of the navigation prototype has been completed and localization and shadowing prototypes are under construction.

3. Clinical Leadership in Aged Care (CLiAC) Project Leadership is key in any organisation and residential care facilities are no exception. Professor Chenoweth is part of a team conducting a cluster randomised controlled trial to test the effectiveness of an aged care clinical leadership program for middle managers, aiming to improve their managerial competencies and effectiveness in aged care practice.

4. National Quality of Life in Residential Aged Care

Professor Chenoweth is leading a national Australian study to: (a) investigate quality of life (QoL) for people with dementia in Australian residential aged care facilities (RACFs) from multiple perspectives; (b) explore the relationship between facility characteristics, staff care, family member and resident factors and QoL for people with dementia in Australian RACFs; and (c) assess the effectiveness of self-report instruments for measuring QoL of persons with dementia in RACFs.

5. DCM EPIC Trial

A team from the UK invited Professor Lynn Chenoweth to join them in a replication of the CADRES study which she led. The UK study is a cluster randomised controlled trial across 20 sites evaluating the clinical and cost-effectiveness of Dementia Care Mapping (DCM) in addition to Usual Care versus Usual Care Alone for people with dementia living in care homes in the UK.

Research translation into practice

1. Research mentorship based on findings from Community Caregiver Coaching Project: nurses, social workers and dementia support staff of DBMAS, NSLHD, Chinese Community Association, and Alzheimer's Australia NSW.
2. Research mentorship of aged care managers and nurses from Anglican Retirement Villages and Montefiore Home based on findings from Rhythm of Life Project and PCECAT Project.
3. Conducting HALT Project Champion Training for health care professionals in non-pharmacological prevention and reduction of behavioural and psychological symptoms of dementia in the residential aged care facility (3 day course). HALT Research Project. Course 1- February 19-21; Course 2- April 8-11, Course 3, November 10-12.
4. Presentation of aged care research priorities for the Asia-Pacific region to visiting academic nurses from Sat Yen Sun University September 24.
5. IDEAL project Palliative Care Support Nurse training in person-centred palliative dementia care case conference (5 day course) March 10-14.

6. IDEAL Study

Care for dementia at the end of life presents different challenges. This cluster randomised controlled trial is evaluating the effectiveness and cost of facilitated case conferencing versus usual care for improving end of life outcomes in aged care residents with advanced dementia in aged care facilities and their families. Facilitated case conferencing occurs over three months for all intervention sites and includes families, GPs and palliative care specialists.

7. HALT Study
(Halting Antipsychotic Use in Long-Term Care)

Professor Chenoweth has been a key member of the team led by Professor Brodaty on a Department of Health and Ageing funded project to reduce use of antipsychotics in nursing homes. Antipsychotics which are prescribed to over a quarter of nursing home residents are associated with side effects such as stroke and death. The HALT study collaborates with dementia care specialists, GPs, nurses and aged care workers to reduce inappropriate antipsychotic medication use in long-term resident users and correspondingly to reduce complications, rates of decline and mortality without consequently increasing behavioural and psychological symptoms, and to demonstrate that HALT is a nationally applicable and sustainable model. Professor Chenoweth provides training to nurse champions on how to manage behavioural complications of dementia; the champions in turn train the nurses.

8. Transitional Care for Patients with Dementia

This study is examining the hospital discharge process and transitional care occurring for patients with dementia and their carers.

9. Living with Dementia in Retirement Villages: Investigating the Experiences of Retirement Village Residents with Dementia

Little is known about the experiences of people with dementia living in retirement villages. Professor Chenoweth is ascertaining the extent to which people with dementia are well supported to age in place through the provision of community care services and informal support from other members of the village community.

10. PAIN-ED: Assessment and Management of the Cognitively Impaired Older Person Presenting to Emergency Departments with Musculoskeletal Conditions or Injuries.

Previous research demonstrated that older people with cognitive impairment presenting to ED with musculoskeletal conditions of injuries take longer to receive analgesia compared to younger or non-impaired patients. This study is a cluster randomised controlled trial that compares pain scores and analgesic administration in cognitively impaired and cognitively intact older people diagnosed with a long bone fracture; determine how emergency nurses currently assess, monitor and manage cognitively impaired and/ or cognitively intact older persons with painful conditions or injuries; and determine if the PAINAD tool improves time to analgesia for cognitively-impaired older persons aged 65 years or more.

11. Rhythm of Life – Second Phase Project

Anglican Retirement Villages have engaged Professor Chenoweth to evaluate the quality of organisational culture, care and lifestyle services and care environments of their retirement villages aged care facilities against person-centred standards, and evaluate achievements against recommended improvements. A report has been submitted to the ARV funding body.

12. PCECAT Project

The Montefiore Home Aged Care Facilities engaged Professor Chenoweth to evaluate the quality of their organisational culture, care services and care environments against person-centred standards, and evaluate achievements against recommended improvements.

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SMART Trial Published 2014

The Study of Mental and Resistance Training (SMART), led by Professor Maria Fiatarone Singh of the University of Sydney in collaboration with CHeBA, was a randomised, double-blind, double-sham controlled trial of 100 adults with mild cognitive impairment (MCI).

Resistance training significantly improved global cognitive function, with maintenance of executive and global benefits over 18 months.

Participants were randomised to 2 supervised interventions: active or sham physical training (high intensity progressive resistance training vs seated calisthenics) plus active or sham cognitive training (computerized, multidomain cognitive training vs watching videos/quizzes), 2-3 days/ week for 6 months with 18-month follow-up. The trial showed that resistance training significantly improved global cognitive function, with maintenance of executive and global benefits over 18 months. Cognitive training only attenuated decline in Memory Domain at 6 months.

Fiatarone Singh MA, Gates N, Saigal N, Wilson GC, Meiklejohn J, Brodaty H, Wen W, Singh N, Baune BT, Suo C, Baker MK, Foroughi N, Wang Y, Sachdev PS, Valenzuela M The Study of Mental and Resistance Training (SMART) study—resistance training and/or cognitive training in mild cognitive impairment: a randomized, double-blind, double-sham controlled trial. J Am Med Dir Assoc. 2014 Dec;15(12):873-80

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Rodents May Help Find Cure for Alzheimer's Disease

An international research team, including CHeBA scientists has found that a Chilean rodent, *Octodon degus*, may provide a natural model for Alzheimer's disease.

The world-first study, published in the journal *Brain Pathology*, shows that pathological changes observed in *Octodon degus* closely correlate with the progression of Alzheimer's disease in humans. The *Octodon degus* live longer than more common rat species (typically seven years or more) and the amyloid-beta protein found in their brains more closely resembles that of humans (amyloid-beta protein is the main component of the brain plaques found in Alzheimer's patients).

CHeBA's Dr Braidy says research into neurodegenerative disorders such as Alzheimer's disease, has been limited by the reliability of available disease models. "None of the current models mimic the full range of changes occurring during Alzheimer's disease. In fact, several models rely on introducing foreign genes into organisms, so we don't know how reliable they are and the success rate of therapeutic treatments using these models has been poor."

Professor Sachdev and co-author of the paper, says: "Naturalistic models of later onset Alzheimer's disease are urgently needed and the *degu* looks promising in this regard. Since this animal does not live in Australia, and importation for research may prove to be difficult, our collaboration with the Chilean researchers is of great scientific value".

> "Naturalistic models of later onset Alzheimer's disease are urgently needed and the *degu* looks promising in this regard."
> PROFESSOR PERMINDER SACHDEV

PhD Completion

In 2014, Dr Yanhong (Catherine) Dong was awarded her PhD under the supervision of Dr Melissa Slavin and Professor Sachdev from CHeBA, and Associate Professor Christopher Chen and Associate Professor Simon Collinson from the National University of Singapore.

Thesis: Cognitive outcome after stroke: Detection of vascular cognitive impairment, prognosis, neuropsychological patterns, and the efficacy of revascularization

> "I was inspired by the great team of enthusiastic researchers at CHeBA who are devoted to academic research and working hard to make a difference in policy and practice through scientific evidence."
> DR CATHERINE DONG

Stroke is a leading cause of chronic disability and second leading cause of death globally. Vascular cognitive impairment (VCI) is one of the major sequelae of stroke and transient ischemic attack (TIA) with negative functional impact and elevated risk for institutionalization, dependency and death. Therefore, the overarching aim of this thesis is to characterize neuropsychological patterns of post-stroke VCI and improve outcome after stroke by establishing optimal VCI screening, prognosticating cognitive and functional outcome and investigating the efficacy of the external carotid-internal carotid (EC-IC) bypass revascularization neurosurgical intervention. The findings include, firstly, the widely used cognitive screening instruments, both the Montreal Cognitive Assessment (MoCA) and the Mini-Mental State Examination (MMSE), were equivalent and moderately sensitive in detecting VCI 3–6 months after stroke. However, the addition of a visuomotor processing speed measure can improve the accuracy of VCI screening. Secondly, the neurocognitive status measured by the MoCA and the MMSE at the subacute stroke phase (i.e., within two weeks after vascular events) could predict both cognitive outcome and functional outcome at 3–6 months later. Thirdly, the cognitive performance of ischemic stroke/TIA patients was worse than stroke-free non-demented controls, globally as well as in all individual domains except the episodic verbal memory, which was relatively spared. This study also supports the impact of lesion location and severity on the pattern of cognitive deficits. Finally, the EC-IC bypass surgery in carefully selected severe intracranial steno-occlusive disease patients could result in significant improvement in cerebral hemodynamics and performance in verbal memory and executive function. These findings provide evidence for routine VCI screening, customized rehabilitation and discharge planning at the subacute stroke phase for better prognosis in patients at a higher risk for significant VCI and/or functional decline. It also provides a well-characterized neuropsychological profile to aid differential diagnoses in post-stroke VCI and effective cognitive end-point measures in therapeutic intervention, as well as the preliminary evidence of EC-IC revascularization as a promising intervention for patients with severe steno-occlusive disease.

Our Community

"In the long term, an increased investment in dementia research is the only hope we have for the development of medical interventions to delay, stop or reverse the diseases that lead to dementia."

Professor Henry Brodaty

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CHeBA Wins $50,000 from Dick Smith

"With grant funding becoming increasingly competitive, support from the community in philanthropic endeavours is crucial to advance our research projects and work toward healthier brain ageing." PROFESSOR PERMINDER SACHDEV

CHeBA was awarded one of two $50,000 cheques given by the Dick Smith Foods Foundation in their 2014 "1 million to charity" competition.

The CHeBA community proved to be formidable competition, staying neck and neck throughout the final stages of the first wave with joint winner Top Blokes Foundation. An additional 36 charities received smaller donations.

The degree of support from the community for CHeBA's research was overwhelming and encouraging.

"With grant funding becoming increasingly competitive, support from the community in philanthropic endeavours such as this one is crucial to advance our research projects and work toward healthier brain ageing and better clinical care of age-related diseases such as Alzheimer's and other dementias," said Professor Sachdev

CHeBA currently has five longitudinal studies examining various aspects of cognitive ageing and dementia, including neuroepidemiology, neuropsychology, neuroimaging, genetics/genomics, proteomics, stem cells, metabolomics and neuroinflammation. Recently CHeBA was successful in identifying genetic markers that predict levels of a blood protein marker of cognitive ageing and early dementia. Since the official launch of CHeBA in 2012, there has been a significant increase in collaboration and the development of a number of international partnerships with consortia. The intention at CHeBA is to build upon these resources and develop novel and innovative research themes. A major focus will be on biomarker research using genomics, proteomics and neuroimaging. In addition, promising post-doctoral fellows at CHeBA will give a new impetus to the bench-to-community approach allowing for translation of the research.

Richard Grellman

ARIA Hosted Corporate Lunch

On 4 November 2014, ARIA Restaurant once again generously hosted a corporate lunch to continue CHeBA's connection with the corporate community.

"If dementia were a country it would be the world's 18th largest economy and as a business it would be the largest global enterprise."
PROFESSOR HENRY BRODATY

30 business leaders were invited to hear guest speaker Richard Grellman AM, whose wife Suellen has advanced young onset Alzheimer's disease. Mr Grellman relayed his personal journey and introduced CHeBA's initiative The Dementia Momentum; to be launched in March 2015 and of which he will continue to be Spokesman. Professor Brodaty spoke on the economics of dementia.

Climb for a Cause

On 16 March 2014 CHeBA Champion Stephanie Campbell endured an horrific skydiving accident. Coming in to land on her 57th solo skydive, Stephanie's parachute passed through turbulent air and collapsed high above the ground.

Stephanie Campbell and group at Climb for a Cause

"It shouldn't have to end this way. This isn't going to happen to me. I started to worry about a possible genetic link, so I started to think about what I could do to reduce the risk."
CHEBA CHAMPION STEPHANIE CAMPBELL ON THE DEATH OF HER GRANDMOTHER FROM DEMENTIA.

She fell onto her back at 60km/h and broke nine out of 12 vertebrae in her mid back, six ribs, her right wrist, punctured both lungs, and sustained a severe concussion and swelling in her right eye.

After being airlifted to the PA Hospital by CareFlight Group Queensland paramedics she spent 10 days in the trauma ward recovering from her injuries. Doctors marvelled that she had survived the accident, was not paralysed and could be treated conservatively without surgery. Motivated by a desire to make her recovery count, Stephanie incredibly spent her time developing a fundraising initiative for CHeBA by teaming up with Story Bridge Adventure Climb in Brisbane. Aptly titled Climb for a Cause, this campaign kicked off in July 2014 with support from Queensland's Minister for Health, Hon Lawrence Springborg, who attended the launch of Climb for a Cause week on 13 July.

Public Forums

Better Brain. Better Life Series

CHeBA joined forces with Genworth in an effort to help change the future of ageing through a series of public forums promoting strategies for better brain health.

Speakers at Rockdale forum

"We are delighted to have Genworth on board as platinum sponsor of CHeBA's series of *'Better Brain. Better Life'* forums."
PROFESSOR PERMINDER SACHDEV

PJ Lane

On 24 July 2014, over 600 people packed the John Clancy auditorium at the University of New South Wales to attend the first in a series of four educational public forums to be conducted over 2014 and 2015 entitled '*Better Brain. Better Life*'. More than 200 study participants from CHeBA's three major research projects: the Sydney Memory & Ageing Study, the Older Australian Twins Study and the Sydney Centenarian Study attended to hear the latest outcomes from the research to which they are generously contributing.

The forum was opened by the well-known actor and official Ambassador for CHeBA, PJ Lane, who provided the audience with a personal insight into Alzheimer's which his father, Don Lane, was diagnosed with some years before he passed away. The Mayor of Randwick, Councillor Scott Nash, delivered a supportive community address and confirmed Randwick City Council's commitment to creating a dementia-friendly city and increasing public awareness.

The '*Better Brain. Better Life*' forums are designed to emphasise the modifiable risk factors for Alzheimer's disease and other dementias so that the public are able to adopt strategies to assist in preventing or delaying the onset of age-related cognitive disorders such as dementia.

Collectively, the message of these talks is not only to showcase the wonderment of the brain and the latest research coming out of CHeBA, but also that we have the capacity to improve our brain health.

"With the possibility of Alzheimer's disease and other dementias affecting three million Australians by 2050, increased investment in community campaigns alongside our research is essential to help change the future of ageing." PROFESSOR HENRY BRODATY

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Connecting for Successful Ageing

Five hundred seniors filled the auditorium at The Juniors in Kingsford to discover the benefits of social connection for successful ageing on 12 November 2014.

"Connecting for Successful Ageing" was a joint project of the Aged Care Psychiatry Service, Eastern Suburbs Mental Health Service and CHeBA, which focused on how older people can stay socially connected.

Current research shows that older people who are socially isolated are at greater risk of physical and mental health problems. Socialising and group activities for older people not only prevents loneliness, but positively influences general health and well-being.

Acclaimed social researcher and author Hugh Mackay gave the key note address at the forum.

Human Rights Commission Talk

In a talk to the Australian Human Rights Commission on 19 August 2014, Professor Brodaty called for better recognition of the contribution that older Australians make to society and more opportunities for intergenerational collaboration to help combat ageism. He said the positive contribution of older people to society often remained invisible.

Henry Brodaty

Professor Brodaty also called for a rethink on Gross Domestic Product (GDP) as a measure of Australia's economic health because it failed to capture the positive impact of population ageing on the national economy. He said as a metric, GDP was ageist because it excluded the value of volunteering and household-provided care and services, of which older Australians were big contributors.

> "The common stereotype is that older people are decrepit, they are not functional, they are a drain on our society … but the facts are actually quite different." PROFESSOR HENRY BRODATY

"The common stereotype is that older people are decrepit, they are not functional, they are a drain on our society and they go into nursing homes but the facts are actually quite different," Professor Brodaty told the Sydney audience.

He said the overwhelming majority of older people lived in private dwellings in the community and a significant number of people over 65 were still in paid employment.

"Older Australians are active contributors. Almost half of 65-74-year-olds provide unpaid assistance to someone outside the house. One third are volunteering through organisations, two-thirds are in social or support groups, and one quarter, despite having relatively low incomes, are financially supporting somebody outside their house either a child or a younger relative."

Older people were contributing "big time to our society," he said.

Professor Brodaty said Australia also needed to replace the idea of an intergenerational competition for resources with "cross-generational" resource allocation and greater opportunities for collaboration. He pointed to intergenerational education and community programs that supported a more integrated society as key examples.

Professor Brodaty has visited one of the world's first intergenerational schools in Cleveland, Ohio, which has purposefully included older adults into the design of the school's teaching and learning model to promote the sharing of skills and knowledge between generations. Other innovative programs have connected aged care residents with local preschools for mutual benefit.

Intergenerational competition for resources such as healthcare and jobs was also a false dichotomy and investments were required at both ends of the life spectrum, he said. "We need cross-generation resources to advance the welfare of all of us."

Turning to the attitudes of the medical profession, Professor Brodaty said ageist views in the health system also should be stamped out, especially in the area of mental health where depression can be seen as a natural part of ageing.

He said older people were not a burden on health resources but "core business for health" and the health system could become more efficient by eliminating waste such as unnecessary treatments.

CHeBA Champions

The CHeBA Champion initiative continues to build strongly with outstanding outreach in the media over 2014. We now have CHeBA Champions across NSW, ACT, QLD and SA, as well as our first international Champion who is based in San Francisco.

> "I'm going to do everything I can today, to stave off any chance of getting Alzheimer's. I am passionate about encouraging others to do the same thing."
> KERI KITAY, CHEBA CHAMPION

In 2015 we wish to broaden our scope further and reach Western Australia, the Northern Territory and Tasmania. Many of our CHeBA Champions are now not only participating in fitness events for CHeBA, but are raising awareness through other achievements as well. Some of the key highlights from 2014 include:

- Public school education forums
- CHeBA Champion Nardia Norman published a book on fitness and health with 10% of sales going to CHeBA

We are eager to promote the modifiable risk factors for Alzheimer's disease and other dementias to more young Australians, and to engage a wider number of people in this initiative.

City 2 Surf

Team CHeBA proudly promoted positive ageing in the 2014 City 2 Surf with team members in their 60s, 70s and 80s.

"By improving physical activity by just 5%, as many as 100,000 fewer Australians would develop dementia by 2050."

Our youngest runner was just 14 years of age and Mr Graham Gates, her 84 year old grandfather, completed the course for the second time for CHeBA. Another sensational representative of positive ageing in Team CHeBA was Mr Colin Blake from Coogee. Mr Blake has participated in the previous 40 City 2 Surf events and won a family category with his two sons in the 1990s. 80 year old Derek Nelson from Bronte, who has run every City 2 Surf since the initial event in 1971 was an inspiration to our younger runners and completed the course in under 2 hours. Mr Andrew Tosti, whose mother Maria passed away earlier this year with dementia, demonstrated his commitment to research by joining Team CHeBA and making a donation to the Centre in honour of his mother.

Team CHeBA also included many of our CHeBA Champions - the Fitness Ambassadors for the Centre as well as staff from the official Sponsor of the CHeBA Champions, Intellectual Ventures. Our Co-Directors Professors Brodaty and Sachdev practised what they preach by running the event, as well as Marketing & Communications Officer Heidi Mitchell, CHeBA's Dr Nicola Gates and three generations of the Gates family, Dr Jacqueline Wesson and daughter, and other friends of the Centre and family members.

G20

In 2014 CHeBA launched a petition calling on Prime Minister Tony Abbott to place dementia on the agenda of the Group of Twenty (G20) meeting held in Brisbane on 15-16 November 2014.

"Dementia is a global problem – not just a rich country's problem. This is what we wish to highlight at the G20."
PROFESSOR PERMINDER SACHDEV

The petition was supported by Alzheimer's Australia. Professor Sachdev said that dementia featured prominently at the G8 forum and it was hoped this momentum could be carried forward as its impact on G20 countries like China, India and Brazil was even greater and growing rapidly.

The worldwide costs of dementia will exceed 1 per cent of global GDP in 2010, at US$604 billion. If dementia care were a country, it would be the world's 18th largest economy, he said.

"Reports from individual countries such as the UK suggest that dementia is one of the costliest illnesses – and yet research and investment is at a far lower level than for other major illnesses," said Professor Sachdev. Part of the petition read: "In many parts of the world, research into dementia is non-existent. This, combined with the relative neglect of dementia research in rich countries, has created a major gap between the disability and suffering attributable to dementia and the research investment into its diagnosis, treatment and appropriate care.

"Greater research funding will help develop new treatments, but more importantly, exploit the current knowledge to develop strategies to prevent dementia or delay its onset. The G8 has set ambitious targets. We ask Mr Abbott to take the lead and make it a truly global fight against the dementia time bomb."

The petition received over 12,000 signatures.

CHeBA in the Media

ADI Report - Dementia and risk reduction: An analysis of protective and modifiable factors

Evidence in the report suggests that if we enter old age with better developed, healthier brains we are likely to live longer, happier and more independent lives

Evidence is mounting that simple lifestyle changes such as regular exercise and a healthy diet can delay the onset of Alzheimer's disease, which is the most common form of dementia, said Professors Brodaty and Sachdev.

The CHeBA dementia experts have pointed to the World Alzheimer Report 2014, which calls for dementia to be a public health priority alongside other major non-communicable diseases.

The report, '*Dementia and Risk Reduction: An analysis of protective and modifiable factors*', shows that control of diabetes and high blood pressure, along with measures to encourage people to quit smoking and reduce their cardiovascular risk, have the potential to reduce the risk of dementia, even in late-life.

Global researchers commissioned to compile the report by Alzheimer's Disease International found that diabetes can increase the risk of dementia by 50 per cent. Obesity and lack of physical activity are important risk factors for diabetes and hypertension, and should therefore also be targeted, the researchers said.

Evidence in the report suggests that if we enter old age with better developed, healthier brains we are likely to live longer, happier and more independent lives, with a much reduced chance of developing dementia. Brain health promotion is important across the life span, but particularly in mid-life, as changes in the brain can begin decades before symptoms appear.

Professor Brodaty said evidence is accumulating that it's possible to delay the onset of Alzheimer's disease yet most Australians are unaware there are steps they can take now to achieve this.

"These steps are simple lifestyle choices such as regular exercise, healthy diet, stimulating our brains and attending to our health such as stabilising blood pressure, limiting sugar intake and better managing our cholesterol. It's never too late – or too early - to start such a program to improve not only our brain health but our overall health."

CHeBA is seeking funding to establish a register of people aged 55 to 75 who are interested

in maintaining their brain health. The next step will be a five-year internet-based national dementia prevention trial. This will involve a lifestyle intervention to benefit brain health as well as checks for raised blood pressure and/or cholesterol, diabetes and depression.

The full report can be found at: **www.alz.co.uk/worldreport2014**

Big Ideas: Towards A World Without Dementia

Dementia, characterised by a steady decline in our thinking ability and the eventual loss of our identity, is one of the diseases we fear most.

Despite it costing more than $5 billion a year to the health and aged care system, and registering as the third leading cause of death in Australia, dementia research remains grossly and disproportionately under-funded when compared to medical research for other diseases, such as cancer. Current projections estimate that by the middle of this century almost a million Australians will have dementia and there will be far fewer younger Australians, proportionally, to care for them.

However, a $200 million injection of Australian government funds over five years has raised the profile of dementia research and with it, possibilities for prevention, treatment and cure.

In an episode of Radio National's *Big Ideas aired on 16 October 2014*, Professor Brodaty joined a number of expert panel members discussing the current state of dementia research, preventative measures and care. Although there is currently no cure, Professor Brodaty said there are measures available to slow down progress of the disease.

"Dementia is a slow disease. It doesn't mean a person's life, when they get the diagnosis, changes from one day to the next, unless they let it, and there is much that we can do," explained Professor Brodaty.

"People can have a very positive life, even with a diagnosis of dementia. Many people live with some sort of disability … it might be chronic heart failure. It might be severe asthma. It might be daily injections for diabetes. People live with these conditions and live well and learn to compensate for them," he says.

According to Professor Brodaty, another major focus for dementia research is diagnostic screening. Lumbar punctures to analyse protein profiles of the cerebral spinal fluid have been found to give a 90 per cent accuracy of diagnosis in people with Alzheimer's and possibly even people with pre-Alzheimer's.

"The field is moving now to pre-clinical diagnosis and that's quite a controversial area," he said. "Would you want to know the diagnosis? Because there is currently no treatment that can actually stop the Alzheimer's disease, or any other form of dementia."

The *Big Ideas* panel consisted of Professor Henry Brodaty AO; journalist and President of Alzheimer's Australia Ita Buttrose AO; Professor Kaarin Anstey, Director of the Centre for Research on Ageing, Health and Wellbeing at ANU; Zoe Terpening, a clinical neuropsychologist from The Brain and Mind Research Institute at Sydney University; and Christine Bryden, dementia advocate and writer.

Full audio and video footage can be accessed at: **http://www.abc.net.au/tv/bigideas/stories/2014/10/16/4108449.htm**.

FIGHT ALZHEIMER'S SAVE AUSTRALIA
FIGHTDEMENTIA.ORG.AU

Creating a Dementia Friendly Nation with Alzheimer's Australia

During Dementia Awareness Month throughout September 2014, Alzheimer's Australia, with support of CHeBA, called on the community to join them in Creating a Dementia-Friendly Nation – that is, creating communities where people living with dementia are respected, valued and supported to maintain a good quality of life. Letters to the editor were published across all NSW electorates, calling on community members to better understand dementia, recognise the social isolation often associated with dementia and undertake small actions to make a significant difference to the lives of people living with dementia.

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Donor Support & Partners

Major Donors

The Centre for Healthy Brain Ageing has been able to conduct significant research into the ageing brain with the support of our two major donors, **Thomas Foundation** and **The Montefiore Home**, who have partnered with CHeBA since the launch of the Centre in 2012.

The Thomas Foundation supports CHeBA's research with the objective of providing better assessment and care for people with Alzheimer's disease and other dementias. A number of projects were funded by the Thomas Foundation in 2014, including dance therapy in nursing homes, transcranial direct current stimulation combined with cognitive training and identifying transcriptional markers of the ageing brain.

CHeBA and The Montefiore Home share a mutual goal of improving the quality of life of the older population and Professor Henry Brodaty is the Montefiore Chair of Healthy Brain Ageing. We are enormously grateful to The Montefiore Home, David Freeman AM and his team for the ongoing support and interest in CHeBA's research.

Thomas Foundation

MONTEFIORE

Government & Grant Funding

Australian Government National Health and Medical Research Council NHMRC

Australian Government Australian Research Council

NIH National Institutes of Health

Alzheimer's Australia Dementia Research Foundation

YULGILBAR The Yulgilbar Foundation

The Sachdev Foundation

We thank the following individuals who made generous donations to CHeBA in 2014:

Mrs Sandra di Bella
Mr Peter Bracs
Mr Paul Cave
Mrs Cecily Chittick
Mrs Cherry Cordner
Mrs Dolores Gardiner
Mr Kenneth Griffith
Dr Owen Hellyer
Mrs Catherine Kalokerinos
Mr Ron Myers
Mr Derek Nelson
Dr Ian Paterson
Mr Graeme Pettigrew
Mr Patrick Regan
Mr Thomas Regan
Mrs Clara Robert
Mr John Pravit Tantipech
Mr Johan Theo Van der Velde
Mrs Liz Woolfson

Sponsors & Donations

In 2014, the **Dick Smith Foods Foundation** awarded CHeBA $50,000 as winners of the first round of their $1 million to charity competition.

Story Bridge Adventure Climb partnered with CHeBA Champion Stephanie Campbell to deliver Climb for a Cause where part of the proceeds of all tickets sold went to CHeBA's research.

Intellectual Ventures remained the major sponsor of the CHeBA Champions in 2014.

In 2014, **Genworth** became the platinum sponsor of the series of Better Brain. Better Life public forums and sponsored the development of educational material for distribution at these forums and online.

Avant was the sole sponsor of the 2014 CHeBA hosted Neuropsychiatry Narratives training weekend for psychiatrists, registrars and trainees.

Our Partners

The **Dementia Collaborative Research Centre** based at UNSW is one of three DCRCs funded by the National Health and Medical Research Council. They conduct research to improve the diagnosis, reduce the risk of dementia, and improve the lives of those people living with dementia, their families and carers through over 160 research projects with more being added all the time. Each DCRC has links to other research centres around Australia. The DCRC-ABC is an important component of CHeBA. While it has its own independent management and funding, it contributes to the greater whole and provides important opportunities for collaboration. The Director of the DCRC-ABC, Professor Henry Brodaty, is Co-Director of CHeBA.

The **Neuropsychiatric Institute (NPI)** is a tertiary referral unit that specialises in the diagnosis and treatment of cognitive and psychiatric disorders associated with medical and neurological illnesses. It is unique in Australia in bringing together expertise within Psychiatry, Neurology, Neuropsychology, Neurophysiology and Neurosurgery to bear upon complex diagnostic issues. The NPI offers a number of specialised programs. It is also at the fore-front of research into neuropsychiatric disorders. The Director of NPI, Professor Perminder Sachdev, is Co-Director of CHeBA.

Key Studies

"With rising figures representing an enormous social and economic burden and no available cure, dementia prevention is a critical area for research development."

Professor Henry Brodaty

Key Studies

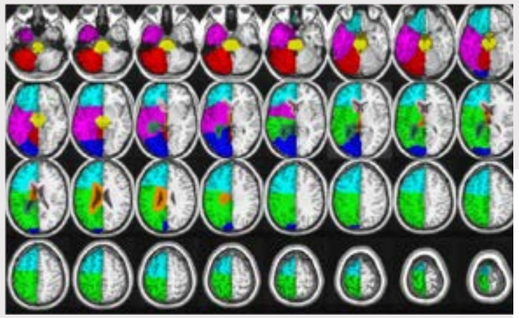
Overview

The composition of Australia's population is projected to change considerably as a result of population ageing. Research is needed to assist the public health system better plan for the future and may assist younger people make better lifestyle choices to improve their quality of life as they grow older. CHeBA runs a number of longitudinal studies which are investigating factors associated with healthy brain ageing and cognitive decline. Our research is intended to inform national health policy and service delivery, as well as brain ageing research and treatment in Australia and internationally.

Sydney Memory & Ageing Study (MAS)

Study Co-ordinator: **Dr Simone Reppermund**

Dr Reppermund is a post-doctoral research fellow at CHeBA and an alumni mentee on CHeBA's Capacity Building Grant program to develop promising junior researchers into international leaders in their field. Her research interests include depression and cognitive function, cognitive impairment, and measures of everyday living activities in old age. She has published many peer-reviewed papers and the importance of her work has been widely recognised and awarded, including by the International College of Geriatric Psychoneuropharmacology.



Overview

The Sydney Memory & Ageing Study (MAS) investigates neurocognitive function and its change over time (cohort age range 70-90 years at baseline). This research enables us to compare normative cognitive ageing with pathological cognitive decline, including Alzheimer's disease, vascular dementia and frontotemporal dementia. Sydney MAS aims to develop and refine measures for early diagnosis and prognosis of brain ageing disorders, examine risk factors and biomarkers (such as blood tests and MRI scans) for cognitive decline, and identify possible protective factors against dementia. We are also interested in identifying and testing novel treatment strategies.

To date, our research has yielded a large amount of data on many aspects of brain ageing and dementia. We have studied a wide range of risk factors for cognitive impairment, including genetic determinants, arterial stiffness, dietary mineral intake, glucose disorders, inflammatory markers and lifestyle factors. The study has been very productive (90 papers published and 66 in preparation or submitted).

MAS aims to develop and refine measures for early diagnosis, examine risk factors and biomarkers for cognitive decline, and identify possible protective factors

MAS is also a participant in a number of international research consortia, including COSMIC, ICC-Dementia, BrainInflame, PROMOTE, CHARGE, ENIGMA, EuroDiscoTWIN and PERADES.

Achievements

- Informant memory complaints were found to be better than participant complaints in predicting cognitive and functional decline in participants as well as diagnosis over time.
- Participants with hippocampal atrophy were found to maintain normal cognitive function by selectively activating the posterior part of their brain when undertaking a memory task. This provides new evidence that the back part of the brain may be important for compensating against degeneration in the hippocampus (the classic memory area).
- Cognitive impairment in participants was found not to be associated with distress in their informants (family/friends). Informants' distress increased only when *they* identified some impairment in the participant.
- Late-life cognitive decline was found to be associated with an increase in neuroticism scores. An increase in neuroticism or negative affect scores may be a sign of MCI or dementia.
- Reduced white matter integrity was found to be associated with late-life depression and predicts future depressive symptoms; whereas a past history of depression is not related to extent of white matter changes. Disruption to white matter integrity may be a biomarker to predict late-life depression. (This paper was selected by UNSW Medicine as paper of the month in September 2014).
- Depressive symptoms and antidepressant use were found to be associated with greater fall risk in older people, independent of reduced executive and physical functioning.
- Dr Reppermund was invited to give a key note talk at the Society for Mental Health Research Conference in Adelaide.
- Several conference presentations were made by the falls group in Sydney and Vancouver reporting on the role of cognition, anxiety and muscle mass on balance and mobility.
- Dr Kochan presented two posters at the Alzheimer's Associated International Conference in Copenhagen, the first presenting neuropsychological normative data based on the MAS sample; the second reporting findings that variability in reaction time at age 70-78 years appears to be a robust marker of mortality risk (independent of biomedical risk).

Older Australian Twins Study (OATS)

Study Co-ordinator: **Dr Jocelyn Bowden**

Dr Jocelyn Bowden has a Bachelor of Human Movement Science, a Bachelor of Science (Honours), and a PhD examining the neurophysiology of ageing and stroke. She has a background in neurological rehabilitation.

"Twins are a great source of determining if traits are genetic or environmental, and we are doing a four-year follow-up to assess how much is due to genes or to lifestyle factors."
PROFESSOR PERMINDER SACHDEV

Overview

The Older Australian Twins Study is one of the largest and most comprehensive ageing studies involving older twins in Australia. It is a multi-centre, longitudinal study that commenced in 2007. Study participants are identical and non-identical twin pairs aged 65 years and older. Participants undergo rigorous medical and cognitive function tests, provide blood samples and have a magnetic resonance imaging (MRI) scan of their brain. Information about environmental factors, such as medical and psychosocial history, lifetime physical and mental activity, and nutrition is also collected. Baseline, two-year and four-year follow-up tests are carried out to measure change. The four-year follow-ups

assessments will be completed by the end of 2015. Data from the first wave of assessments has made significant contributions to understanding the genetic factors underlying aspects of cognition, brain structure and the role of proteins in healthy ageing. Our researchers have examined genetic influences on processing speed, memory, planning and problem solving, as well as the role of mental and physical activity in maintaining a healthy brain. MRI and blood data has contributed to studies examining the heritability of brain structure and function, the role of brain metabolites, and epigenetics to progress research into memory and learning.

Achievements

- 2-year follow-up assessment data (Wave 2) were collated and released in July 2014. 450 participants had Wave 2 assessments, while 403 participants gave blood samples and 292 had MRI scans.
- A study by Masters student Sri Chandana Kanchibhotla and colleagues used OATS brain imaging data to examine the relative influence of genetic and environmental factors on the microstructure of the corpus callosum (published in *PLoS One*, 2014).
- Former Honours and current PhD student Jessica Lazarus and colleagues had an accepted publication in the *Journal of Alzheimer's Disease* on the relationship between DNA methylation and memory performance in the OATS cohort.
- OATS contributed to several projects as part of the international EuroDiscoTWIN consortium. This collaboration examines diabetes and other heritable conditions in twin cohorts. Existing collaborations with the ENIGMA (Enhancing Neuroimaging through Genetic Meta-analysis) and CHARGE (Cohorts for Heart & Ageing Research Genetic Epidemiology) consortia continued throughout the year.

Sydney Centenarian Study (SCS)

> "Centenarians tend to be independent, optimistic, cheerful, busy. They are very adaptive, flexible and resilient."
> DR CHARLENE LEVITAN

Overview

The SCS is studying a cohort of individuals who have successfully reached the extreme end of life (95 years and above) in order to determine the genetic and environmental factors that contribute to successful ageing. We are taking a broad approach to elucidate all factors that may be of interest in investigating this population. The findings will shed light on which factors are particularly important for ageing well, which in turn will allow us to inform lifestyle choices in younger and middle aged Australians. The findings will also inform decisions to improve the quality of life of older Australians, and plan for future older generations. This is particularly important as we have an ageing population which will present a disproportionate burden on the health system unless we are prepared.

Achievements

- 350 participants were recruited into the study and the majority were followed up every 6 months.
- About 55% of people 95 years and above met criteria for dementia. Rates of heart disease and diabetes were lower than in octogenarians, but hearing and visual deficits were common in centenarians.
- Rates of psychological distress were low and satisfaction with life high (mean 5.91 out of a maximum of 7).
- Brain volumes, both of the grey and white matter, continue to decline in the very old, but the pattern of decline is different from that seen in young-old individuals (<85 years). Structural MRI can distinguish amnestic but not non-amnestic MCI in the very old, and the structural correlates of MCI were different in the very old compared to the young-old. White matter lesions are very common and extensive in centenarian brains, but they do not relate to cognitive impairment.
- The SCS is one of the studies in the International Centenarian Consortium for Dementia, which is meeting in Sardinia in June 2015.
- The study is supporting one PhD student and one Honours student.

CHeBA's Research

"With general consensus among researchers that genetic makeup contributes to longevity and health at a rate of only 30 per cent, there is a great deal that we can do to improve our behavioural and lifestyle habits to strive for a better future for ourselves."

Professor Henry Brodaty

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Groups

Epidemiology

Group Leader: **Professor Perminder Sachdev**

Professor Sachdev is the Co-Director of CHeBA and Clinical Director of the Neuropsychiatric Institute at the Prince of Wales Hospital. He occupied the first chair of Neuropsychiatry in Australia, with ground-breaking research across a number of fields. He played a leading role in the development of higher training in neuropsychiatry through his leadership of the International Neuropsychiatric Association, and the Neuropsychiatry Section of the RANZCP. Recently, he has contributed to the diagnosis of dementia as the only Australian member of the Neurocognitive Disorders Workgroup for the DSM-5.

Aims

The Epidemiology Group is interested in studying the patterns, causes and effects of neurocognitive disorders, in particular dementia, in elderly populations in Australia and internationally. The Group analyses longitudinal cohorts from CHeBA's own studies – the Sydney Memory and Ageing Study, the Older Australian Twins Study, the Sydney Centenarian Study and the Sydney Stroke Study – as well as from international studies grouped into consortia, including the CHeBA-led COSMIC, STROKOG and ICC-Dementia. Another important aspect of this work is genetic epidemiology, which uses various approaches including genome-wide association studies and Mendelian randomisation methods to examine risk factors for dementia and other neurocognitive disorders.

Achievements

- We found informant memory complaint questions were better than participant complaints in predicting cognitive and functional decline as well as diagnoses over 4 years.
- One of our studies provided gender- and age-specific distributions for six anthropometric measurements for the elderly that could be used as reference values for the Australian elderly population to identify individuals at a greater risk of disease. The prevalence of obesity and being overweight is common in the elderly population as is metabolic syndrome defined by waist to hip ratio. Arterial stiffness is recognised as a risk factor for heart disease and dementia. One of our studies showed that it also increased the risk of falls in older people.

Genetics & Genomics

Group Leader: **Dr Karen Mather**

Dr Mather is an Alzheimer's Australia Dementia Research Foundation Postdoctoral Fellow. Her major research interest is to gain a better understanding of the genetic and environmental factors involved in human ageing and age-related decline and disease. The genetic factors that may be involved include variation at the nucleotide level, gene-gene and gene-environmental interactions. Candidate gene and genome-wide association approaches are being used to identify novel genetic variants associated with ageing-related measures. Dr Mather has a strong interest in epigenetics, which refers to the factors that can influence gene expression but do not involve changes to the DNA code. Epigenetic processes include DNA methylation, the addition of chemical groups to DNA-associated proteins known as histones and RNAs that do not encode protein. Exciting work is being undertaken in our Group examining DNA methylation and non-coding RNA variation and its relationship to ageing and age-related measures, such as memory performance.

Aims

The Genetics & Genomics Group has grown out of our interest in the genetic and epigenetic factors involved in brain ageing and age-related disease. Heritability studies suggest that there is a genetic component to most age-related traits. To fully understand ageing and age-related disease, we need to better understand how both genetics and environment

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contribute to these processes. Successful grants have enabled us to collect genetic samples in addition to demographic, lifestyle, neuroimaging and health data that facilitates genetic studies investigating brain ageing and age-related disease.

Achievements

- We continue to collaborate on GWAS meta-analyses examining age-related and neuroimaging phenotypes with the international consortia, CHARGE and ENIGMA. This has been a fruitful collaboration with several papers currently under review or accepted.
- Several manuscripts, which use data from our CHeBA cohorts, were submitted or accepted by peer-reviewed journals.
- Dr Mather received a Yulgilbar Foundation Alzheimer's Grant to undertake cutting edge research examining the relationships between long non-coding RNA and an early marker of Alzheimer's disease, age-related memory performance.
- Dr Mather was awarded a Gold Star UNSW Grant for her proposed study (investigating the genetics of white matter hyperintensities) to improve the application for resubmission in 2015.
- During 2014, two of Dr Mather's jointly-supervised students published their research work on epigenetics and cognitive performance in older adults (Lazarus et al., accepted 2014) and the heritability of white matter integrity of the corpus callosum in older adults (Kanchibhotla et al, 2014).
- Media coverage included:
  a. Health and Ageing Australia: 'Researchers shed light on the genetics of memory', **http://www.transformingthenation.com.au/2014/11/researchers-shed-light-genetics-memory**. This article reported on our collaboration with the CHARGE consortium investigating the genetics of memory in a large cohort of ~30,000 participants (Debette et al., Biological Psychiatry). Results from the Sydney Memory and Ageing Study contributed to this paper.
  b. Epibeat: 'The role of epigenetics in cognitive ageing', **http://www.epibeat.com/aging-environment-disease/epigenetics-in-cognitive-ageing/2112/** This article was based on a review published in 2014 (Mather et al., *Int Journal Geriatric Psychiatry*).

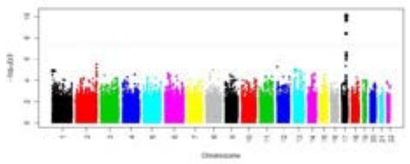
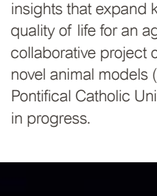


Figure 1. Apolipoprotein H (ApoH) is a circulating protein that carries lipids around the body. Levels of ApoH have been associated with age-related cognitive performance and decline in the Sydney Memory and Ageing Study. This Manhattan plot shows the results of a genome-wide association study using CHeBA cohorts, which identified genetic variants associated with ApoH levels on chromosome 17. The black dots at the top RHS of the graph above the dashed line indicate the identified genetic variants for ApoH levels (p values < 1 x 10^{-8}).

Molecular Biology & Stem Cells

Group Leaders: **Honorary Associate Professor Kuldip Sidhu & Dr Nady Braidy**



Hon. Associate Professor Kuldip Sidhu

Hon. Associate Professor Sidhu is the CEO and Founding Director of Cell Therapeutics Pty Ltd and President of the Society for Brain Mapping and Therapeutics (2013-2014). His research focus is on neural stem cells derived from both embryonic and non-embryonic sources for developing future cell therapies for various neurodegenerative diseases, like Alzheimer's, Parkinson's and other neuronal diseases. His lab was the first to produce two hESC lines, Endeavour (E) 1 & 2, from Australia and have produced over 100 induced pluripotent stem cell clones from Alzheimer's patients for studying disease progression and possible therapeutic applications.

Dr Nady Braidy

Dr Braidy is an NHMRC Early Career Postdoctoral Research Fellow. He is utilising CHeBA biospecimens for understanding the brain and the ageing process. His work is committed to discovering the fundamental causes and possible treatments for age-related neurodegenerative disorders such as Alzheimer's, Parkinson's, and Huntington's diseases, as well as on genetic and metabolic changes that take place as organisms grow old. Working individually and collaboratively across labs and disciplines, his Group is continuing to uncover novel insights that expand knowledge and promise to enhance quality of life for an ageing population. An international collaborative project on developing and validating novel animal models (with Professor Nibaldo Inestrosa, Pontifical Catholic University of Chile, Santiago, Chile) is in progress.

Aims

The Molecular Biology & Stem Cells Group aims to investigate the molecular basis of ageing, with the objective of identifying potential molecular targets to slow the ageing process. It is developing animal models of ageing, including the South American rodent *Octodon degu* which is a possible natural model of Alzheimer's disease. Additionally, cellular models of neurodegenerative diseases are being developed using induced pluripotent stem cells (iPSCs).

Achievements

- Hon. Associate Professor Sidhu received the International Pioneer in Medicine Award at the World Congress of the Society of Brain Mapping and Therapeutics.
- Dr Braidy received the Science and Industry Endowment Fund, Australian Academy of Science Fellowships to attend the 64th Lindau Nobel Laureate Meetings.
- Dr Braidy received the Chilean Postdoctoral Prize and the UNSW School of Medical Sciences Citation Classic prize for a research publication which exceeds 50 citations within 5 consecutive years, for his work on "Age Related Changes in NAD^+ Metabolism Oxidative Stress and Sirt1 Activity in Wistar Rats", published in the journal *PLoS One*.
- Altered metabolism of the essential pyridine nucleotide nicotinamide adenine dinucleotide (NAD^+) in the ageing brain was found to provide the hypothesis for neurobiological mechanisms mediating the behavioural, cognitive and neurophysiological changes associated with the ageing process.
- Our work further identifies the NAD^+ glycohydrolase CD38, as a novel and potentially effective therapeutic target for oxidative stress mediated CNS disorders and Alzheimer's disease.
- Our characterisation of the differential expression of a new class of NAD+ dependent enzyme, known as sirtuins, provides additional evidence for the role of sirtuins in regulating brain function at different stages of development. It also identifies the potential for pharmacologically targeting specific sirtuins to establish cell-specific effects within the brain.
- We are the first to demonstrate neuron-to-neuron transmission of alpha-synuclein in enteric neurons, providing renewed evidence for the Braak's hypothesis that Parkinson's disease may initiate in the enteric nervous system before alpha-synuclein aggregates accumulate in the brain.
- Our current work seeks to identify 'natural' models to elucidate the neurobiological basis of AD, and develop effective therapeutic strategies that can be translated into human clinical trials. Collaborative work with Professor Nibaldo Inestrosa (Pontifical Catholic University, Santiago, Chile) has demonstrated that the rodent, *Octodon degus* develops Aβ deposits, neurofibrillary tangles (NFTs) containing hyperphosphorylated tau protein, altered cholinergic transmission and cognitive deficits analogous to those observed in AD. Natural animal models better represent the full pathophysiology of AD and are not only a viable alternative to transgenic models, but are arguably the preferable model.
- Induced pluripotent stem cells we derived and characterised from individuals with Alzheimer's and Parkinson's were distributed under MTA to other institutes (University of Wollongong and Genea Pty Ltd) for research and development purposes.

"Ageing in a dish"

One of the biggest challenges in Alzheimer's research is finding appropriate human cell models for understanding the progression of the disease.

Hon. Associate Professor Sidhu, Co-Leader of the Molecular Biology & Stem Cells Group, is a pioneer in the field of patient-derived stem cells (known as induced pluripotent stem cells or iPSCs), which allow a brain disease process to be modelled in a petri dish. Hon. Associate Professor Sidhu has previously developed a number of lines of iPSCs in the CHeBA Stem Cell Laboratory, which have been used widely for research & development in university and commercial institutes. He is currently collaborating on two NHMRC grants administered by the University of Wollongong, using iPSCs to better understand the processes involved in Alzheimer's disease

Complex changes in the membrane: Lipid dyshomeostasis in Alzheimer's disease cells

More than 30 million people world-wide suffer from sporadic (late-onset) Alzheimer's disease (AD), yet the central question of what drives the cellular changes that lead to the disease remains unanswered. Using iPSCs from the skin of sporadic AD patients, we are now able to model patient cell 'ageing in a dish' and by carefully controlling the environment in which the cells grow and

develop, we can study how the genetic make-up of sporadic AD patient cells leads to differences in neuronal function and survivability compared to cells from non-sufferers of the disease. Using this approach we have found that neurons from AD patients show increased markers of ageing and increased neuronal excitability that lead to increased cell death. One of the important aspects of this cellular model is that we can monitor molecular changes in the cells step-by-step to build up a chronological picture of pathological events. Consequently, the model can now be used to understand how individual components of the system contribute to disease. Using state-of-the-art techniques we have determined that AD post-mortem tissue shows profound changes in lipid species, including reductions in polyunsaturated fatty acids, particularly phosphatidylethanolamine. Importantly, we have identified similar changes in these lipid species in our cellular model of sporadic AD. These changes presented early in development, suggesting that lipid alterations may be an early pathological event.

Isoform-dependent ApoE processing by human induced pluripotent stem cells (iPSCs). A novel approach linking ApoE genotype and Alzheimer's disease risk

Apolipoprotein-E (ApoE) genotype is the single most important risk factor for late-onset Alzheimer's disease (AD). Although there are several postulated pathways by which ApoE may affect neurobiology, the exact pathways by which different ApoE isoforms influence AD remain unknown. We previously reported that ApoE is proteolytically cleaved in the human brain in an ApoE isoform-dependent manner. Moreover, we showed that proteolytic processing of ApoE generates a stable ~25 kDa fragment (referred to from here on as "ApoE25") that is present at lower levels (i.e. 50% reduced) in brain tissue from *ApoE4* as compared to *ApoE3* subjects. We have recently discovered that cell culture medium from human iPSC-derived neurons contains ApoE fragments that appear by western blotting to be identical to those we have previously detected in the brain. This project will be the first to identify the pathway leading to ApoE25 generation in an *in vitro* humanised system. Moreover, it will be the first to provide direct evidence for a biological/neuroprotective role for ApoE25 and thereby potentially reveal a new therapeutic target for AD. Given that several independent laboratories around the world have detected ApoE25 in the human brain, the novel data resulting from this project would represent a major advance for the AD field.

Neuroimaging

Group Leader: **Associate Professor Wei Wen**

Associate Professor Wen is the director of the NeuroImaging Laboratory (NiL) at CHeBA. The NiL is an important and successful component of CHeBA, hosting several research students and visiting fellows. Associate Professor Wen's main research interest is neuroimaging with a focus on brain ageing, including structural and functional neuroimaging, brain network analysis and imaging genetics.

Aims

The Neuroimaging Group is dedicated to researching the ageing of the human brain. By studying structural and functional magnetic resonance imaging and other neuroimaging modalities, we aim to improve understanding of brain ageing pathways, which in turn will lead to clinical advances in prediction, diagnosis and treatment. Our neuroimaging studies address normal ageing, mild cognitive impairment (MCI) and dementia.

Achievements

- Associate Professor Pierre Lafaye de Micheaux, from the Department of Mathematics and Statistics, Université de Montréal, Canada was a visiting fellow in our Lab (July 2013 – June 2014). Together, we investigated heritability and genetic influence of brain structures in older individuals using OATS data. We mapped heritability for both cortex and subcortical structures, including extracting three dimensional surface information for subcortical structures for the first time. Our study demonstrates a complex but patterned genetic architecture of the older human brain. An understanding of this pattern will assist in the refinement of phenotypes for the discovery of the genetic blueprint of the human brain.
- We continue to collaborate on several neuroimaging genome-wide association studies examining age-related neuroimaging phenotypes with the international consortia ENIGMA. This has been a fruitful collaboration with one article ("Common genetic variants influence human subcortical brain structures") recently published in *Nature*, and several manuscripts currently under review.
- We commenced a series of studies to investigate the relationship between the blood level of MIC-1/GDF15 and brain grey matter and white matter, in both cross-sectional and longitudinal settings.
- Our recent work which investigated the network organisation of the healthy elderly connectome has been accepted by *NeuroImage*, a prestigious journal in the neuroimaging community. Our findings provide insights into healthy brain ageing and provide a benchmark for the study of neurodegenerative disorders.
- A stream of high quality publications have emanated from the Neuroimaging Group in 2014.

Neuroinflammation

Group Leader: **Professor Julian Trollor**

Professor Trollor is a Neuropsychiatrist and holds the inaugural Chair of Intellectual Disability Mental Health at the University of New South Wales (UNSW). He also heads the Department of Developmental Disability Neuropsychiatry within the School of Psychiatry at UNSW. He is involved in diverse research programs including ageing and cognitive decline in intellectual disability, intellectual disability in the criminal justice system, human rights and healthcare in intellectual disability, and ageing studies in the general population. At CHeBA, he studies brain imaging correlates of cognitive syndromes in late life, the effects of cardiometabolic and inflammatory factors in brain ageing and cognitive syndromes in special populations, such as people with intellectual disabilities.

Aims

Metabolic and inflammatory factors have recently been proposed as key risk factors in cognitive ageing and age-related brain disorders, such as the dementias. The Neuroinflammation Group is aiming to evaluate the influence of these factors on brain ageing and the modulating effects of genetic susceptibility, physical health, lifestyle and nutrition.

Achievements

- We showed that high pulse wave velocity (a measure of arterial stiffness) was an independent risk factor for falls in community-dwelling older people.
- Our systematic review revealed an association between arterial stiffness, cerebral small vessel disease and decreased cognitive function. Key methodological limitations were identified to improve future studies.
- In a community-dwelling elder sample, we showed that overweight individuals had higher global cognitive function and executive function scores than normal-weight individuals.
- We showed that community dwelling older people with new onset diabetes or impaired fasting glucose had a greater decline in cognitive function compared to people with normal glucose regulation, suggesting that preventing deterioration in glucose metabolism in the elderly may help preserve brain structure and function.

Neuropsychiatry

Group Leader: **Professor Perminder Sachdev**

Aims

CHeBA Neuropsychiatry is a collaborative group composed of staff from CHeBA and the Neuropsychiatric Institute (NPI) at the Prince of Wales Hospital, Sydney. The NPI is a tertiary referral unit that specialises in the diagnosis and treatment of cognitive and psychiatric disorders associated with medical and neurological illnesses. It is unique in Australia in bringing together expertise within Psychiatry, Neurology, Neuropsychology, Neurophysiology and Neurosurgery to bear upon complex diagnostic issues. The Neuropsychiatry Group is at the forefront of diagnostic research into neuropsychiatric disorders, in particular dementia, stroke and Parkinson's disease, and the use of brain stimulation for treatment. The Group also provides important education services for clinicians and trainees, including hosting an annual Neuropsychiatry Training Weekend.

Achievements

- The NPI continues to be a leading tertiary centre for the assessment and management of complex neuropsychiatric cases, as well as being at the forefront of training in Neuropsychiatry. NPI staff are helping to develop the neuropsychiatry training curriculum for the RANZCP.
- Dr Rowan Keighran, a Neuropsychiatry Fellow, completed one year of his fellowship and obtained a position at Newcastle Hospital.
- A new Neuropsychiatry Fellow (Dr Lauren Taylor) was appointed.
- Two new research projects (epilepsy and drug-induced movement disorders) were started.

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Neuropsychiatry Training Weekend: Key Developments in Neuropsychiatry

CHeBA and the Neuropsychiatric Institute co-hosted the inaugural Neuropsychiatry Training Weekend on 14-15 March 2014. The event was a great success with the majority of participants reporting a rewarding professional development experience.

The neuropsychiatric approach has become increasingly relevant in recent years to general psychiatrists, psychiatric trainees, neurologists and neuroscientists alike, and this weekend was packed with lectures aiming to provide a foundation of relevant knowledge. Participants were given access to key readings from each of the speakers; all opinion-leaders in their respective areas of practice and research, allowing them to build on the content delivered in the weekend in their own time.

The program opened with an afternoon introducing key topics in the basic sciences with lectures in neurochemistry, neurogenetics and neuroanatomy, all presented in an expert manner by speakers comfortable in the translational potential of their fields. Many attendees were heard to comment on their surprise at hearing non-clinical subject matter dealt with in such an engaging and contemporary manner. The final workshop on neuroimaging provided a wonderful segue into the next days' clinically focussed content.

Day two brought with it engaging, cutting-edge lectures that aimed to familiarise attendees with key developments in neurotherapeutics, with a specific focus on the emerging field of brain stimulation therapies. An interactive workshop on drug-induced movement disorders covered issues relevant to all specialist care providers in attendance, building on and updating core clinical skills in this area. The final module of the weekend was in many ways the highlight providing state of the art overviews in movement disorders such as Parkinson's and Huntington's diseases, epilepsy and intellectual disability neuropsychiatry, all presented by practitioners with a wealth of clinical knowledge and academic expertise, covering their respective topics with aplomb.

All in all, this was a weekend not to be missed, with an emphasis on the delivery of contemporary teaching in neuropsychiatry, such educational weekends being few and far between.

Speakers at the 2014 Neuropsychiatry Training Weekend were Professor Sachdev, Professor Iain McGregor, Dr Karen Mather, Associate Professor Pascal Carrive, Professor Colleen Loo, Dr Adith Mohan, Dr Paul Silberstein, Dr Clement Loy, Associate Professor Ernest Somerville and Professor Julian Trollor.

Neuropsychology

Group Leaders: **Dr Nicole Kochan & Dr Teresa Lee**

Dr Nicole Kochan

Dr Kochan is an NHMRC Early Career Research Fellow at CHeBA. She has primary responsibility for the neuropsychology arm of the Sydney Memory and Ageing Study and is a chief investigator of the Sydney Centenarian Study. She concurrently works as a Clinical Neuropsychologist at the Neuropsychiatric Institute, Prince of Wales Hospital. Her major interest is improving the clinical diagnosis of mild neurocognitive disorders in the elderly using neuropsychological assessment. In her PhD work, she developed a "memory stress test" for use with functional MRI scans to identify older adults at increased risk of developing dementia. Her current research is focused on early identification of Alzheimer's disease and other dementias through the development of sensitive cognitive measures, including computerised tests and the establishment of Australian neuropsychological normative data. Another research focus addresses the challenge of diagnosing cognitive impairment in individuals from cultural and linguistic diverse minorities (CALD) by examining specific cultural, linguistic and educational factors that may influence cognitive performance.

Dr Teresa Lee

Dr Lee is a Research Fellow at CHeBA, a Conjoint Senior Lecturer in the School of Psychiatry, UNSW, an Honorary Associate in Psychology, and a Senior Clinical Neuropsychologist at the Neuropsychiatric Institute, Prince of Wales Hospital, where she has practised as a clinician for 25 years. She has been a Chief Investigator of the Older Australian Twins Study (OATS) since its inception in 2007. Her role in OATS includes overseeing the cognitive assessments, data collection and management, and conducting research into the genetic and environmental influences in the neuropsychological functioning in old adults. In addition to conducting neuropsychological assessment, she supervises other clinical psychologists in cognitive assessment, as well as teaching students and registrars in psychiatry. She is a member of the Australian Psychological Society, and holds endorsement in two (Clinical Neuropsychology and Clinical Psychology) areas of clinical practice.

Aims

Our research aims to advance scientific knowledge in relation to the cognitive changes occurring in the brain in normal ageing, mild neurocognitive syndromes and dementia, using neuropsychological methods. We have established strong collaborative links with other researchers in CHeBA, and are actively involved in research investigating the associations between memory and other areas of cognition with brain structure, genetics, bilingualism, medical comorbidities, inflammatory markers and falls in the older adult population. We have collected extensive neuropsychological data from three large cohorts of older adults – The Memory and Ageing Study, The Sydney Centenarian Study and The Older Australian Twin Study. More than 2000 subjects ranging in age from 65 to 100+ have undergone longitudinal assessments using a large number of well-validated psychometric measures. These unique datasets will be used to create much needed normative data for older adults which will be extremely valuable in clinical and research settings by enhancing diagnostic accuracy of mild neurocognitive disorders and dementia. We have developed our own in-house computerised test battery called 'Sensus' which is being validated as a brief cognitive assessment tool. Sensus includes Simple and Complex Reaction Time tests, the well-known Stroop Test with an additional set-shifting trial, and a visuospatial associative memory test. Sensus can be self-administered with minimal supervision required. Scoring is automatic for most tests and the test data are generated by computer software.

Achievements

- In 2014, Dr Kochan co-authored 12 publications including a topic review in *Current Psychiatry Reports* with Dr Nicola Gates evaluating the status of computerised and on-line testing for late-life neurocognitive disorders. She has presented her research work on normative data and computerised measures at the Alzheimer's Association International Conference in Copenhagen.
- Together with the Genetics and Genomics Group, we have collaborated with the CHARGE consortium and produced a number of publications reporting important genome-wide association findings in relation to cognitive ageing based on multiple international cohort studies.
- Professor David Bunce who holds the Leadership Chair in Cognitive Psychology at Leeds University UK made a 2-week visit in February to work with Dr Kochan other members of the Sydney Memory and Ageing Study. They developed a collaborative research program with the principal focus being

to examine response time variability gathered from computerised reaction time tasks and its association with future development of dementia, structural brain changes and mortality. Their first publication together is currently under review.

- A review paper: "The contributions of twin studies to the understanding of brain ageing and neurocognitive disorders" (Lee & Sachdev, 2014) was published in *Current Opinions in Psychiatry*, which includes a review of neuropsychological and neuroimaging findings of OATS.
- Publications using the OATS cognitive data included: "DNA methylation in the Apolipoprotein-A1 gene is associated with episodic memory performance in healthy older individuals", *Journal of Alzheimer's Disease* (Lazarus, Mather, Armstrong et al. 2014) and "Genetic contributions to variation in general cognitive function: a meta-analysis of genome wide association studies in the CHARGE Consortium" (N = 53 949), *Molecular Psychiatry* (Deary, Davies, & Armstrong et al. 2014).
- Analyses of cognitive data have been submitted to the consortium CHARGE, focusing on verbal learning and memory.
- As OATS is currently conducting their second follow-up (Wave 3) assessments, plans have been made to computerise the questionnaires and to provide on-line assessments for newly recruited participants. Data from neuropsychological assessments collected at Wave 2 are being prepared for release, and this will enable longitudinal studies to be conducted. More work has been planned on investigating the genetic and environmental influences on other cognitive functions, such as language/verbal abilities. We also await progress from various investigators who have requested cognitive phenotypes from OATS, including episodic verbal and visual episodic memory.

Proteomics

Group Leader: **Dr Anne Poljak**

Dr Poljak is a senior research scientist in the Bioanalytical Mass Spectometry Facility (BMSF), a post-doctoral fellow in the School of Psychiatry, and lecturer (conjoint) Faculty of Medicine UNSW, where her group is involved with qualitative and quantitative mass spectrometry of proteins, peptides and their post-translational modifications. Over the last 10 years, Dr Poljak has engaged in full time research with a neurochemistry focus. Her work on the chemistry of nervous system diseases has included (1) aetiology of the Alzheimer's brain and delirium, (2) plasma biomarkers for ageing and age related conditions including mild cognitive impairment (MCI), dementia and delirium, (3) characterisation of peptides in pheochromocytoma, (4) the role of oxidative stress in amyotrophic lateral sclerosis. Her published work includes more than 60 research papers in international peer reviewed journals, having in excess of 1700 citations (Scopus H index 21).

Aims

The Proteomics Group is a collaborative group composed of staff and students from CHeBA, the Neuropsychiatric Institute (NPI) and the MW Analytical Centre Bioanalytical Mass Spectrometry Facility (BMSF) at UNSW. The Group was formed to apply state-of-the-art analytical techniques to the advancement of biomarker and pathophysiology research in the areas of normal ageing, mild cognitive impairment (MCI), Alzheimer's disease and other age-related neurodegenerative conditions. While proteomics is a major focus area, the Group utilises a broad spectrum of technologies and scientific approaches, including NMR, electron microscopy, confocal and fluorescence microscopy, FTIR spectroscopic imaging, LA-ICPMS mass spectrometric imaging as well as lipidomics and metabolomics techniques.

Achievements

- We received funding from several granting bodies, including the Sachdev Foundation for work on the topic of "Normal brain ageing, Alzheimer's disease and the role of plasma in pathology and biomarker discovery"; UNSW Faculty of Medicine, Major Research Equipment & Infrastructure Scheme for "Improved accessibility and long-term storage of biospecimens from the Centre for Healthy Brain Ageing's (CHeBA) longitudinal cohorts"; and Rebecca L. Cooper Medical Research Foundation funding for work on "Apolipoprotein levels and post-translational modifications as blood biomarkers for early stages of Alzheimer's disease".
- Dr Julia Müenchhoff received the Best Poster Prize award at the MW Analytical Centre Outreach Symposium held at UNSW on 24th October for her work on the topic of "iTRAQ-based plasma protein profiling of mild cognitive impairment across two independent cohorts".
- We have collectively published in excess of 40 papers in international scientific journals and delivered oral and poster presentations at a number of national and international conferences. Some key publications include work by: Dr Braidy on Mapping NAD^+ metabolism in the brain of ageing Wistar rats: potential targets for influencing brain senescence" published in the journal *Biogerontology*; Dr Müenchhoff on "Plasma protein profiling of mild cognitive impairment and Alzheimer's disease across two independent cohorts" published in the *Journal of Alzheimer's Disease*; Dr Fei Song on "Plasma protein profiling of mild cognitive impairment and Alzheimer's disease using iTRAQ quantitative proteomics" published in the journal *Proteome Science*; Tharusha Jayasena's PhD candidacy work on "Upregulation of glycolysis pathway enzymes and increased cytotoxicity in glial cells treated with Alzheimer's disease plasma" has been accepted for publication in *PLoS One*; and Dr Poljak's work on "Quantitative proteomics of delirium CSF" published in *Translational Psychiatry*.

Consortia

International research consortia provide opportunities for researchers to share and compare data from existing studies, allowing systematic examination of brain ageing issues on a larger scale.

"Research is an international enterprise and dementia affects all communities. The future of dementia research is in being able to bring the scores of international studies together for a common purpose."
PROFESSOR PERMINDER SACHDEV

Researchers at CHeBA are studying the process of human ageing to determine the factors that influence the trajectory of healthy ageing and cause age-related diseases, including dementia. At CHeBA, we are taking this line of investigation to the next level by making it international. Many research groups from around the world have asked similar questions and established cohorts in their local area. Since dementia and ageing are universal concerns, CHeBA researchers seek to harness the power of these international studies by bringing them into large consortia. These consortia not only provide large sample sizes necessary to address some of the questions, they also provide the ability to replicate the findings of one study in another in a different geographical and ethnic group, and also determine which risk and protective factors are truly universal.

CHeBA leads a number of international consortia: COSMIC, ICC-Dementia, BrainInflame, STROKOG and PROMOTE. Additionally, CHeBA is a member of the following consortia: CHARGE (Cohorts for Heart and Ageing Research in Genetic Epidemiology), ENIGMA (Enhancing Neuro Imaging Genetics through Meta-Analysis), PERADES (Defining Genetic, Polygenic and Environmental Risk for Alzheimer's disease) and EuroDiscoTWIN (European Discordant Twin Study).

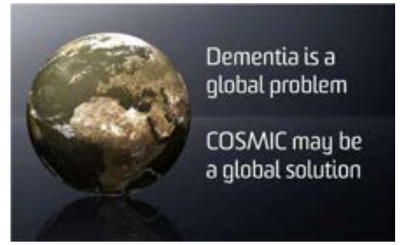
BrainInflame

Overview

Founded in January 2013, the BrainInflame during Ageing Consortium is the first of its kind to focus on inflammation related to brain function and aims to attract international participation to further research understanding. Ageing is associated with enhanced systemic and brain inflammation, which may be linked to vascular damage, metabolic derangement and neuronal dysfunction, resulting in cognitive decline and depression. The study of risk and protective factors for inflammation, and the underlying molecular and neuronal mechanisms in relation to brain health, is an important objective of neuroscience research internationally. BrainInflame's research strategy entails both human and animal research, applying a forward and backward translation process. Current members of BrainInflame include the University of Adelaide, the University of Melbourne, the Queensland Brain Institute, the University of Groningen (The Netherlands), the University of Marburg (Germany) and the Royal College of Surgeons in Ireland.

The objectives of BrainInflame are:

1. To examine the relationship between systemic and inflammatory markers and brain dysfunction (cognitive impairment, cognitive decline and depression).
2. To examine the genetic basis of inflammatory markers and brain dysfunction.
3. To identify new inflammation-related genes and protein markers associated with neuropsychiatric disorders.
4. To relate systemic inflammatory markers with changes in grey and white matter.
5. To analyse gene expression profiles of inflammatory genes over time and relate to the development of brain dysfunction.
6. To pool and harmonise larger-scale studies for further systematic examination.
7. To conduct meta-analyses.



COSMIC

Overview

Established in 2012, COSMIC (Cohort Studies of Memory in an International Consortium) aims to bring together cohort studies of cognitive ageing internationally in order to facilitate a better understanding of the determinants of cognitive ageing and neurocognitive disorders. The two main objectives are to:

1. Harmonise shared, non-identifiable data from cohort studies that longitudinally examine change in cognitive function and the development of dementia in older individuals (60+ years).
2. Perform joint or mega-analyses using combined, harmonised data sets that yield collated results with enhanced statistical power, in addition to comparisons across geographical regions.

The geographical regions and countries represented by the member studies include: Asia (China, Hong Kong, Japan, Korea, Singapore), Australia, Europe (France, Greece, Italy, Spain, The Netherlands, UK), North America (Canada, USA), and South America (Brazil).

Progress

1. Our first project, "The prevalence of mild cognitive impairment in diverse geographical and ethnocultural regions: the COSMIC collaboration", was completed in mid 2014, and a revised manuscript submitted to *Alzheimer's & Dementia* in December. The project applied uniform criteria to harmonised data from 11

studies from USA, Europe, Asia and Australia, and determined prevalence estimates for mild cognitive impairment. Compared to previously published estimates, this approach resulted in far less variation in the prevalence of mild cognitive impairment internationally. The overall prevalence was around 6% and increased with age, though did not differ between the sexes or main races/ethnicities represented (whites and Chinese). Not completing high school increased the likelihood of mild cognitive impairment, and the non-amnestic subtype was more prevalent than the amnestic subtype.

2. A poster detailing the first project was presented at the Alzheimer's Association International Conference 2014 in Copenhagen, Denmark: Sachdev et al. Prevalence of mild cognitive impairment (MCI) in diverse ethno-cultural and geographical regions internationally: the COSMIC collaboration. *Alzheimer's & Dementia* 2014;10(Supp. 4): P582.
3. A proposal for the second COSMIC project was developed by the Sydney team and accepted by the Scientific Steering Committee. This project aims to compare neuropsychological test performance across different cohorts, and to investigate cognitive decline and its associated risk and protective factors. At least 16 studies have provided or promised to provide data for this project, including a number of the original member studies who did not contribute to the first project, and studies newly recruited in 2014.
4. A number of new studies were recruited in 2014, increasing the range of ethnocultural and geographical regions represented by COSMIC members:
   - São Paulo Ageing & Health Study (Brazil)
   - Hellenic Longitudinal Investigation of Aging and Diet (Greece)
   - Sasaguri Genkimon Study (Japan)
   - Bambui Cohort Study of Ageing (Brazil)
   - Hisayama Study (Japan)
   - Maastricht Ageing Study (The Netherlands).

A number of further studies have expressed interest in joining COSMIC and are currently under negotiation. Their membership would extend the range of ethnocultural and geographic regions even further to include India, Indonesia, Malaysia, Mexico and Nigeria.

ICC-Dementia

Overview

Formulated in 2012, ICC-Dementia (International Consortium of Centenarian studies – Dementia) is a dementia work group of the International Consortium of Centenarian (ICC) studies brought together to apply standard diagnostic criteria for dementia to centenarian cohorts around the world. The group will combine data from population-based, longitudinal cohort studies to identify common risk and protective factors and biomarkers for dementia (in particular Alzheimer's disease (AD) and vascular dementia (VaD)), mild cognitive impairment (MCI), age-related cognitive decline and geriatric depression. The group hopes to find factors that predict successful brain ageing into the 11th decade of life that are robust across cohorts. This will spearhead an international effort to promote successful brain ageing. Currently, ICC-Dementia includes studies from Australia, Japan, South Korea, Germany, Sweden, Sardinia, Italy, Denmark and USA.

Progress

1. A paper describing the methodology is in preparation and will be submitted shortly.
2. The next meeting of the ICC will occur in Sardinia, Italy, in June 2015. Preliminary work from ICC-Dementia will be presented at that meeting.

PROMOTE

Overview

Founded in 2013, PROMOTE stands for Psychosocial Research Consortium to advance mental health of older people in the Asia Pacific region. It is co-led by Professor Brodaty (CHeBA) and Associate Professor Yun-Hee Jeon at the University of Sydney.

Psychosocial research is an umbrella term that covers causes and risk factors, mediating factors and contexts and outcomes. In psychogeriatrics it applies to mental disorders and behaviours occurring in older people, to their family carers, to professional carers, to systems of care, and to interactions with the environment. Approaches to psychosocial research derive from diverse sociological, psychological and social epidemiological paradigms, and from different theoretical frameworks.

Often the poor cousin to biological and clinical research, psychosocial research struggles to gain publication in high ranking journals, compete for research grants or to gain academic kudos. Yet many major advances in psychogeriatrics have been psychosocial and these have led to improvements in quality of life for older people with mental disorders and their families and cost savings for the community.

Despite their rapidly ageing populations and the projections that Asia-Pacific countries will account for half the world's older population with mental disorders within a generation, psychosocial research is poorly developed in this region. Furthermore, as local research conducted in many of the countries in the region is often published in their own language little is known about their research outside their countries. By bringing together prominent investigators from six Asia-Pacific countries to describe local psychosocial research initiatives in psychogeriatrics, PROMOTE proposes to lay the foundations for the establishment of a regional consortium to advance psychosocial research and to enable collaboration, joint research programs, mentoring, training and dissemination of findings, and to facilitate cross-cultural knowledge translation.

Progress

A study of the quality of care is being undertaken in Hong Kong, Korea, China and Australia using quality indicators developed by EURODEM, a European consortium on which PROMOTE is modelled. It is becoming clear that these indicators do not apply well in the Asia-Pacific region. Discussions are in progress with potential collaborators from Singapore, Thailand and Indonesia.

STROKOG

Overview

STROKOG (consortium of longitudinal studies of cognitive disorders following stroke/ TIA/ small vessel disease) was developed under the auspices of VASCOG (Society for the Study of Vascular Cognitive and Behavioural Disorders) in 2014 to bring together international studies that have examined post-stroke or other high vascular risk cohorts longitudinally, with cognitive decline and dementia (including sub-types) as primary outcome variables. The included studies (N=22; total sample >9000; 15 countries) have rich neuropsychological and MRI data, and some recent studies have included amyloid imaging in sub-samples. A number of studies have CSF and/or plasma available for biomarker studies, and participant enrolment in brain banks for neuropathology. It is the first international effort to harmonise work on post-stroke dementia and is being led by CHeBA researchers. Currently, STROKOG includes studies from Australia, China, Finland, France, Germany, Hong Kong, Korea, Nigeria, Poland, Singapore, South Africa, Sweden, The Netherlands, UK and USA.

Progress

1. STROKOG has been welcomed by vascular cognitive disorders researchers.
2. So far, 22 studies, representing all continents, have joined the consortium with a total sample size of more than 9000.
3. A meeting of STROKOG has been arranged for September 2015 in Tokyo as part of the biannual VASCOG meeting.
4. A method paper is currently being prepared for publication.

CHeBA Brain Donation Program

Dr Kristan Kang, Data Manager, is the co-ordinator of the Brain Donation Program.

Overview

The CHeBA Brain Donation Program collaborates with a number of other brain bank networks, including the Sydney Brain Bank, the Victorian Brain Bank Network, the Queensland Brain Bank and the Australian Brain Bank Network.

Progress

1. In 2014, 4 new brains were donated to the CHeBA Brain Donation Program.
2. 10 additional research participants have signed up to donate to the program.

The CHeBA Brain Donation Program collects brain tissue from donors sourced from the Memory & Ageing Study (MAS), Older Australian Twins Study (OATS), and the Sydney Centenarian Study (SCS). As all our donors have participated in our longitudinal research, CHeBA possesses rich and extensive pre-mortem clinical, behavioural, and biomarker data on its donors. This allows a unique opportunity to analyse post-mortem brain tissue and neuropathology relative to pre-mortem health, and the possibility of studying the neural pathology and outcomes of normal ageing and dementia at the microscopic level. Our research participants range from healthy 'controls' to those with mild cognitive impairment and dementia, as well as including rare phenotypes such as the extreme-elderly (95+ years) and twins. This allows for the opportunity to do detailed research into multiple aspects of ageing including healthy ageing, dementia and cognitive decline, as well as the role of genetics in ageing.

Current Projects 2014

Abeta (Aβ) peptides in plasma

CHeBA staff: Anne Poljak, John Crawford, Henry Brodaty, Melissa Slavin (conjoint), Nicole Kochan, Julian Trollor, Wei Wen, Karen Mather, Perminder Sachdev

Other investigators: Associate Professor George Smyth (SOMS, UNSW), Dr Amelia Assareh (University of New England, formerly CHeBA), Ms PC Ng (formerly Brain & Ageing Research Program)

Project description: Correlation of plasma Aβ with cognition and brain volumetrics in mild cognitive impairment (MCI).

Aims:

- Determine if plasma Aβ peptides 1-40 and 1-42 may be potential peripheral markers to assist in diagnosis of MCI and/or Alzheimer's disease (AD).
- Explore the possibility that plasma Aβ peptide levels are correlated with brain volumetric and cognitive changes.

Design & method: Cross-sectional design using W1 MAS data and ELISA assays to quantify plasma levels of Aβ peptides 1-40 and 1-42.

Progress to date: Manuscript titled "The relationship between plasma Aβ levels, cognitive function and brain volumetrics: Sydney Memory and Ageing Study" is currently under review with *Current Alzheimer Research*.

Benefits:

- Potential biomarkers to assist in diagnosis of predisposition to MCI and/or AD.
- Explore the possibility that plasma Aβ peptide levels are correlated with brain volumetric and cognitive changes.

Outputs: 5 conference presentations, 4 invited oral presentations, 2 publications, 1 manuscript in review.

Funding: NHMRC, ARC, Rebecca L. Cooper Medical Research Foundation, Alzheimer's Australia Rosemary Foundation.

Date commenced: 2007

Expected date of completion: Ongoing

Analysis of DNA methylation variation in the *apolipoprotein-A1* gene and its relationship with episodic memory performance in older adults

CHeBA Staff: Karen Mather, Anne Poljak, Perminder Sachdev, Anbupalam Thalamuthu, Teresa Lee, Nicole Kochan, Jessica Lazarus (Hons/PhD student)

Other investigators: Dr Fei Song (formerly CHeBA), Dr Nicola Armstrong (University of Sydney), Associate Professor John Kwok (NeuRA, UNSW), Associate Professor Margaret J. Wright (QIMR Berghofer Institute), Professor David Ames (National Ageing Research Institute; Royal Melbourne Hospital)

Project description: Levels of plasma *apolipoprotein A* levels have been associated with age-related cognitive performance and decline. An Honours project examining DNA methylation variation in the *apolipoprotein A* gene and age-related memory performance was undertaken using participants from the Sydney Memory and Ageing Study. This work was based on preliminary data from a project examining genome-wide methylation in memory-discordant identical twins from the Older Australian Twins Study.

Aims: To examine whether DNA methylation variation in the *APOA1* gene was associated with episodic memory performance and ApoA1 protein levels.

Design & method: In the Sydney Memory and Ageing Study, methylation analysis of the apolipoprotein A gene was undertaken using pyrosequencing. Plasma apolipoprotein A1 levels had been previously assayed and memory performance assessed. Linear regression analyses were undertaken to assess the relationships between *APOA1* gene methylation and (i) plasma apolipoprotein A1 levels and (ii) memory performance.

Progress to date: Analyses are complete and the results are being prepared for publication.

Benefits: The results suggest that an epigenetic mechanism, DNA methylation variation, may contribute to control of *apolipoprotein A1* gene expression and memory performance.

CHeBA's Research
39 Groups
48 Consortia
53 Current Projects 2014
74 Completed Projects 2014
78 CHeBA Collaborators

Output: The results were written up as a successful Honours thesis by Ms Lazarus. This work has now been accepted for publication in a peer-reviewed journal.

Funding: NHMRC, ARC, Commonwealth Scientific and Industrial Research Organisation Flagship Collaboration Fund, Alzheimer's Australia Dementia Research Foundation Postdoctoral Fellowship.

Date commenced: February 2013

Expected date of completion: January 2015

Apolipoproteins in plasma (particularly ApoA1, ApoD and ApoH)

CHeBA staff: Julia Müenchhoff, Anne Poljak, Fei Song, Nady Braidy, Nicole Kochan, Wei Wen, John Crawford, Julian Trollor, Henry Brodaty, Perminder Sachdev

Other investigators: Professor Mark Duncan (University of Colorado), Professor John Attia (University of Newcastle), Associate Professor Peter W. Schofield (University of Newcastle), Dr Mark McEvoy (University of Newcastle), Professor Ralph Martins (Edith Cowan University)

Project description: Quantification of apolipoprotein levels in mild cognitive impairment and Alzheimer's disease plasma in a variety of population based cohorts, from Sydney and elsewhere in Australia.

Aims:

- Determine if apolipoprotein changes observed in MCI and AD plasma, relative to normal controls, would be reproducible across independent cohorts of similar design.
- Identify which of the apolipoproteins change with age and/or are dysregulated in MCI and AD.
- Correlate plasma apolipoprotein changes with cognitive domain scores and brain volumetrics.
- Study the mechanisms of action, expression changes with age, and dysregulation in neurodegenerative diseases of ageing, including animal models for apolipoproteins ApoA1, ApoD, ApoJ and ApoH.

Design & method: Both cross-sectional and longitudinal designs are used. Cohorts include: Sydney MAS (all 4 waves), Hunter Community Study (HCS), Dominantly Inherited Alzheimer's disease Network (DIAN), Older Australian Twins Study (OATS) and Sydney Centenarian Study (SCS). Cellular and animal models of ageing and AD are in the planning phase.

Progress to date: Experiments are ongoing, with numerous conference presentations, several published manuscripts, and both local and international collaborators involved.

Benefits:

- Potential biomarker panel to assist in diagnosis of predisposition to MCI and/or AD.
- Identify robust biomarkers, which show consistent change across studies.
- Understand the effect of plasma apolipoprotein changes on cognition and brain volumetrics.
- Determine how plasma apolipoprotein levels change with age, particularly advanced old age.
- Understand the role of specific apolipoproteins (ApoA1, ApoD, ApoJ and ApoH) in the ageing brain.

Output: 1 conference presentation, 2 publications, 4 manuscripts in preparation.

Funding: NHMRC, Rebecca L. Cooper Medical Research Foundation, Alzheimer's Australia Rosemary Foundation, Sachdev Foundation, UNSW Faculty of Medicine FRG and Early Career Researcher Grants.

Date commenced: 2006

Expected date of completion: Ongoing

Brain proteomics: Differential expression of the proteome in AD brain

CHeBA staff: Anne Poljak, Nady Braidy, Tharusha Jayasena, Perminder Sachdev

Other investigators: Professor Catriona MacLean (Monash University), Associate Professor George Smythe (SOMS, UNSW), Associate Professor Mark Raftery (BMSF, UNSW), Professor Glenda Halliday (NeuRA, UNSW), Dr Claire Shepherd (NeuRA, UNSW)

Project description: Proteomic expression difference profiling in Alzheimer's disease cortical brain regions.

Aims:

- Determine if there are brain regional differences in the proteome profile comparing normal and AD brain sections.
- Determine if proteomic expression correlates with level of brain pathology (Braak stage).
- Identify age-related changes in the brain proteome profile.

Design & method: Case control design using Brain Bank tissue (Victorian Brain Bank Network and NSW Brain Bank) from age-matched normal control and AD brain tissue in 65-75 year and ≥90 year age groups. An iTRAQ proteomics approach will be employed.

Progress to date: Tissue samples have been fractionated into 5 subcellular fractions and proteomics experiments performed using iTRAQ methodology.

Benefits:

- Proteomics is a discovery-based approach, and as a research tool may provide a signpost for novel proteins and pathways to provide insight into AD pathogenesis
- By identifying deregulated proteins, which may not have previously been linked to AD, the potential exists for discovery of novel mechanisms of disease causation. Furthermore, these data will provide the impetus and rationale to follow new research leads.

Output: 5 conference presentations, 4 invited oral presentations, 3 publications, 2 manuscripts in preparation.

Funding: NHMRC, Rebecca L. Cooper Medical Research Foundation.

Date commenced: 2007

Expected date of completion: Ongoing

Defining the role of inflammation in depression during ageing

CHeBA staff: Perminder Sachdev, Simone Reppermund, Julian Trollor

Other investigators: Professor Bernhard Baune (University of Adelaide)

Project description: This study builds on two well-characterised ageing cohorts, with the aim to assay systemic inflammatory biomarkers (proteins and gene-expression) derived from bloods to determine contribution of these biomarkers to depression. Samples were collected at the time of in-depth assessments, including a psychiatric assessment. These assessments establish current and previous diagnoses and severity of depressive symptoms. Serum has been collected for both cohorts across multiple time-points, and genome-wide genotype data are already available. Through the prospective study of inflammatory signalling proteins and depression diagnosis, we will clarify the biological role of inflammation in these mood states. In order to capitalise on the rich resources available in the fourth wave of MAS (DNA, RNA, serum), we will take a cross-sectional approach with the aim to identify gene expression that predicts protein levels, and extend these findings to the genetic data by identifying expression quantitative trait loci (eQTLs) for these gene systems. Based on our findings we will target genetic analyses to variants that show evidence for being functional. We will investigate if these eQTLs predict lifetime depression in this sample, and utilise machine-learning methods to determine the best prediction model (using gene expression, proteomic, and genetic data) we have available with our data. This predictive model will then be tested in the OATS sample with targeted gene expression and protein assays run and analysed.

Aims:

- To understand the prospective relationship between inflammation and depression during ageing, through the investigation of the bidirectional relationship between inflammatory biomarkers in the Sydney Memory and Ageing Study [MAS].
- To investigate the molecular underpinnings of inflammation during aging by using genetic, gene expression, and proteomic data.
- To develop an inflammation based prediction model of depression (consisting of genetic, gene expression and proteomic data in the context of inflammation) during aging in MAS (discovery sample) and to replicate in a second ageing sample, the Older Australian Twins Study [OATS].

Design & method: Use longitudinal study to develop a predictive model of lifetime depression using quantitative genetics, and then test in another cohort.

Progress to date: Genetic analyses have been performed; data analysis is proceeding.

Benefits:

- The first of its kind to address the question of bi-directionality between inflammation and depression in ageing.
- Improved understanding of the biological and molecular underpinnings of inflammation and depression
- Could lead to early identification of risk factors and to novel and improved pharmacotherapies for depression in late life.

Output: Two conference presentations.

Funding: NHMRC

Date commenced: January 2014

Expected date of completion: December 2016

Diagnosing major depression in older Australian adults: Is there evidence for age-related bias?

CHeBA staff: Gavin Andrews (conjoint), Perminder Sachdev

Other investigators: Dr Louise Mewton (NDARC, NSW, formerly CHeBA), Dr Matthew Sunderland (NDARC, UNSW, formerly CHeBA), Dr Natacha Carragher (NDARC, UNSW), Dr Phillip Batterham (Australian National University).

Project description: Nationally representative surveys provide valuable information regarding the pervasiveness, risk factors, and service use associated with major depressive disorder (MDD) in the community. This information is utilised by mental health policy makers to direct limited funding towards subgroups of the population that would benefit from targeted prevention and treatment programs (Jenkins, 2001). It is crucial that epidemiologic surveys, research studies, and policy makers assess MDD and accurately estimate prevalence and incidence rates using methods that are valid for different age groups. Likewise, it is essential that clinicians accurately determine a suitable diagnosis for patients of all ages to facilitate a positive treatment outcome. However, there is significant controversy in the literature regarding the accuracy of the diagnostic criteria for MDD in older adults. The current project aims to address the pressing need to clarify the validity of mental health assessment methods used to diagnose DSM-IV MDD in older individuals (aged 65+) within the Australian population.

Aims:

- Investigate the extent of age-related bias in the endorsement of DSM-IV MDD criteria used to estimate prevalence rates in the 2007 Australian National Survey of Mental Health and Wellbeing.
- Examine the sources of bias in older adults' interpretation of, and their capacity to respond to, self-reported questions that operationalise the diagnostic criteria for MDD.
- Propose recommendations to revise the way MDD is assessed in older adults.

Design & method: To achieve these objectives this study will utilise a complementary two-step procedure that first makes use of sophisticated statistical techniques in large epidemiological datasets followed by a series of cognitive interviews in a small target sample of older Australian adults.

Progress to date: Expert review of diagnostic symptoms completed, cognitive interview designed, recruitment commenced.

Benefits:

- A comprehensive understanding of the potential presence of age-related bias in prevalence estimates of MDD in old age Australian adults.
- A reliable and statistically-driven estimate of the relative impact of age-related bias on the current Australian MDD prevalence estimates in the old age population. The prevalence will be revised taking into account the impact of age-related bias.
- A greater understanding of the potential factors associated with old age that contributes to age-related bias in the assessment of MDD.
- A set of practical recommendations, based on empirical results, to revise the way MDD is assessed in the old age population for future epidemiological and clinical studies conducted in Australia and internationally.

Funding: NHMRC

Date commenced: January 2013

Expected date of completion: December 2015

The expression and distribution of sirtuins in the brain and CNS and their role in AD (Formerly called Association between sirtuin single nucleotide polymorphisms and functional markers of brain health in ageing)

CHeBA staff Tharusha Jayasena, Anne Poljak, Nady Braidy, Perminder Sachdev

Other investigators: Associate Professor George Smythe (SOMS, UNSW), Associate Professor Ross Grant (SOMS, UNSW; Australasian Research Institute; Sydney Adventist Hospital), Associate Professor Matthias Klugmann (SOMS, UNSW; NeuRA, UNSW; Prince of Wales Hospital), Dr Ling Zhong (BMSF, UNSW), Associate Professor Mark Raftery (SOMS, UNSW; BMSF, UNSW)

Project description: Develop an MRM mass spectrometry based quantitative method for assaying all 7 human sirtuins, and apply this approach to study changes in sirtuin expression levels in ageing and disease. Both human plasma and cerebrospinal fluid (CSF) samples, as well as cell culture and animal models, will be used.

Aims:

- Develop a stable isotope based MRM mass spectrometric quantitative assay for human sirtuins.
- Explore the distribution and expression level of sirtuins in the mammalian brain.
- Explore expression of sirtuins in plasma and CSF and variation with age and in AD and MCI.

Design & method: Stable isotope based MRM mass spectrometric quantitative assay for human sirtuins, based on sirtuin specific peptides will be used to assay tissue extracts and fluids such as CSF and plasma. Immunohistochemistry approaches will be used to explore brain distribution of sirtuins.

Progress to date: Experiments are ongoing, results have been presented at conferences and a review paper has been published.

Benefits: Understand the role of all 7 mammalian sirtuins in ageing and neurodegenerative diseases of ageing. These proteins are epigenetic regulators that may be influenced by cellular energy status and exogenous polyphenolic compounds. Modulation of their actions by lifestyle changes presents a potential approach to improving health in old age.

Output: 7 conference presentations, 4 published research papers, 3 manuscripts in preparation.

Funding: NHMRC, Rebecca L. Cooper Medical Research Foundation, UPRA PhD scholarship to Tharusha Jayasena.

Date commenced: 2008

Expected date of completion: Ongoing

Genetics of apolipoproteins

CHeBA staff: Karen Mather, Anbupalam Thalamuthu, Anne Poljak, Perminder Sachdev et al.

Other key investigators: Dr Fei Song (formerly CHeBA), Dr Nicola Armstrong (University of Sydney), Dr Chris Oldmeadow (University of Newcastle), Professor John Attia (University of Newcastle), Associate Professor Margaret J. Wright (QIMR Berghofer Institute, Brisbane, Australia), Professor David Ames (National Ageing Research Institute; Royal Melbourne Hospital)

Project description: Apolipoproteins are important transporters of lipids in the circulation and lymphatic systems. Apolipoprotein levels in the Sydney Memory and Ageing Study have been previously associated with cognitive performance and decline. Heritability of seven plasma apolipoproteins was assessed using data collected from the Older Australian Twins Study. The majority of apolipoproteins showed a significant genetic component. A genome-wide association study using three cohorts of middle-aged to older adults, the Sydney Memory and Ageing Study, the Older Australian Twins Study and the Hunter Community Study was undertaken.

Aims: To identify genetic variants associated with plasma apolipoproteins in mid to late life.

Design & method: Plasma apolipoproteins were measured using an immunoassay method. Genome-wide genotyping data imputed to Hapmap 2 was used for analyses. Genome-wide association studies for plasma apolipoproteins were undertaken and meta-analyses performed. Replication was undertaken in an independent cohort.

Progress to date: Analyses are complete and the results are being prepared for publication.

Benefits: Potential benefits from this work include a better understanding of the contributions of genetics to plasma levels of apolipoproteins.

Output: This work is currently being written up for publication. This work was presented at the Alzheimer's Association International Conference in Copenhagen in 2014.

Funding: NHMRC, ARC, Commonwealth Scientific and Industrial Research Organisation Flagship Collaboration Fund Grant, Alzheimer's Australia Dementia Research Foundation Postdoctoral Fellowship.

Date commenced: February 2013

Expected date of completion: June 2015

Genetics of grip strength

CHeBA Staff: Jessica Chan (Medicine student), Karen Mather, Anbupalam Thalamuthu, Perminder Sachdev

Other key investigators: Dr Nicola Armstrong (University of Sydney) Dr Chris Oldmeadow (University of Newcastle), Professor John Attia (University of Newcastle), Professor Stephen Lord (NeuRA, UNSW), Dr Jasmine Menant (NeuRA, UNSW), Associate Professor John Kwok (NeuRA, UNSW), Professor Peter Schofield (NeuRA, UNSW)

Project description: This project was an independent learning project undertaken by a 4th year Medicine student. Grip strength is an indicator of muscle strength and is a predictor of mortality and morbidity in older adults. Previous studies suggest grip strength has moderate to high heritability. Using two cohorts of middle-aged to older adults, the Sydney Memory and Ageing Study and the Hunter Community Study, this project sought to examine the genetics of muscle strength.

Aims: To identify genetic variants associated with a marker of muscle strength, grip strength, in mid to late life.

Design & method: Hand grip strength was measured using standard methods. Genome-wide genotyping data imputed to Hapmap 2 was used for analyses. A candidate gene study examining previously identified genetic variants from the literature and biologically relevant genes was undertaken using linear regression. A genome-wide association study for grip strength was also undertaken.

Progress to date: Analyses are complete and the results are being prepared for publication.

Benefits: Potential benefits from this work include a better understanding of the contributions of genetics to muscle strength, specifically, grip strength.

Output: The results were written up as the final report for a successful Medicine Independent Learning Project by Jessica Chan. This work has now been submitted as a manuscript to a peer-reviewed journal.

Funding: NHMRC, Alzheimer's Australia Dementia Research Foundation Postdoctoral Fellowship.

Date commenced: February 2013

Expected date of completion: January 2015

Genetics of white matter hyperintensities

CHeBA staff: Karen Mather, Wei Wen, Perminder Sachdev et al.

Other key investigators: Dr Amelia Assareh (University of New England, formerly CHeBA), Dr Nicola Armstrong (University of Sydney), Professor Peter Schofield (NeuRA, UNSW), Associate Professor John Kwok (NeuRA, UNSW), Professor Simon Easteal (Australian National University), Associate Professor Margaret J. Wright (QIMR Berghofer Institute), Professor David Ames (National Ageing Research Institute; Royal Melbourne Hospital)

Project description: White matter hyperintensities (WMHs) are regions of hyperintensity observed on neuroimaging scans of middle-aged to older adults and are associated with negative health outcomes such as cognitive and physical impairments. The aetiology of white matter hyperintensities is unclear but is thought to be ischemic in origin. Heritability studies suggest WMHs have a genetic component.

Aims: To identify genetic variants associated with white matter hyperintensities.

Design & method: WMH burden was estimated from neuroimaging scans of participants from the Sydney Memory and Ageing Study (Sydney MAS), the Older Australian Twins Study (OATS) and the PATH Through Life Study (administered by the Australian National University). Genome-wide genotyping data imputed to Hapmap 2 was used for analyses in Sydney MAS and OATS. In PATH, specific genetic variants were genotyped using standard methods. Candidate gene analyses were undertaken for WMHs in PATH. Genome-wide association studies for WMH measures were undertaken in Sydney MAS and OATS and meta-analyses performed.

Progress to date: Analyses are complete for the candidate gene studies. The results of the GWAS are still being assessed and a manuscript is being written for publication.

Benefits: Potential benefits from this work include a better understanding of the contributions of genetics to WMHs.

Output: A manuscript has been published on the candidate gene work in the *American Journal of Hypertension*. A manuscript on the GWAS results is being prepared.

Funding: NHMRC, ARC, Commonwealth Scientific and Industrial Research Organisation Flagship Collaboration Fund Grant, PhD scholarship from the Dementia Collaborative Research Centre – Assessment and Better Care, UNSW, Alzheimer's Australia Dementia Research Foundation Postdoctoral Fellowship.

Date commenced: 2012

Expected date of completion: June 2015

Genome-wide Association Studies (GWAS) of brain measures in collaboration with the ENIGMA consortium (Enhancing Neuroimaging Genetics through Meta-Analyses Consortium)

CHeBA staff: Karen Mather, Wei Wen, Anbupalam Thalamuthu, Perminder Sachdev et al.

Other key investigators: Dr Nicola Armstrong (University of Sydney), Associate Professor John Kwok (NeuRA, UNSW), Professor Peter Schofield (NeuRA, UNSW), Associate Professor Margaret J. Wright (QIMR Berghofer Institute), Professor David Ames (National Ageing Research Institute; Royal Melbourne Hospital)

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Project description: Genetics plays an important role in brain structures, as shown by heritability studies. The ENIGMA consortium, comprised of a number of international studies, seeks to find genetic variants associated with different brain measures such as subcortical volumes.

Aims: To identify single nucleotide polymorphisms (SNPs) for various brain measures.

Design & method: A genome-wide association study (GWAS) was performed on subcortical volumes using the Sydney Memory and Ageing Study and the Older Australian Twins Study. Our data contributed to a meta-analysis of GWAS results at the discovery stage. We are also contributing to other studies examining the genetics of other brain measures.

Progress to date: GWAS results for subcortical volume measures have been submitted to ENIGMA. Other analyses are currently being completed.

Benefits: Identification of genetic variants associated with various brain measures may lead to a greater understanding of the role of genetics in brain structures over the lifespan and to psychiatric and neurodegenerative disease.

Output: A manuscript detailing the result of the meta-analyses for subcortical volumes was recently submitted by ENIGMA to the journal, *Nature*.

Funding: NHMRC, ARC, Commonwealth Scientific and Industrial Research Organisation Flagship Collaboration Fund Grant, Alzheimer's Australia Dementia Research Foundation Postdoctoral Fellowship.

Date commenced: 2012

Expected date of completion: Ongoing

Genome-wide Association Studies (GWAS) of various measures including cognitive performance in collaboration with the CHARGE consortium (Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium)

CHeBA staff: Perminder Sachdev, Karen Mather, Anbupalam Thalamuthu, Wei Wen, Nicole Kochan, Teresa Lee et al.

Other key investigators: Dr Amelia Assareh (University of New England, formerly CHeBA), Dr Nicola Armstrong (University of Sydney), Associate Professor John Kwok (NeuRA, UNSW), Professor Peter Schofield (NeuRA, UNSW), Associate Professor Margaret J. Wright (QIMR Berghofer Institute), Professor David Ames (National Ageing Research Institute; Royal Melbourne Hospital)

Project description: Heritability studies suggest genetic variation plays a major role in many age-related measures, including cognitive performance. The CHARGE consortium, comprised of a number of international studies, seeks to find genetic variants associated with different cognitive measures such as processing speed and general cognitive ability and other ageing-related measures.

Aims: To identify single nucleotide polymorphisms (SNPs) associated with cognitive performance and other measures.

Design & method: Genome-wide association studies (GWAS) have been performed on various measures using the Sydney Memory and Ageing Study and the Older Australian Twins Study. Our GWAS data has contributed to meta-analyses of GWAS results either at the discovery or replication stage of CHARGE studies.

Progress to date: For several of these studies, analyses have been completed and manuscripts have been written and are currently under peer review or are accepted. For others, CHARGE is still assessing the results.

Benefits: Identification of genetic variants associated with various measures such as cognitive performance may lead to clarification of the biological underpinnings underlying these measures. For the cognitive analyses, these results may potentially lead to targeting of those at risk of age-related cognitive decline and novel preventative or therapeutic strategies.

Output: Currently, papers are under review/accepted and include GWAS of verbal memory, executive functioning and processing speed.

Funding: NHMRC, ARC, Commonwealth Scientific and Industrial Research Organisation Flagship Collaboration Fund Grant, Alzheimer's Australia Dementia Research Foundation Postdoctoral Fellowship.

Date commenced: 2012

Expected date of completion: Ongoing

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Heritability and genetic influence of brain structures and brain networks

(Formerly Heritability and genetic correlations of cortical and subcortical structures)

CHeBA staff: Wei Wen, Anbupalam Thalamuthu, Alistair Perry (PhD student), Perminder Sachdev, Karen Mather, Jiyang Jiang (PhD student)

Other investigators: Associate Professor Pierre Lafaye de Micheaux (Université de Montréal, Canada), Dr Wanlin Zhu (Beijing Normal University), Associate Professor Margaret J. Wright (QIMR Berghofer Institute, Brisbane, Australia), Professor David Ames (National Ageing Research Institute; Royal Melbourne Hospital)

Project description: A greater understanding of the genetic contributions to the structure of the human brain at older ages will assist in the elucidation of the pathways associated with normal and pathological brain ageing. Prior research suggests brain structures have moderate to strong heritability. However, few studies have examined the heritability of the shape of subcortical structures. Nor have the genetic correlations between bilateral hemispheric structures been considered. In 2013, we started a comprehensive heritability and genetic correlation analysis of cortical and sub-cortical structures of the human brain, utilising neuroimaging data from the MAS and the OATS. The study of twins offers an excellent strategy to examine the relative contributions of genetic and environmental influences on brain structures. We began to extend our study to human brain networks in late 2014 and this part of the work is well underway.

Aims: To estimate heritability and genetic correlations of cortical, sub-cortical structures and structural and functional networks of the human brain.

Design & method: We are studying over 400 twins aged 65 years and over (age range 65-88) with high resolution magnetic resonance imaging (MRI) to investigate the genetic patterning of the cerebral cortex and seven subcortical structures, using cortical thickness and surface deformation as the imaging phenotype in a vertex-wise approach. To study the genetic contributions to interesting neuropsychological and clinical aspects such as brain efficiency and recovery after brain lesions, we are studying brain networks by constructing structural brain networks using DTI scans processed using probabilistic models.

Progress to date: We have mapped heritability for both cortex and subcortical structures. This is the first large study of older twins of both sexes. Both the cortex and subcortical structures were examined. For the latter, three dimensional surface information was extracted for the first time. Bilateral symmetry for genetic influences was examined. Shared genetics between cortical areas and subcortical structures were investigated.

The study of genetic influence on the human connectome is now well underway. We are carrying out computations for this section of the study and we are expecting to start gathering data and statistical analysis in early 2015.

Benefits: Our study demonstrates a complex but patterned genetic architecture of the older human brain. An understanding of this pattern will assist in the refinement of phenotypes for the discovery of the genetic blueprint of the human brain.

Output: Two manuscripts are completed.

Funding: NHMRC, Alzheimer's Australia Dementia Research Foundation Postdoctoral Fellowship.

Date commenced: July 2013

Expected date of completion: December 2015

Improving clinical diagnosis of mild neurocognitive disorders using neuropsychological assessment

CHeBA staff: Nicole Kochan, Perminder Sachdev, Henry Brodaty, Melissa Slavin (conjoint), John Crawford

Other investigators Professor Kaarin Anstey (Australian National University), Professor David Bunce (University of Leeds, UK), Professor John R Crawford (University of Aberdeen, Scotland), Dr Amanda Miller-Amberber (University of Sydney)

Project description: Clinical diagnoses of mild neurocognitive disorders using neuropsychological assessment is challenging in Australia because US normative data are typically used for comparison and cognitive problems are subtle and difficult to detect.

Aims:

- To establish Australian normative data for neuropsychological measures which are used in the assessment of cognition in older adults and which form part of diagnostic evaluations of dementia and other age-related cognitive disorders.
- To facilitate interpretation of neuropsychological test performance in persons of non-English speaking background by investigating the influence of cultural, linguistic and educational factors.
- To evaluate the clinical utility of computerised neuropsychological testing for the early detection of neurocognitive disorders in older adults and to investigate the additional value over traditional neuropsychological measures for predicting future cases of mild cognitive impairment (MCI) and dementia.
- To evaluate the potential of a computerised neuropsychological test battery as a more culture-fair measure of cognition compared to traditional neuropsychological measures in older adults from culturally and linguistically diverse (CALD) backgrounds.

Design & method: Data for this project will be primarily drawn from the MAS, which has a longitudinal prospective design.

Component 1: Australian normative data

This normative study will use demographic and neuropsychological data from Wave 1 to construct normative data. Native English speakers (those that learned English before the age 10) (N=878) from the baseline MAS cohort will be used in the development of normative data. The sample of NESB participants (N=159) will be used to investigate cultural, educational and linguistic influences on neuropsychological test performance. To date, 12 tests have been administered to the MAS participants from seven cognitive domains. Multiple measures are available for each test. Multiple linear regression analyses will be used to examine the influence of demographic variables (age, years of education, sex) on raw scores for each test. The proportion of variance explained by each variable will inform the relevant set of variable(s) that will be adjusted for. For the analysis of the NESB sample, education, linguistic and cultural factors will be entered into a multiple regression analysis to establish an appropriate regression equation that can be used to adjust performance for these variables in NESBs.

Component 2: Computerised neuropsychological test battery

Demographic, clinical and neuropsychological (from both paper-and-pencil and computerised tests) data and diagnostic classifications (cognitively normal, MCI and dementia) from Waves 1 (baseline), 2 (2 years later) and 3 (4 years later) will be used. The clinical validation component of the study will use a cross-sectional design. The SENSUS battery will be administered to patients at the POWH Memory Disorders Clinic. Diagnostic and neuropsychological data will also be collected.

Progress to date:

Component 1:

Normative data analyses completed in the native English speaker sample, beta version of normative software program completed, and main manuscript is in preparation. Specific demographic and linguistic associations of cognitive performance on traditional neuropsychological tests in culturally and linguistic diverse individuals have been identified. We identified two main factors that influenced performance on tests in CALD individuals: 1) the degree of English language dominance and acculturation in day-to-day life, and 2) the individual's past and current exposure to English. In the main, these factors affected verbally-based test performance but not exclusively.

Component 2:

The clinical study conducted at the Prince of Wales Hospital has commenced and approximately half the participants have been recruited. The first study using approximately 800 MAS participants and examining the utility of reaction time measures obtained via the computerised test battery is completed and a manuscript is under review. The analyses for all the computerised measures in predicting dementia and mild cognitive impairment have been completed. The predictive values for individual measures and the overall composite measure are high and compare favourably to more traditional cognitive measures. A manuscript is in preparation.

Benefits: The new data will improve practice in clinical and research settings in Australia, and possibly in other English-speaking countries such as Britain. The findings obtained from the project will also potentially provide information on the most effective types of measures for identifying neurocognitive disorders in the elderly and for flagging the likelihood of future cognitive decline, as well as suggesting more appropriate methods of assessing cognitive functioning in older adults of CALD backgrounds than are traditionally used. The findings will be widely disseminated to clinical and research communities in Australia and overseas. The findings will be translated into a set of recommendations for Neuropsychologists and Clinical Psychologists who assess ethnic and linguistic minority clients. The benefits of computerised testing of cognition include greater accessibility (particularly for those in remote areas where there are no specialist services), reduced burden on the individual because of briefer testing, greater accuracy of data collected and improved sensitivity compared to current cognitive screening measures.

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Output: 5 conference abstracts/presentations, 1 invited presentation, 1 publication under review.

Funding: DCRC – Assessment and Better Care, UNSW, NHMRC Early Career Fellowship.

Date commenced: March 2012

Expected date of completion: December 2016

Inflammatory markers and brain structure

CHeBA staff: Jiyang Jiang (PhD student), Wei Wen, Julian Trollor, Perminder Sachdev

Other investigators: Associate Professor David Brown (St Vincent's Centre for Applied Medical Research)

Project description: Using circulating inflammatory markers and magnetic resonance imaging (MRI), recent studies have associated inflammation with brain volumetric measures. We examine whether an elevated level of systemic MIC-1/GDF15 serum levels would correlate with brain atrophy in cortical and subcortical regions, and that brain volume is a mediator of the previously observed relationships between MIC-1/GDF15 serum levels and cognition.

Aims:

To examine the relationship of serum levels of a divergent transforming growth factor – beta (TGF-β) superfamily cytokine, Macrophage Inhibitory Cytokine – 1 (MIC-1/GDF15), with human brain volumes, in a community-dwelling sample aged 70-90 years over two years.

To examine the relationship of serum levels of CRP and IL-6 with human brain volumes and brain network properties.

Design & method: We approach the possible relationship between brain structures and an emerging novel inflammatory biomarker, Macrophage Inhibitory Cytokine-1 (MIC-1/GDF15), which is a member of the transforming growth factor-β (TGF-β) superfamily. The serum MIC-1/GDF15 concentration for both Wave 1 and Wave 2 was determined using an enzyme-linked immunosorbent assay (ELISA). We used T1-weighted MRI scans which were obtained by the MAS at both Wave 1 and Wave 2. We analysed the scans using the FMRIB Software Library and FreeSurfer. Serum levels of other markers such as CRP and IL-6 have also been examined.

Progress to date: Our preliminary results showed a significantly negative association between MIC-1/GDF15 serum levels and both subcortical and cortical grey matter volumes. Increases in MIC-1/GDF15 serum levels were associated with decreases in cortical grey matter volume over two years. MIC-1/GDF15 serum levels were inversely associated with grey matter volumes both cross-sectionally and longitudinally.

Benefits: This is the first study that has investigated the relationship between the blood level of MIC-1/GDF15 and brain grey matter volume, in both cross-sectional and longitudinal settings.

Output: One journal paper has been accepted and another is under review.

Funding: NHMRC.

Date commenced: January 2013

Expected date of completion: March 2016

Longevity and transcriptomics

CHeBA staff: Karen Mather, Anbupalam Thalamuthu, Perminder Sachdev et al.

Other key investigators: Dr Nicola Armstrong (University of Sydney), Dr Michael Janitz (School of Biotechnology and Biomolecular Sciences, UNSW)

Project description: Long-lived individuals are examples of successful ageing, many of whom have avoided age-related disease until very late in their lives. This project seeks to identify RNA differences between long-lived individuals (aged 95+) and younger controls using the cutting edge technique of RNA sequencing.

Aims: To identify mRNAs and long ncRNAs associated with longevity.

Design & method: RNA was extracted from peripheral blood samples from the Sydney Memory and Ageing Study and the Sydney Centenarian Study. RNA sequencing will be undertaken, data cleaned and analyses undertaken.

Progress to date: The RNA sequencing has been completed and the data cleaned. Initial analyses have been undertaken.

Benefits: Potentially this work will identify RNA biomarkers of longevity, which may aid in the identification of those who are at risk for age-related decline and disease and also increase our understanding of the ageing process.

Output: The analyses are being undertaken and a manuscript is being prepared.

Funding: NHMRC, Alzheimer's Australia Dementia Research Foundation Postdoctoral Fellowship.

Date commenced: December 2013

Expected date of completion: December 2016

The Older Australian Twins Study

CHeBA staff:

Investigators: Perminder Sachdev, Henry Brodaty, Julian Trollor, Wei Wen, Teresa Lee, Karen Mather, John Crawford, Ambupalam Thalamuthu

Study Coordinator: Jocelyn Bowden

Research Assistant: Tanya Duckworth

Administrative Assistant: Suzy Forrester

Data Manager: Kristan Kang

Other investigators and staff:

Investigators:

Professor David Ames (National Ageing Research Institute)

Professor Nick Martin (QIMR Berghofer Medical Research Institute)

Associate Professor Margaret J. Wright (QIMR Berghofer Medical Research Institute)

Professor Bernhard Baune (University of Adelaide)

Professor Peter Schofield (NeuRA)

Professor Katherine Samaras (Garvan Institute)

Research Assistants: Natalie Garden (QIMR Berghofer Medical Research Institute)

Christel Lemmon (National Ageing Research Institute)

Administrative Assistant: Lynette Bon (National Ageing Research Institute)

Project description: Funding was received to undertake four-year follow-up assessments for participants recruited to the Older Australian Twins Study (OATS). OATS is the largest and most comprehensive ageing study with elderly twins ever undertaken in Australia. It is a multi-centre, longitudinal study that commenced in New South Wales in 2007 and in Queensland and Victoria in 2008. Two-year and four-year follow-up tests are carried out to measure change in cognition and physical health. Study participants are identical and non-identical twin pairs aged 65 years and older, living across the eastern seaboard. 623 participants were recruited initially with 450 participants re-tested at their two-year follow up. Participants undergo rigorous medical and cognitive function tests, are asked to provide bloods samples and have a magnetic resonance imaging (MRI) scan of their brain. Information about environmental factors, such as medical and psychosocial history, lifetime physical and mental activity, and nutrition is collected as well as feedback from an informant (the participant's spouse or relative who knows him/her well) about the participant's memory and thinking and daily functions.

Aims:

- To maintain a well-characterised cohort of MZ and DZ twin pairs for longitudinal data.
- Continuing follow-up of the OATS cohort for the relative genetic and environmental contributions to mild cognitive impairment and dementia.
- Further elaboration of endophenotypes of dementia, including amyloid load.
- Exploration of the genetic basis of cognitive decline and brain changes in old age, as part of international consortia.

Design & method: Participants were recruited, mainly through the Australian Twins Registry, during Wave 1 of the study. The Wave 3 assessment repeats some aspects of the Wave 1 and 2 assessments, but is more focused on current state and interval history. Assessments are performed by a Research Assistant (RA) either in participants' homes or at one of the research facilities (duration 3-4 hours). Neuroimaging will be performed if the participant agrees to a scan. Blood is collected by an experienced phlebotomist and processed using our existing collaboration with South Eastern Area Laboratory Services (SEALS), or bloods can be collected by an experienced phlebotomist at an established collection centre, or at the participants own home. Where appropriate, cognitive diagnosis (normal, MCI, and Dementia by subtype) are made by two experienced clinicians (Professor Julian Trollor and Professor Perminder Sachdev) and one senior clinical neuropsychologist (Dr Teresa Lee) after presentation of the data at consensus case conference.

Interview, medical assessment and neuropsychological assessment include:

- Change in demographics: age, gender, education, marital status, occupation (current or retired), relationship between participant and informant.
- Interval psychiatric and medical history, including history of current medications, and modified Structured Clinical Interview DSM-IV.
- Interval medical examination including height and weight to allow BMI calculation, blood pressure and heart rate.

- Motor examination (timed walk test, lateral stability, speech, hand grip test, parkinsonian features), spirometry test and visual acuity.
- Assessment of subjective memory impairment, current and retrospective cognitive activities, social and physical activity, and family history questionnaire. Life time experiences, social networks and successful ageing are also examined through various modified questionnaires.
- Depression Scale 15 item, Kessler Psychological Distress Scale, World Health Organisation Disability Assessment Schedule II, Positive and Negative Affect Scale, Satisfaction with Life Scale, and Assessment of Quality of Life.
- Repeat detailed neuropsychological examination for performances in attention, memory, visuospatial function, language, executive function, speed of information processing, simple and complex reaction time, fine motor skills, mini-mental state examination and clock drawing.
- Informant Questionnaire about the participant: Cognitive Decline in the Elderly to confirm change in vascular risk factors, interval HRT use, Change In Cognition with Age Questionnaire, Clinical Dementia Rating Scale, Bayer ADL, Neuropsychiatric Inventory, and Apathy Evaluation Scales.
- Informant Questionnaire about the informant: Assessment of Quality of Life, Kessler Psychological Distress Scale, World Health Organisation Disability Assessment Schedule II, and, if caring for the participant, an in-house developed assistance and burden rating scale.

Blood tests and genetics:

- Blood is collected in consenting participants to investigate correlates of cognitive function (FBC, clinical chemistry screen, TSH, fasting cholesterol, homocysteine, Vitamins B12, and folic acid). Serum/plasma biomarkers of oxidative stress include biomarkers of lipid peroxidation, markers of DNA/RNA oxidation and markers of protein oxidation/nitrosylation. Inflammatory markers measured include pro- and anti-inflammatory markers.

Progress to date:

- 2-year follow-up assessment data (Wave 2) were cleaned and data released in mid 2014. 450 participants had Wave 2 assessments. Blood samples were collected from 403 participants, and MRI scans from 292 participants. DNA samples are available for 582/623 participants, with a further 41 either missing or who did not consent to samples.
- 4-year follow-up assessments (Wave 3) are ongoing. As of December 2014, 286 participants (70%) had been re-tested. Blood samples have been collected from 252 participants and MRI scans performed for 174 participants. 218 informant interviews have been completed. Wave 3 data collection will be completed in late 2015.
- Continued collaboration with the ENIGMA (Enhancing Neuroimaging through Genetic Meta-Analysis), CHARGE (Cohorts for Heart & Ageing Research Genetic Epidemiology) and EuroDiscoTWIN (diabetes and other hereditable conditions in twin cohorts) consortia.
- New project looking at RNA sequencing study on twins discordant for memory commenced (Dr Karen Mather).
- There have been 14 requests for access to OATS data in 2014. 11 are new requests, 2 are updated project requests, and there is one new project collaboration request from the Integrative Analysis of Longitudinal Studies of Aging in the USA.
- To date, the study has recruited 26 participants as brain donors.
- The OATS Online extension has progressed. The protocol and CRFs have been finalised, and the protocol amendments approved by both UNSW Ethics and Medicare Australia. ATR will approve once the complete package is available. Emails for participants and informants have been drafted, as have OATS procedures and operating guidelines, which will be finalised in 2015.
- Ongoing studies include genome-wide association studies (GWAS), DNA sequencing and methylation studies, epigenetic studies, Alzheimer risk score updates and hippocampal volume, heritability of plasma apolipoprotein levels and cognition, and several neuropsychology studies.
- Imaging data has been used in work on brain structure heritability, and the heritability of white matter fibre tracts and their functional connectivity.
- Funding from UNSW will help us re-organise the stored biospecimens in 2015 to improve accessibility for future studies.
- Other collaborations are being investigated with national and international researchers.

Benefits: Data from OATS Wave 1 has made significant contributions in relation to understanding the genetic factors underlying many aspects of cognition and brain imaging parameters. Salient findings have emerged which will assist in the understanding of genetic contributions to cognitive functions such as processing speed, executive ability and episodic memory, and which support the cognitive reserve hypothesis. The heritability of brain structures, both cortical and subcortical, brain spectroscopic metabolites and markers of small vessel disease, such as lacunar infarction and white matter hyperintensities, have been examined and can inform future genetic investigations. Work on amyloid imaging and functional magnetic resonance imaging is proceeding and epigenetic studies are progressing. Longitudinal data from this cohort has the potential to inform research in cognitive ageing into the future, and offers an excellent resource for collaborative work.

Output:

- 3 peer-reviewed journal publications were published, and another 3 were submitted.
- 2 conference proceedings from international conferences (*Organisation for Human Brain Mapping Conference*; *Alzheimer's Association International Conference*).
- Update of OATS component of CHeBA website.
- Progress on the OATS online data collection site.

Funding: NHMRC.

Date commenced: January 2013

Expected date of completion: December 2015

The organisation of the elderly connectome (Formerly called Structural topological organisation of the elderly brain)

CHeBA staff: Alistair Perry (PhD student), Wei Wen, Anbupalam Thalamuthu, Perminder Sachdev

Other investigators: Professor Michael Breakspear (QIMR Berghofer Medical Research Institute)

Project description: Prior investigations of human structural brain networks have elucidated core features of human structural brain networks. We provide the first study of structural topological organisation, particularly in reference to the crucial role of hub-regions, in the elderly brain. Here, diffusion-weighted imaging was performed on 115 cognitively normal subjects (74-96 years) from the MAS study. The second component of this project involves investigation of functional connectivity in the same participants using resting-state fMRI. Previous research has established a link between structural and functional connectivity in human brain networks. We are interested in examining how the nature of this relationship affects cognitive performance in the elderly. We identify spatio-temporal resting-state patterns of functional connectivity within our population, and examine whether structural and functional connectivity changes within these networks is predictive of cognitive performance.

Aims:

- To examine the core features of structural networks in the elderly brain and how this compares to previously published data in adults.
- To examine whether changes in both structural and functional connectivity is predictive of cognitive performance in the elderly
- To examine whether age-related changes in cognition can be predicted by changes in structural and functional connectivity

Design & method: The present study investigates a cognitively normal population drawn from the MAS study (74-96 years). High-angular probabilistic tractography was performed on the diffusion-weighted images of each subject. Structural networks were then constructed, representing connectivity between 512 predefined brain regions. We sought to investigate the architectural features of hub-regions, left-right asymmetries, and sexual dimorphisms. In these participants, functional networks were also constructed, representing the functional connectivity between the same predefined brain regions. We identified functional networks highly similar in their resting-state spatio-temporal patterns, using principal independent components analysis. Brain regions within these networks were then investigated as regions-of-interest to examine whether structural and functional changes in connectivity is predictive of cognitive performance. The effects of age on the relationship between connectivity and cognition is also examined.

Progress to date: We have discovered very interesting findings regarding the structural topology of the elderly brain, which have never been observed within the field. These findings have been submitted to *NeuroImage* for publication, which is currently undergoing revision. For example, we observed that the topology of hub-regions is consistent with adult connectomic data, and more importantly, their architectural features reflect their ongoing vital role in network communication. We also found substantial sexual dimorphisms, and striking lateralizations in structural connectivity within this population. In terms of the second component of this project, we have found a strong correlation between the integration of functional connectivity in perceptuo-motor networks and processing speed.

Benefits: We have been able to implement sophisticated technical advancements in constructing connectivity information acquired from diffusion imaging, and resting-state fMRI. This is a major beneficiary to the CHEBA neuroimaging lab. In addition, this body of work provides a thorough systematic investigation of brain structure in the cognitive elderly. This is a great benchmark for the field studying neurodegenerative disorders such as AD.

Output: 1 conference presentation (*SBMT* 2014), 1 publication under revision (*NeuroImage*)

Funding: NHMRC.

Date commenced: January 2014

Expected date of completion: March 2016

Oxidative stress in AD (Formerly called Understanding oxidative stress in the brain to prevent neurodegenerative diseases)

CHeBA staff: Anne Poljak, Nady Braidy, Nicole Kochan, Wei Wen, John Crawford, Julian Trollor, Henry Brodaty, Perminder Sachdev

Other investigators: Professor Mark Duncan (University of Colorado, USA), Professor John Attia (University of Newcastle), Associate Professor Peter W. Schofield (University of Newcastle), Dr Mark McEvoy (University of Newcastle), Professor Ralph Martins (Edith Cowan University)

Project description: Quantification of oxidative stress and glycation markers (*o*- and *m*-tyrosine, carboxymethy-lysine) in mild cognitive impairment and Alzheimer's disease plasma in a variety of population based cohorts, from Sydney and elsewhere in Australia.

Aims:

- Determine if protein oxidation and/or glycation changes in MCI and AD plasma, and to check for reproducibility across independent cohorts of similar design.
- Identify which of the markers change with age and/or are dysregulated in MCI and AD.
- Correlate protein oxidation levels with cognitive domain scores and brain volumetrics.

Design & method: Both cross-sectional and longitudinal designs are used. Cohorts include: Sydney MAS (all 4 waves), Hunter Community Study (HCS), Dominantly Inherited Alzheimer's disease Network (DIAN), Older Australian Twins Study (OATS) and Sydney Centenarian Study (SCS). Cellular and animal models of ageing and AD are in the planning phase.

Progress to date: Experiments are ongoing, with numerous conference presentations, several published manuscripts, and both local and international collaborators involved.

Benefits:

- Potential biomarker panel to assist in diagnosis of predisposition to MCI and/or AD.
- Identify robust biomarkers, which show consistent change across studies.
- Understand the effect of plasma protein oxidation changes on cognition and brain volumetrics.
- Determine how plasma protein oxidation levels change with age, particularly advanced old age.
- Understand the role of specific mechanisms of oxidation; hydroxyl radical *vs* glycation, in ageing and neurodegenerative disease.

Output: 4 conference presentation, 4 invited oral presentations, 1 publication, 1 manuscript in preparation.

Funding: NHMRC, ARC, Rebecca L. Cooper Medical Research Foundation, Alzheimer's Australia Rosemary Foundation, Sachdev Foundation, UNSW Faculty of Medicine FRG and Early Career Researcher Grants.

Date commenced: 2004

Expected date of completion: Ongoing

Personality and Total Health Through Life Project (PATH)

CHeBA staff: Perminder Sachdev, Wei Wen, Karen Mather, Anne Poljak, Julia Müenchhoff

Other investigators: Professor Kaarin Anstey (Australian National University), Associate Professor Peter Butterworth (Australian National University), Dr Nicholas Cherbuin (Australian National University)

Project description: The PATH Project, run by the Centre for Research on Ageing, Health and Wellbeing, Canberra, is a large, on-going, population-based, longitudinal cohort study comprising approximately 7500 participants ranging from early to late adulthood. The project aims to track and define the lifespan course of depression, anxiety, substance use and cognitive ability, identify environmental risk and protective factors within these domains, and examine the relationships between depression, anxiety and substance use with cognitive ability and dementia. PATH has resulted in over 100 publications, and is unique among cohort studies in its age range and duration of follow-up.

Aims: PATH aims to investigate the causes of three classes of common mental health problems:

- Anxiety and depression.
- Alcohol and other substance abuse.
- Cognitive functioning and dementia.

The project investigates four broad themes that are relevant to each of these problems: ageing vs cohort effects; social, psychological, nutritional and genetic risk factors; and co-morbidity of mental health problems.

Design & method: PATH has 3 epidemiological cohorts (20-24, 40-44 and 60-64 years) to be followed up fourth yearly for 20 years. The two older cohorts are of interest to CHeBA and comprise 2530 individuals aged 40-44 years, and 2551 individuals aged 60-64 years at Wave 1 assessment.

Progress to date: Our group has taken responsibility for the neuroimaging and clinical chemistry components of the study. The study is now in its 4th wave (12 years from baseline), and the Wave 4 assessments of the 60+ cohort were completed in 2014.

Benefits:

- Obtaining measures of genetic, biological (including MRI), psychosocial and lifestyle risk and protective factors for mental health and wellbeing.
- Assessment of participants across the full adult lifespan, permitting investigation of developmentally significant, but under studied periods such as midlife.
- Recruitment and follow up of a young-old population, providing important pre-clinical data for studying the development of age related changes in memory and cognition.

Output: Full details, see **crahw.anu.edu.au/research/projects/personality-total-health-path-through-life**. 4 publications with CHeBA co-authors in 2014.

Funding: NHMRC.

Date commenced: 1999

Expected date of completion: Ongoing

Plasma proteomics biomarkers

CHeBA staff: Julia Müenchhoff, Anne Poljak, Tharusha Jayasena (PhD student), Nicole Kochan, Julian Trollor, Henry Brodaty, Perminder Sachdev

Other investigators: Dr Fei Song (formerly CHeBA), Associate Professor George A. Smythe (SOMS, UNSW), Professor Mark Duncan (University of Colorado, USA), Associate Professor Mark Raftery (BMSF, UNSW), Professor John Attia (University of Newcastle), Associate Professor Peter W. Schofield (University of Newcastle), Dr Mark McEvoy (University of Newcastle), Professor Ralph Martins (Edith Cowan University)

Project description: Plasma protein profiling of mild cognitive impairment and Alzheimer's disease in a variety of population based cohorts, from Sydney and elsewhere in Australia

Aims:

- Determine if proteomic changes observed in MCI and AD plasma, relative to normal controls, would be reproducible across independent cohorts of similar design.
- Identify specific plasma proteins and protein families that are dysregulated in MCI and AD and validate these using ELISA assays and/or western blotting.
- Correlate the effects of plasma proteome changes with cognitive domain scores and brain volumetrics.

Design & method: Both cross-sectional and longitudinal designs are used. Cohorts include; Sydney MAS (all 4 waves), Hunter Community Study (HCS), Dominantly Inherited Alzheimer's disease Network (DIAN), Older Australian Twins Study (OATS) and Sydney Centenarian Study (SCS). Proteomics (iTRAQ) screening is initially used, followed by western blot and multiplex ELISA of specific proteins of interest, such as the apolipoprotein family.

Progress to date: Experiments are ongoing, with numerous conference presentations, several published manuscripts, and both local and international collaborators working on current projects or validating proteomics data.

Benefits:

- Potential biomarker panel to assist in diagnosis of predisposition to MCI and/or AD.
- Identify robust biomarkers, which show consistent change across studies.
- Understand the effect of plasma proteome changes on cognition and brain volumetrics.

Output: 11 conference presentations, 4 invited oral presentations, 4 publications, 4 manuscripts in preparation.

Funding: NHMRC, ARC, Rebecca L. Cooper Medical Research Foundation, Alzheimer's Australia Rosemary Foundation, Sachdev Foundation, UNSW Faculty of Medicine FRG and Early Career Researcher Grants.

Date commenced: 2006

Expected date of completion: Ongoing

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The prevention and management of mental disorders in older Australians (Capacity Building Grant)

CHeBA staff: Perminder Sachdev, Henry Brodaty, Karen Mather, Nady Braidy, Nicole Kochan, Simone Reppermund, Wei Wen, Anne Poljak, Brian Draper (conjoint), Gavin Andrews (conjoint)

Other investigators: Professor Stephen Lord (NeuRA, UNSW), Professor Helen Christensen (Black Dog Institute), Professor Jacqueline Close (NeuRA, UNSW), Prof John Piggott (CEPAR, UNSW), A/Prof Olivier Piguet (NeuRA, UNSW), Professor Felicia Huppert (Cambridge University), Professor Philip Mitchell (School of Psychiatry, UNSW), Professor Peter Schofield (NeuRA, UNSW), Prof Gilles Guillemin (Macquarie University), Professor Maree Teesson (NDARC, UNSW), Professor Michelle Moulds (School of Psychology, UNSW)

Previous team investigators (2009-2013): Dr Melissa Slavin (conjoint), Associate Professor Nick Titov (now Macquarie University), Associate Professor Michael Valenzuela (now University of Sydney), Associate Professor Lee-Fay Low (now University of Sydney), Dr Louise Mewton (now NDARC, UNSW), Dr Matthew Sunderland (now NDARC, UNSW), Dr Jasmine Menant (NeuRA, UNSW), Dr Adrienne Withall (SPHCM, UNSW)

Project description/aims:

1. Understanding health and disease in older people living in the community, and improving their health and well-being through priority health approaches. Six streams have been identified to comprise the research agenda that team investigators (TIs) will address:
   i. Optimising the use of epidemiological mental health data in the elderly;
   ii. Identifying at-risk individuals;
   iii. Establishing risk factors for cognitive ageing;
   iv. Positive and successful ageing;
   v. Preventing dementia and/or delaying its onset; and
   vi. New services for cognitively impaired older Australians.
2. Finding new evidence to inform policy and practice relating to the care of the elderly.
3. Developing the careers of potential future research leaders in this area through mentoring and training.

Design & method: Each TI has 1 primary mentor, 1 secondary mentor and 1 or more additional mentors. TIs undertake two reviews per year to assess performance and support/training needs, as well as attending targeted mentoring and training programs to support research and leadership skills development.

Progress to date/Output/Benefits: Since 2009, the CBG has supported 12 researchers with a range of specialities, including genetic epidemiology, proteomics, neuropsychology, classification and assessment of psychiatric disorders in the elderly, online treatment of geriatric anxiety and depression, aged care service delivery, cerebrovascular damage and cognition, successful ageing, protective factors for cognitive decline, falls, gait and dizziness. To date, they have produced over 120 publications, been awarded more than $11 million in competitive grants and supervised 33 higher degree research students. TIs have been widely recognised through promotions, prizes and awards (including, in 2014, Dr Braidy receiving The Science and Industry Endowment Fund Australian Academy of Science Fellowship to attend the 64th Lindau Nobel Laureate Meeting).

Funding: NHMRC.

Date commenced: January 2009

Expected date of completion: December 2015

The role of polyphenolic compounds in modulating AD pathology

CHeBA staff: Tharusha Jayasena (PhD student), Anne Poljak, Nady Braidy, Perminder Sachdev

Other investigators: Associate Professor George A Smythe (SOMS, UNSW), Professor Gerald Münch (University of Western Sydney)

Project description: Assess the effect of polyphenolic compounds on Aβ oligomer and aggregate formation and the effect on cells exposed to Aβ monomers and oligomer formed during "ageing" *in vitro*.

Aims:

- Determine whether polyphenolic compounds such as curcumin, resveratrol and others will affect *in vitro* Aβ oligomer and aggregate formation.
- Determine whether cells exposed to Aβ oligomers and aggregates suffer adverse metabolic effects, compromised cell permeability and early apoptosis.
- Explore whether polyphenolic compounds will ameliorate some of these effects.

Design & method: Controlled experimental design, testing the effect of presence or absence of polyphenolics on Aβ aggregate formation *in vitro* and effects on cells exposed to Aβ aggregates *in vivo*. Aggregate formation will be monitored by isothermal calorimetry, gel electrophoresis and electron microscopy. Effects on cells will be monitored using cell viability assays, microscopy, mitochondrial function and proteomics.

Progress to date: Experiments are ongoing. Some of the results having been presented at conferences and a manuscript reviewing this area has been published.

Benefits:

- Potential development of low toxicity strategies for AD prevention and/or treatment of MCI/early AD.
- Better understand the effects of polyphenolic compounds on Aβ aggregation.
- Identify specific, naturally occurring polyphenolic compounds which may slow or prevent Aβ aggregation.

Output: 2 conference presentations, 1 invited oral presentations, 1 publication.

Funding: NHMRC, Rebecca L. Cooper Medical Research Foundation, UPRA PhD scholarship to Tharusha Jayasena.

Date commenced: 2011

Expected date of completion: Ongoing

The Sydney Centenarian Study (SCS)

CHeBA staff: Perminder Sachdev, Henry Brodaty, Charlene Levitan (conjoint), Karen Mather, John Crawford, Nicole Kochan, Gavin Andrews (conjoint), Kristan Kang

Project description: The SCS is studying a cohort of individuals who have successfully reached the extreme end of life in order to determine the genetic and environmental factors that contribute to successful ageing. We are taking a broad approach to elucidate all factors that may be of interest in investigating this population. The findings will shed light on which factors are particularly important for ageing well, which in turn will allow us to inform lifestyle choices in younger and middle aged Australians. The findings will also inform decisions to improve the quality of life of older Australians, and plan for future older generations. This is particularly important as we have an ageing population which will present a disproportionate burden on the health system unless we are prepared.

Aims:

- Determine the prevalence of major medical and neuropsychiatric disorders in individuals aged ≥95.
- Establish tools for the valid assessment of cognitive function in centenarians.
- Examine brain structure and function in centenarians and relate it to neuropathology.
- Determine the major genetic and environmental factors that influence longevity and normal cognitive function.
- Explore the determinants of "successful ageing".

Design & method: Individuals 95 years and older were recruited from seven electoral districts in Sydney using the electoral roll and multiple other strategies to obtain a representative sample. Physical and mental health and cognitive status were assessed using standard instruments in multiple sessions in the participants' places of residence, with assessments adapted to each individual. An informant was interviewed, and participants invited to donate a blood sample, do an autobiographical interview, undergo an MRI scan and enrol into the brain donation program.

Progress to date: Follow up is still underway. About 55% of people 95 years and above meet criteria for dementia. Rates of heart disease and diabetes were lower than in octogenarians, but hearing and visual deficits were common in centenarians. Rates of psychological distress were low and satisfaction with life high (mean 5.91 out of a maximum of 7). Brain volumes, both of the grey and white matter, continue to decline in the very old, but the pattern of decline is different from that seen in young-old individuals (<85 years). Structural MRI can distinguish amnestic but not non-amnestic MCI in the very old, and the structural correlates of MCI were different in the very old compared to the young old. White matter lesions are very common and extensive in centenarian brains, but they do not relate to cognitive impairment.

Benefits: By understanding the neurocognitive disorders in the very old, their determinants, their pathological correlation and functional outcomes, we will be in a better position to monitor or moderate risk factors for this age group. Equally, our enhanced appreciation of protective factors may be valuable in educating younger populations in relation to healthy ageing. The information gathered in this study will assist in planning of health and social systems for the exceptionally old.

Output: 1 paper published, 1 paper under review, 2 manuscripts are in preparation.

Funding: NHMRC.

Date commenced: October 2008

Expected date of completion: December 2015

The Sydney Memory & Ageing Study (MAS)

CHeBA staff: Henry Brodaty, Perminder Sachdev, Julian Trollor, Brian Draper (conjoint), Nicola Kochan, Kristan Kang, John Crawford, Kate Maston, Adam Theobald, Karen Mather, Wei Wen, Simone Reppermund

Project description: The MAS began in 2005 to examine the clinical characteristics and prevalence of mild cognitive impairment (MCI) and related syndromes, to determine the rate of change in cognitive function over time and to investigate risk and protective factors for cognitive decline and dementia. It is one of the largest longitudinal studies of this kind in Australia and has resulted in many scientific publications and several national and international collaborations. At the core of our program are five longitudinal cohorts that have been systematically assessed with a comprehensive range of tools. They cover the age range from 40 to 100+ years. The focus is on cross-sectional neurocognitive function and its longitudinal change over time, terminating with neuropathology.

Aims:

- To determine the rate of change in cognitive function over time.
- To examine the clinical characteristics and prevalence of mild cognitive impairment (MCI) and related syndromes, including Alzheimer's disease, vascular dementia and frontotemporal dementia.
- To develop and refine measures for early diagnosis and prognosis and biomarkers.
- To examine risk factors for and protective factors against cognitive decline and dementia

Design & method: At the baseline assessment from 2005 to 2007, 1037 non-demented individuals aged 70-90 were recruited from two areas of Sydney, following a random approach to 8914 individuals on the electoral roll. They underwent detailed neuropsychological and medical assessments and donated a blood sample for clinical chemistry, proteomics and genomics. A knowledgeable informant was also interviewed. Structural MRI scans were performed on 544 of the participants, and subgroups participated in studies of falls and balance, metabolic and inflammatory markers, functional MRI and prospective memory. The group had their final detailed neuropsychological assessments at Wave 4 (6 year follow-up) and will continue to be followed up annually by telephone with the end point being dementia or death.

Progress to date:

- The longitudinal cohorts have been followed up and yielded a large amount of data on many aspects of brain ageing and dementia. Acquisition of 7-year follow-up data was completed in 2014, with 8- and 9-year follow-up data collection currently taking place.
- We have studied a wide range of risk factors for cognitive impairment, including genetic determinants (including white matter lesions, hippocampus, subcortical brain structures, grey matter volumes), arterial stiffness, dietary mineral intake, glucose disorders, inflammatory markers (e.g. MIC-1, IL6) and lifestyle factors.
- Collaborations include: COSMIC – COhort Studies of Memory in International Collaboration: an international collaboration of longitudinal studies of ageing (led by CHeBA); BrainInflame: an international collaboration for the study of neuroinflammation and its impact on cognition and mood disturbance (led by CHeBA); PROMOTE: modelled on a similar European consortium, PROMOTE aims to enhance psychosocial research into mental illness and ageing by bringing together researchers from Japan, Korea, China, Singapore, Taiwan, Australia and other countries in the Asia-Pacific region to increase collaboration, foster cross-country comparisons and build capacity (co-led by CHeBA); a number of international genetics consortia: CHARGE, ENIGMA, PERADES.

Benefits: Our research has found modifiable factors which influence neuropsychiatric disorders, in particular cognitive decline. This can be translated into effective intervention and policy for optimal treatment programs that are affordable, acceptable and practical in the Australian context. International collaborations provide opportunities for researchers to share and compare data from existing studies, allowing systematic examination of brain ageing issues on a larger scale.

Output: 90 published papers, 66 papers in preparation or submitted, several conference presentations in Vancouver, Sydney, Adelaide and Copenhagen.

Funding: NHMRC.

Date commenced: September 2005

Expected date of completion: Ongoing

Towards understanding the role of long non-coding RNA in age-related memory decline – an early marker of Alzheimer's disease

CHeBA staff: Karen Mather, Anbupalam Thalamuthu, Perminder Sachdev et al.

Other investigators: Dr Nicola Armstrong (University of Sydney)

Project description: Prior studies suggest epigenetics may play a role in late-onset Alzheimer's disease. However, few studies have examined the role of long non-coding RNAs (ncRNAs) and an early marker of Alzheimer's disease, age-related memory loss.

Aims: To identify long ncRNAs associated with age-related memory performance.

Design & method: RNA will be extracted from peripheral blood samples from identical twins discordant for memory performance from the Older Australian Twins Study. RNA sequencing will be performed.

Progress to date: Identical twin pairs discordant for memory performance have been identified and RNA extracted.

Benefits: Identified long ncRNAs may be useful as biomarkers of early Alzheimer's disease and may also clarify their role in the pathological mechanisms leading to the disease. Ultimately, it may suggest clinical diagnostic, prognostic and treatment strategies for Alzheimer's disease.

Output: None to date.

Funding: Yulgilbar Foundation Alzheimer's Research Program Grant, NHMRC, ARC, Alzheimer's Australia Dementia Research Foundation Postdoctoral Fellowship.

Date commenced: December 2013

Expected date of completion: December 2016

Transcranial direct current stimulation (tDCS) combined with cognitive training to enhance memory in patients with amnestic mild cognitive impairment (aMCI)

CHeBA staff: Adith Mohan, Henry Brodaty, Perminder Sachdev

Other investigators: Professor Colleen Loo, Dr Donel Martin (Black Dog Institute)

Project description: Transcranial Direct Current Stimulation (tDCS) has been shown to enhance cognition in psychiatric patients. A majority of Computer Cognitive Training (CCT) trials have demonstrated improvement in healthy older adults and older adults with MCI. Our trial is the first to test the ability of tDCS to bolster the effects of CCT in older adults with memory problems.

Aims: To investigate an exciting novel approach for improving memory in people diagnosed with amnestic mild cognitive impairment (aMCI): cognitive training (CT) combined with mild non-invasive brain stimulation (transcranial direct current stimulation (tDCS)).

Design & method: Double-blind randomized controlled study. Participants are randomised to one of two conditions: active or sham (placebo) tDCS during CT across 15 sessions (1 hour a session, 3 sessions per week).

Progress to date: Data collection commenced in January 2013. So far we have had 30 study completers and currently one participant has been comprehensively screened and is due to commence treatment in March 2015. Preliminary analysis suggests there is a difference favouring the active tDCS + CT condition on the primary outcome measure assessing learning and memory and on a secondary outcome measure assessing speed of information processing.

Benefits: This research may help to develop new interventions for improving cognition and memory in people at risk for dementia.

Output: The research will be submitted for publication once completed.

Funding: Thomas Foundation, DCRC.

Date commenced: January 2013

Expected date of completion: June 2016

Understanding the genetics of white matter microstructure of the corpus callosum

CHeBA staff: Sri Chandana Kanchibhotla (Masters student), Karen Mather, Anbupalam Thalamuthu, Wei Wen, Perminder Sachdev et al.

Other investigators: Dr Lin Zhuang (formerly CHeBA), Associate Professor Margaret J. Wright (QIMR Berghofer Institute), Professor David Ames (National Ageing Research Institute; Royal Melbourne Hospital)

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Project description: Age-related changes in the corpus callosum are associated with age-related cognitive and physical impairments and neurodegenerative disease. The integrity of the microstructure of the corpus callosum can be assessed using diffusion tensor imaging (DTI). This Masters project investigates the genetics of the microstructure integrity of the corpus callosum. It utilises data from participants of the Older Australian Twins Study and the Sydney Memory and Ageing Study.

Aims: To estimate the heritability and to identify genetic variants for white matter integrity measures of the corpus callosum.

Design & method: White matter integrity measures for the corpus callosum (DTI) were estimated from neuroimaging scans. Heritability was estimated using the twin sample and structural equation modelling. A genome-wide association study (GWAS) has been undertaken using both the OATS sample and the Sydney Memory and Ageing Study.

Progress to date: Heritability analyses are completed.

Benefits: Potential benefits from this work include a better understanding of the contributions of genetics to the integrity of the corpus callosum, an important brain structure which facilitates communication between the two hemispheres.

Output: The heritability of the corpus callosum has been published in the journal, *PLoS One* (Kanchibhotla et al., 2014). A GWAS has been undertaken and the results are being assessed.

Funding: NHMRC, ARC, Commonwealth Scientific and Industrial Research Organisation Flagship Collaboration Fund Grant, Alzheimer's Australia Dementia Research Foundation Postdoctoral Fellowship, Sri Chandana Kanchibhotla was supported by a scholarship from the Dementia Collaborative Research Centre– Assessment and Better Care, UNSW.

Date commenced: 2011

Expected date of completion: June 2015

Vitamin binding proteins in plasma (afamin and vitamin D binding protein VDBP)

CHeBA staff: Anne Poljak, Nicole Kochan, Wei Wen, John Crawford, Julian Trollor, Henry Brodaty, Perminder Sachdev

Other investigators: Dr Fei Song (formerly CHeBA), Professor Hans Dieplinger (Innsbruck Medical University, Austria), Professor John Attia (University of Newcastle), Associate Professor Peter W. Schofield (University of Newcastle), Dr Mark McEvoy (University of Newcastle), Professor Ralph Martins (Edith Cowan University)

Project description: Quantification of vitamin binding protein levels (particularly afamin and vitamin D binding protein) in mild cognitive impairment and Alzheimer's disease plasma in a variety of population based cohorts, from Sydney and elsewhere in Australia.

Aims:

- Determine if vitamin binding protein levels are different in MCI and AD plasma relative to normal controls, and whether observations would be reproducible across independent cohorts of similar design.
- Identify which of the vitamin binding proteins change with age and/or are dysregulated in MCI and AD.
- Correlate plasma vitamin binding protein levels with cognitive domain scores and brain volumetrics.
- Afamin (vitamin E binding) and VDBP are of specific interest, based on our preliminary discovery proteomics data. We plan to assay plasma levels using ELISA quantification.

Design & method: Both cross-sectional and longitudinal designs are used. Cohorts include: Sydney MAS (all 4 waves), Hunter Community Study (HCS), Dominantly Inherited Alzheimer's disease Network (DIAN), Older Australian Twins Study (OATS) and Sydney Centenarian Study (SCS).

Progress to date: Experiments are based on previous screening using the iTRAQ proteomics approach with pooled plasma. Individual plasma samples are currently being assayed using ELISA and both local and international collaborators involved, with provision of additional plasma samples or assay of our samples with validated ELISA.

Benefits:

- Potential biomarker panel to assist in diagnosis of predisposition to MCI and/or AD.
- Identify robust biomarkers, which show consistent change across studies.
- Understand the effect of plasma vitamin binding protein changes on cognition and brain volumetrics.
- Determine how plasma vitamin binding protein levels change with age, particularly advanced old age.
- Understand the role of specific vitamin binding proteins (afamin and VDBP) in the ageing brain.

Output: 2 of our plasma proteomics publications are the basis for this work. Assays are currently in progress.

Funding: NHMRC, ARC, Rebecca L. Cooper Medical Research Foundation, Alzheimer's Australia Rosemary Foundation, Sachdev Foundation, UNSW Faculty of Medicine FRG and Early Career Researcher Grants.

Date commenced: 2012

Expected date of completion: Ongoing

Voxel-based resting-state functional connectivity

CHeBA staff: Anbupalam Thalamuthu, Perminder Sachdev, Wei Wen

Other investigators: Dr Haobo Zhang (formerly CHeBA), Professor Yong He (Beijing Normal University, China)

Project description: The resting-state functional network reflects the intrinsic architecture of the brain network. Evidence has shown that individual variations in resting-state functional connectivity strength (rs-FCS) are related to their differences in cognitive performance, and the relationship between rs-FCS and cognition also exists in older adults. While previous studies extracted rs-FCS from coarsely pre-defined regions, this study uses voxel-based rs-FCS to correlate with neuropsychological tests in community-dwelling, cognitively healthy older adults.

Aims:

- To investigate resting-state functional connectivity using whole-brain voxel-based resting-state connectivity measures.
- To investigate the heritability of whole-brain connectivity.

Design & method: We used voxel-based rs-FCS to correlate three neuropsychological tests (episodic memory, language and executive) in 71 community-dwelling, cognitively healthy older adults aged 73-90 years.

Progress to date: Analyses are completed and a manuscript is in preparation.

Benefits: Two implications might be drawn from our findings. Firstly, the intrinsic functional architecture possibly reflects a functional repertoire of neural response. Possibly, the co-activation of spontaneous neuronal activities at rest represents a prepatory state of the brain for quick responses to cognitive tasks, which explains the predictive ability of rs-FCS in task-activated areas to relevant task performance. Secondly, competition might exist between distinct neural systems in the brain intrinsic network architecture. The opposite FCS-cognition relationships between task-activated and task-deactivated areas might stem from the inherent anti-phase relationship between them, which is also evident in neural activation patterns during task and rest. A pervasive competition appears to be embedded in the anti-correlated neural systems, to maximize their allocation of brain resources. The balance derived from such competition might endow an individual with a better ability in certain cognitive functions, whilst providing a disadvantage for other cognitive functions.

Output: A manuscript is in preparation.

Funding: NHMRC, ARC.

Date commenced: July 2013

Expected date of completion: May 2015

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Archiving datasets of the Brain & Ageing Research Program

CHeBA staff: Perminder Sachdev, Henry Brodaty, Kristan Kang

Project description: To archive, and thereby make publicly available, the longitudinal datasets collected by the Brain and Ageing Research Program, School of Psychiatry, University of New South Wales. Each of these datasets contains longitudinal data collected on older people ranging from healthy individuals to those with mild cognitive impairment and dementia. These datasets contain the following types of data:

- cognitive phenotype
- neurocognitive assessment
- psychosocial questionnaires
- medical history + exam
- medication use
- neuroimaging
- blood chemistry
- proteomics
- genetics/genomics.

Aims:

- To facilitate the use of these datasets by researchers internationally, either by themselves or in combination with other comparable datasets, for novel enquiry and/or replication of findings from other cohorts.
- To facilitate collaborative research with and between international research groups studying brain aging and age-related brain diseases
- To archive the following datasets: the Sydney Memory and Ageing Study, the Older Australian Twins Study, the Sydney Centenarian Study and the Sydney Stroke Study.

Design and method: Archiving of data for access to international researchers requires that the data be stored in ASCIII format (de-limited text), and additional setup files be supplied to users for importing data, labels and other metadata into SPSS, SAS and STATA software environments. It also requires a 'codebook' or data-guide document (i.e. data definition statements) to aid and support analysis of archived data. The data will initially be hosted on a UNSW Australia website, and procedures for access by external groups will be developed. Approval from the institutional ethics review board is being sought for this. Eventually, the data will be made available on the NACDA website or an alternative site such as the Alzheimer's disease Neuroimaging Initiative (ADNI) after appropriate local approvals have been obtained.

Benefits: These datasets provide a significant opportunity to the research community because of the depth and breadth of the data collected. The databases invite inquiry from many fields, as well as providing a simple means for multidisciplinary research and projects. Potential fields of inquiry include: Psychology, Psychiatry, Gerontology, Epidemiology, Neuroimaging, Social science, Genetics, Proteomics etc. The datasets permit the replication of findings from other studies of ageing. These contain longitudinal cohort data which allow for the investigation into progression of diseases and neurocognitive disorders. Incidence rates of disorders can be determined, and normal ageing can also be studied. In addition to uni- and bi-variate analyses, the kinds of statistical analyses that could be conducted on these data include: mixed effects models, heritability analysis, structural equation modelling and other multivariate analyses.

Output: The data has been fully archived. A "CHeBA Data" website, which acts as a data directory and portal whereby interested researchers can apply for and access data from the Brain & Ageing Research Program undertaken at the Centre for Healthy Brain Ageing, has been designed and developed. Once the content for the site is complete and uploaded the site will go live.

Funding: National Institute of Health (USA).

Date commenced: January 2013

Date completed: May 2014.

The genetic and environmental determinants of amyloid deposition in older individuals: An amyloid imaging study using the twin design (PiB/PET pilot study)

CHeBA staff: Perminder Sachdev, Wei Wen, Melissa Slavin (conjoint), Anbupalam Thalamuthu, John Crawford, Teresa Lee, Karen Mather

Other investigators: Professor Christopher Rowe (University of Melbourne)

Project description: β-amyloid (Aβ) plaques are one of the hallmark neuropathologies of Alzheimer's disease (AD), but many aspects of their role in the disease are unclear. Until recently, amyloid plaque burden could only be determined post-mortem. Recent developments in neuroimaging allow amyloid burden to be assessed *in vivo* using positron emission tomography (PET), making it possible to examine the relationship between amyloid load and cognitive function in temporal proximity, and to design studies to examine its risk and protective factors. Here we use the power of the twin design to examine the relative contributions of heritable and other risk factors to amyloid deposition in the brains of older individuals, and further investigate its possible contribution to cognitive impairment, in one of the first large studies of its kind. To date, only one small twin study internationally has examined Aβ burden among MZ and DZ twins discordant for cognitive impairment.

Aims:

- To examine genetic and environmental factors and their interactions associated with β-amyloid (Aβ) deposition in the brains of older individuals.
- To determine the heritability of Aβ deposition in the brain as an endophenotype of Alzheimer's disease (AD).
- To determine the shared genetic and environmental variance between amyloid load and i) cognition, ii) cardiovascular disease, and iii) cerebral atrophy.
- To investigate the genetic and environmental risk (and protective) factors associated with amyloid load in older individuals. These factors include:
- Genetic factors such as the apolipoprotein E (*ApoE*) gene, the brain-derived neurotrophic factor (*BDNF*) gene, amyloid pathway genes, and other genetic polymorphisms with possible roles in amyloid deposition.
- Environmental factors such as cognitive reserve (education, complex cognitive activity and exercise), vascular risk factors, traumatic brain injury and depression.
- To investigate the relationship between amyloid load and memory function cross-sectionally, and decline in memory longitudinally, and possible moderation of this relationship by cognitive reserve and cerebral vascular disease.

Design & method: Twin pairs will be recruited from OATS and invited to undertake a PiB-PET scan. *Inclusion criteria*: aged 65 years or older, ability to consent, having a consenting MZ or DZ co-twin, having completed some education in English, and a minimum of at least low average estimated premorbid IQ. *Exclusion criteria*: history of epilepsy, other neurological disorder or a systemic disease impacting on cognitive functioning; current diagnosis of an acute psychotic disorder or major depression.

Findings: PiB-PET scans of 60 participants (17 MZ, 13 DZ pairs) were performed at Austin Hospital, Melbourne as part of the longitudinal Older Australian Twins Study (OATS). The moderate correlation of SUVR in MZ twins and the lack of correlation in DZ twins are noteworthy. However, heritability estimates are moderate, suggesting significant environmental contributions to amyloid deposition. Using 1.5 SUVR as the cut-off for a +ve scan, 6/60 (10%) (2 MZ and 4 DZ) were positive; all were discordant, with their co-twins being –ve. Among the discordant MZ twins, the greatest differences in amyloid deposition were seen in the orbitofrontal area, striatum and the anterior and posterior cingulate gyri. Among the DZ twin pair, similar regional differences in amyloid deposition were seen, with differences also seen in the ventro-lateral prefrontal area and temporal lobe. The amyloid load was not significantly associated with global cognition, memory or any of the other cognitive domains examined in this small sample. The genetic correlations of Global SUVR with memory domain and white matter hyperintensities were low and non-significant.

Benefits: Greater understanding into the role of amyloid deposition in the brains of older individuals and its possible contribution to cognitive impairment.

Output: This study received further funding through an NHMRC project grant for 2015-2017.

Funding: NHMRC.

Date commenced: January 2013

Date completed: December 2014

Is white matter an earlier biomarker than grey matter for Alzheimer's disease?

CHeBA staff: Wei Wen, Perminder Sachdev

Other investigators: Dr Lin Zhuang (formerly CHeBA)

Project description: White matter (WM) loss is a common finding in Alzheimer's disease (AD), but it is unclear whether WM damage is linked to amyloid pathology in AD.

Aims:

- To investigate whether microstructural white matter changes similar to those identified in AD patients can be detected in cognitively normal non-demented individuals destined to develop amnestic mild cognitive impairment (aMCI).
- To examine the relationships between brain amyloid burden as measured by cerebrospinal fluid (CSF) Aβ42 levels and white matter degeneration at different stages of the AD process

Design & method: Data was obtained from the MAS and the Alzheimer's disease Neuroimaging Initiative (ADNI) database. We studied cognitively normal individuals at baseline (Wave 1) of the MAS. The majority remained cognitively stable (CN-stable) in the next few years (Wave 2 and Wave 3) and some were diagnosed with aMCI (CN-aMCI converter) some years later. Structural magnetic resonance imaging and diffusion tensor imaging were acquired at baseline to assess grey matter atrophy and microstructural white matter changes respectively. We also examined CSF $A\beta_{42}$ levels in cognitively normal individuals, early mild cognitive impairment (EMCI), late mild cognitive impairment (LMCI), and AD using ADNI data. Fractional anisotropy (FA) index measuring WM integrity was derived from diffusion tensor imaging (DTI), while grey matter (GM) structural measures including cortical thickness and hippocampal volume were obtained on concurrently acquired MRI structural images.

Findings: This study characterised WM microstructural injury and its relation to hippocampal atrophy at different stages of aMCI. We found that late aMCI individuals with severe memory deficits had significant microstructural WM abnormalities in the limbic WM tracts, while the hippocampus was still intact and did not associate with DTI measures of the fornix in early aMCI. This finding points to the advantage of DTI metrics over traditional MRI volumetrics in providing an earlier and more accurate imaging marker.

Output: 4 peer-reviewed publications, including one published in *Neurology* with an editorial.

Benefits: Our study demonstrates that white matter DTI can be used as a non-invasive biomarker in early diagnosis of AD. DTI is less expensive and more readily available (vs. fluorodeoxyglucose positron emission tomography - FDG-PET, amyloid imaging using Pittsburgh compound B PET - PiB-PET) and less invasive (vs. CSF) than conventionally accepted biomarkers. It also opens up WM degeneration as an independent field of enquiry in AD. The findings obtained from the project will also improve practice in clinical and research by potentially providing information on identifying neurocognitive disorders in the elderly, as well as suggesting more appropriate treatment. The findings will be translated into a set of recommendations for clinicians.

Funding: NHMRC.

Date commenced: July 2012

Date completed: December 2014

Relationship between vestibular function, dizziness and falls in older people community-dwellers

CHeBA staff: Perminder Sachdev, Henry Brodaty

Other investigators: Dr Jasmine Menant (NeuRA, UNSW; formerly CHeBA), Dr Daina Sturnieks, Dr Kim Delbaere, Associate Professor Jacqui Close, Professor Stephen Lord (NeuRA, UNSW)

Project description: Despite evidence of the high prevalence of vestibular vertigo among people aged over 60 years and reports that a large proportion of older people who present to emergency departments due to a fall have a recent history of vestibular impairment, clinical assessments of vestibular function are seldom conducted as part of a fall risk assessment.

Aims: This study examined further the relationship between vestibular function and falls, using a range of vestibular function tests, which should allow the precise identification of the source of the vestibular impairment.

Design & method: This is a cohort study of prospective falls. Older community-dwelling people aged 70 years and over were recruited amongst participants from the Wave 4 of the Sydney Memory and Ageing Study. Participants underwent a multidisciplinary baseline assessment comprising self-report items regarding dizziness episodes and tests of vestibular, cardiovascular, neuromuscular, balance and psychological functioning. Participants were then followed up for falls incidents for a year using monthly falls calendars.

Findings: 312 participants underwent a baseline assessment. All have completed their one year falls follow-up and have received an end of study report detailing their performance in the various domains assessed as well as a composite risk of falls. The data will be analysed in the first semester of 2015.

Output: None to date.

Benefits: If vestibular impairment is identified as a risk factor for falls, the study will determine whether inclusion of vestibular function test(s) into an already validated fall risk screening tool can improve fall risk prediction. Such knowledge will be particularly useful to tailor falls prevention interventions to older people with various sensory impairments.

Date commenced: January 2012

Date completed: December 2014

We think you can dance!

CHeBA staff: Lee-Fay Low (conjoint), Henry Brodaty, Nicole Kochan

Other investigators: Associate Professor Dafna Merom (University of Western Sydney), Shane Carroll (dancer, consultant)

Project description: People with dementia living in residential aged care have low levels of physical activity and exercise programs tend to be poorly attended. *We think you can dance!* is a cognitively-enriched social dance program for people with moderate to severe dementia living in residential aged care facilities.

Aims: The aim of this study is to develop and pilot a cognitively-enriched dance intervention to improve cognition (primary outcome) and physical function in nursing home residents with dementia in comparison to an active control condition.

Design & method: Dancers and researchers collaborated to develop a cognitively-enriched dance program over 5 days. A feasibility pilot was then conducted over 16 weeks with 18 nursing home residents with moderate-severe dementia living in a residential aged care facility. Half the residents were randomised to the dance group and half to an active control group which listened to music and socialised. Cognition, behaviour, physical and daily function were evaluated.

Findings: We demonstrated that we could deliver the dance program safely to residents 3 times a week for 16 weeks without any critical incidents. We delivered 45 of scheduled 48 sessions, 3 were missed due to dance captain illness. We re-assessed 15 (83%) of 18 recruited participants after 4 months (one died, one was transferred, one refused to participate in sessions or assessments). Of the 7 residents we reassessed in the dance group, average attendance was 30 sessions (range 16 to 45). Of the 8 residents in the music group, average attendance was 40 sessions (range 32 to 43). Scheduling of the sessions appeared to significantly influence attendance. In the music group, residents were taken from the dining room to music sessions immediately after breakfast. In the dance group, when we went to collect the residents mid-morning, many were back in bed and refused to attend. When we started serving morning tea in the room where the dance session was held, attendance improved. No serious behavioural incidents or falls occurred during our pilot. While we cannot assign much weight to the quantitative data collected during our pilot, we note promising trends for the Severe Impairment Battery (SIB) and Cohen-Mansfield Agitation Inventory.

Output: The feasibility pilot is in draft. The program has been presented at 1 conference and 3 other events for clinicians and researchers.

Benefits: This study adds to the growing evidence that physical activity may maintain cognitive function in people with dementia, particularly when combined with cognitive and social activity.

Funding: Thomas Foundation.

Date commenced: October 2013

Date completed: October 2014

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CHeBA Collaborators

"International collaboration represents the next phase of medical research in which biomedical scientists, much like physicists, work together on problems too large to be solved by individual researchers." PROFESSOR PERMINDER SACHDEV

Societies/Professional Associations

- Alzheimer's Australia
- Alzheimer's Disease International (ADI)
- Australasian Association of Gerontology (AAG)
- Australasian Society for Psychiatric Research (ASPR)
- International College of Geriatric Psychoneuropharmacology (ICGP)
- International Neuropsychiatric Association (INA)
- International Psychogeriatric Association (IPA)
- Royal Australian & New Zealand College of Psychiatrists (RANZCP)
- International Society of Vascular Behavioural and Cognitive Disorders (VASCOG)

National

Commonwealth

- Australian Government Department of Social Services
- Australian Government Department of Health

Western Australia

- Edith Cowan University, Perth

Tasmania

- University of Tasmania, Hobart

ACT

- Australian National University, Canberra

New South Wales

- University of Newcastle, Newcastle
- University of New England, Armidale
- University of Wollongong, Wollongong

Sydney

- Academic Department for Old Age Psychiatry (ADFOAP), Prince of Wales Hospital
- Australasian Research Institute, Sydney Adventist Hospital
- Australian Catholic University
- Bankstown-Lidcombe Hospital
- Bioanalytical Mass Spectrometry Facility, Mark Wainwright Analytical Centre, UNSW
- Black Dog Institute, UNSW
- Brain Sciences UNSW
- Centre of Excellence in Population Ageing Research (CEPAR), UNSW
- Clinical Research Unit for Anxiety and Depression (CRUfAD), UNSW
- Garvan Institute
- Macquarie University
- National Drug & Alcohol Research Centre (NDARC), UNSW
- Neuropsychiatric Institute (NPI), Prince of Wales Hospital
- Neuroscience Research Australia (NeuRA), UNSW
- School of Biotechnology and Biomolecular Sciences, UNSW
- School of Medical Sciences, UNSW
- School of Psychology, UNSW
- St Vincent's Centre for Applied Medical Research
- University of Sydney
- University of Western Sydney
- University of Wollongong

South Australia

Adelaide

- Flinders University
- University of Adelaide

Victoria

Melbourne

- The Florey Institute of Neuroscience and Mental Health
- La Trobe University
- Monash University
- National Ageing Research Institute
- Royal Melbourne Hospital
- University of Melbourne

Queensland

Brisbane

- Griffith University
- QIMR Berghofer Institute, Brisbane
- Queensland University of Technology
- St Andrew's Medical Institute
- University of Queensland

International

Africa

- University of Ibadan, Nigeria
- University of Natal Kwazulu, South Africa

Asia-Pacific

- Beijing Normal University, China
- Capital Medical University, China
- Peking University, China
- Shanghai Jiaotong University, China
- Institut de Recherche pour le Développement (IRD), Tahiti, French Polynesia
- Institut Louis Malardé, Tahiti, French Polynesia
- Chinese University of Hong Kong, Hong Kong
- Hong Kong Polytechnic University, Hong Kong
- The University of Hong Kong, Hong Kong
- Atma Jaya Catholic University, Indonesia
- Keio University, Japan
- Kyushu University, Japan
- National Center for Geriatrics and Gerontology, Japan
- Tohoku University, Japan
- University of Macau, Macau
- Universiti Putra Malaysia, Malaysia
- Department of Neuropsychiatry, Gyeonggi Provincial Hospital for the Elderly, Republic of Korea
- Hallym University, Republic of Korea
- Seoul National University, Republic of Korea
- National Neuroscience Institute, Singapore
- National University of Singapore, Singapore

Middle East

- Sultan Qaboos University, Oman

Europe

- Innsbruck Medical University, Austria
- Karolinska Institutet, Finland
- University of Helsinki, Finland
- French National Institute of Health and Medical Research (INSERM), France
- University Aix-Marseille, France
- Université Lille Nord de *France, France*
- Ludwig-Maximilians-University, Germany
- Max Planck Institute of Psychiatry, Germany
- Neuroscience Network Düsseldorf, Heinrich Heine University, Germany
- University of Marburg, Germany
- University of Thessaly, Greece
- Golgi-Cenci Foundation, Italy
- Jagiellonian University, Poland
- University of Valencia, Spain
- University of Zaragoza, Spain
- Lund University, Sweden
- University of Gothenburg, Sweden
- Maastricht University, The Netherlands
- University of Groningen, The Netherlands

UK

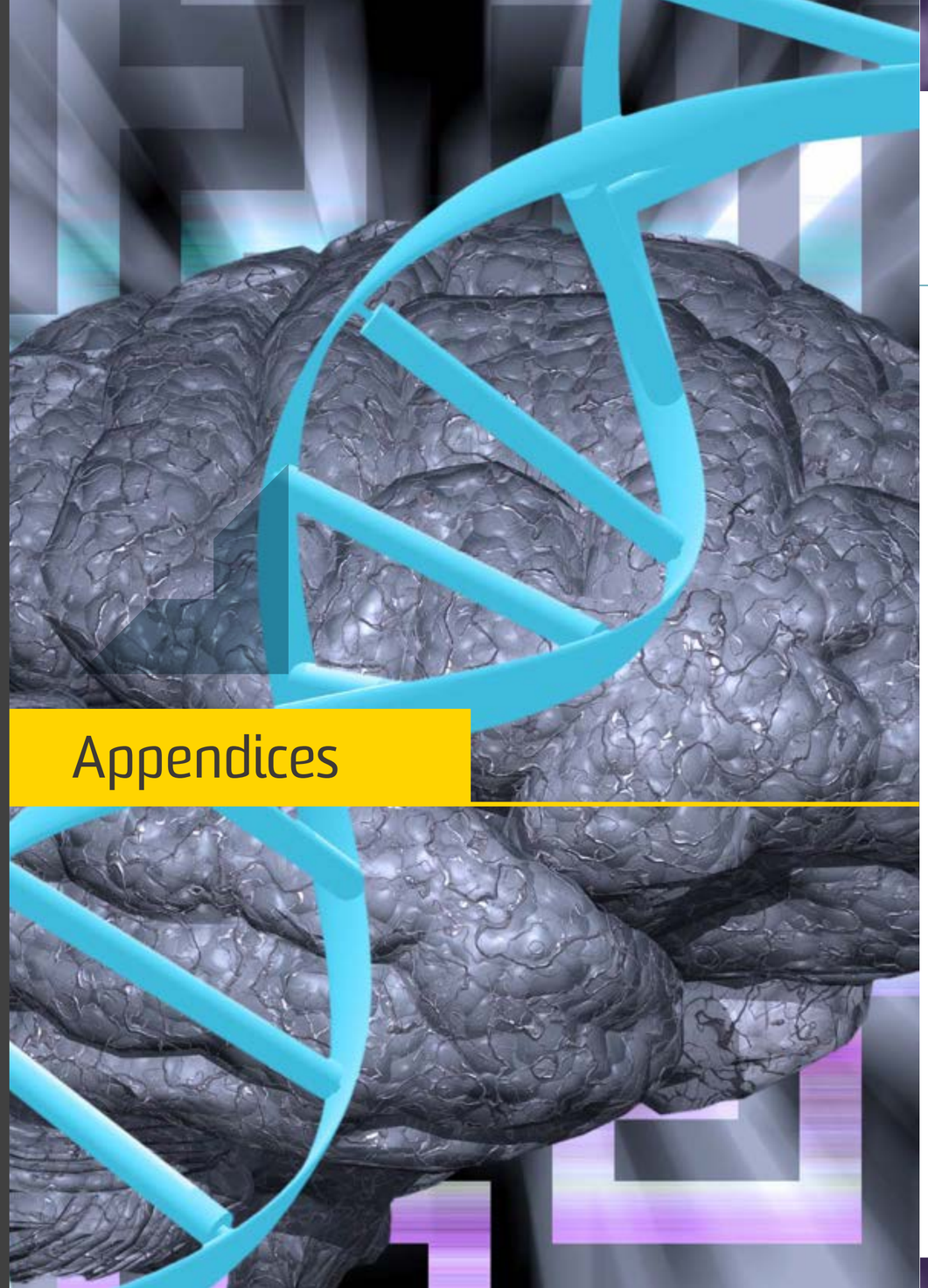
- Cambridge University, England
- Cognitive Function & Ageing Studies, England
- King's College London, England
- Newcastle University, England
- University College London, England
- University of Bradford, England
- University of Leeds, England
- Royal College of Surgeons in Ireland, Ireland
- University of Aberdeen, Scotland
- University of Edinburgh, Scotland
- Swansea University, Wales

North America

- Dalhousie University, Canada
- Université de Montréal, Canada
- Stanford University, California, USA
- University of California, California, USA
- University of Colorado, Colorado, USA
- University of Georgia, Georgia, USA
- Johns Hopkins Medicine, Maryland, USA
- Mayo Clinic, Minnesota, USA
- University of Minnesota, Minnesota, USA
- Boston University, Massachusetts, USA
- Harvard University, Massachusetts, USA
- Cleveland Clinic, Nevada, USA
- Columbia University, New York, USA
- Gertrude H. Sergievsky Center, New York, USA
- Yeshiva University, New York, USA
- University of Pittsburgh, Pennsylvania, USA

South America

- Universidade Federal de Minas Gerais, Brazil
- University of São Paulo, Brazil
- Universidad Católica de Chile, Chile



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Appendix A: Staff List

Leadership

Scientia Professor Henry Brodaty
Co-Director CHeBA, Montefiore Chair of Healthy Brain Ageing

Scientia Professor Perminder Sachdev
Co-Director CHeBA, Leader Epidemiology Group, Leader Neuropsychiatry Group

Angie Russell
Centre Manager

Academic Staff

Dr Nady Braidy
Research Fellow, Co-Leader Molecular Biology & Stem Cell Group

Professor Lynn Chenoweth
Professor of Nursing

Dr Nicole Kochan
Research Fellow, Co-Leader Neuropsychology Group

Associate Professor Lee-Fay Low
Research Fellow
(until December 2014)

Dr Karen Mather
Research Fellow, Leader Genetics & Genomics Group

Dr Adith Mohan
Research Fellow

Dr Julia Müenchhoff
Research Fellow

Dr Simone Reppermund
Research Fellow, MAS Coordinator
(until December 2014)

Dr Anbupalam Thalamuthu
Research Fellow

Associate Professor Wei Wen
Leader Neuroimaging Group, Director Neuroimaging Laboratory

Professional & Technical Staff – Research

Shaily Aggarwal
Research Assistant
(until December 2014)

Dr Jocelyn Bowden
Research Officer, OATS Coordinator

Dr John Crawford
Statistician

Tanya Duckworth
Research Assistant

Therese French
Research Assistant
(until December 2014)

Dr Kristan Kang
Data Manager

Angela King
Research Assistant
(until February 2014)

Dr Darren Lipnicki
Research Officer

Kate Maston
Research Assistant

Sarah Pont
Research Assistant
(until July 2014)

Mamta Sidhu
Research Assistant
(until September 2014)

Adam Theobald
Research Assistant

Claudia Woolf
Research Assistant (Casual)

Professional & Technical Staff – Support

Kate Crosbie
Administrative Assistant – Marketing & Communications (Casual)

Dr Sophia Dean
Administrative Officer

Michele De Permentier
Administrative Assistant
(until March 2014)

Craig Douglass
Administrative Assistant – Marketing & Communications (Casual)

Suzanne Forrester
Administrative Assistant

Heidi Mitchell
Marketing & Communications Officer

Conjoint Staff

Professor Gavin Andrews
Chief Investigator, NHMRC Program Grant ID 568969

Professor Brian Draper
Associate Investigator, Sydney Memory & Ageing Study

Dr Nicola Gates
Lecturer

Dr Teresa Lee
Senior Lecturer, Co-Leader Neuropsychology Group

Dr Charlene Levitan
Adjunct Associate Lecturer

Dr Ora Lux
Lecturer

Dr Anne Poljak
Lecturer, Leader Proteomics Group

Professor Katherine Samaras
Professor of Medicine, UNSW

Honorary Associate Professor Kuldip Sidhu
Co-Leader Molecular Biology & Stem Cells Group

Dr Melissa Slavin
Senior Lecturer

Professor Julian Trollor
Leader Neuroinflammation Group

CHeBA Honorary Research Fellows

Dr Evelyn Smith

Dr Im Quah-Smith

Dr Fei Song

Dr Haobo Zhang

Dr Lin Zhuang

Visiting Fellows

Professor Bernhard Baune (University of Adelaide)
Visiting Professorial Fellow, Leader BrainInflame Consortium
(January 2013- present)

Associate Professor Pierre Lafaye De Micheaux (Université de Montréal)
Visiting Senior Research Fellow in Neuroimaging Group
(July 2013 – July 2014)

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Appendix B: External Appointments

Dr Nady Braidy

- Honorary Fellow, Australian School of Advanced Medicine, Macquarie University
- Adjunct Lecturer, School of Biotechnology and Biomolecular Sciences, University of New South Wales
- Health Services Advisor, Department of Aged Care and Rehabilitation, Bankstown-Lidcombe Hospital, Sydney, Australia
- Editor, *Analytical Cellular Pathology*

Professor Henry Brodaty

- Scientia Professor, Ageing and Mental Health, (previously Professor of Psychogeriatrics, 1990-2010), School of Psychiatry, University of New South Wales (2011-2016)
- Montefiore Chair of Healthy Brain Ageing (2012-present)
- Director, Primary Dementia Collaborative Research Centre, UNSW (2006-present)
- Co-Director Centre for Healthy Brain Ageing, UNSW (2012-present)
- Head (and founder), Memory Disorders Clinic, Prince of Wales Hospital (1985 -present)
- Senior clinician, Aged Care Psychiatry, Prince of Wales Hospital (1990-present)
- President International Psychogeriatric Association (2013-2015)
- CSIRO Prevention Flagship Advisory Committee (2011-2014)
- Chair, Dementia Committee, NHMRC Knowledge Translation Faculty (2013-present)
- International advisor, Institute of Alzheimer's Education Advisory Board, Hong Kong (2013-2015)
- Member, International Advisory Committee of the National Institute of Dementia, South Korea (2013-2015)
- Honorary Professor, Kiang Wu Nursing College, Macau 2014+
- Member, Reference Committee, NSW Policy of Mental Health for Older People and Dementia Care, NSW Department of Health (1993-present)
- Member, Aged Care Reform Implementation Council, Australia (2012-2014)
- Executive member, Australasian Consortium of Centres for Clinical Cognitive Research (AC4R) (2000-present)
- Chair, Scientific Program Committee, Alzheimer's Disease International Annual Congress (2015)
- Theme leader for psychosocial and public health, Scientific Program Committee, Alzheimer's Association International Conference (2014-2016)
- Honorary Professor, Kiang Wu Nursing College, Macau (2014-present)
- Honorary Lifetime Vice-President, Alzheimer's Disease International (ADI) (2005-present)
- Chair ADI Metlife Awards for Psychosocial Research, Alzheimer's Disease International (ADI) (2013-2014)
- Honorary Medical Advisor, Alzheimer's Australia NSW (1992-present)
- Chairman, Dementia Research Foundation Ltd, Alzheimer's Australia (2002-present)
- Chair, National Quality Dementia Care Network Executive Committee, Alzheimer's Australia (2010-present)
- Nutricia, Member, Australian Advisory Board for Nutricia, (2012-present)
- Member, WHO Consultation Group on the Classification of Behavioural and Psychological Symptoms in Neurocognitive disorders for ICD-11 (2012-present)
- Member of Evaluation Board for the Psychiatry, Faculty of the Faculty of 1000 Medicine (2005-present)
- Ambassador, Montefiore Homes (2006-present)
- Chair, Clinical Advisory Committee, Montefiore Homes (2012-present)
- Editorial board for *Aging and Mental Health* (1996-present), *Alzheimer Disease and Associated Disorders : an International Journal* (1995-present), *Alzheimers and Dementia: Journal of the Alzheimers Association* (2005-present), *Australian and New Zealand Journal of Psychiatry* (1981-present), *CNS Drugs* (1999-present), *Dementia and Geriatric Cognitive Disorders* (2010-present), *F1000 Research* (2010-present), *International Journal of Psychiatry in Medicine* (1996-present), *International Psychogeriatrics* (1996-present), *Neurodegenerative Disease Management* (2010-present), *The Australian Journal of Dementia Care* (2012-present)

Professor Lynn Chenoweth

- Professor of Aged & Extended Care Nursing, Faculty of Nursing, Midwifery & Health, University of Technology, Sydney
- Director of the Health & Ageing Research Unit for the South Eastern Sydney & Illawarra Area Health Service
- Lead, NSW Core Committee, Dementia Collaborative Research Centre
- Lead, NSW Expert Advisory Group, Dementia Collaborative Research Centre
- NSW Lead, Planning Committee, Dementia Collaborative Research Centre
- Lead, NSW Steering Committee, Dementia Collaborative Research Centre
- Member, Scientific Committee, Alzheimer's Australia Research Committee
- Member, Research Advisory Group, Parkinson's Australia
- Member, UTS Centre for Mechatronic and Intelligent Systems
- Member, Advisory Group, Carers Australia
- Member, Nursing Curriculum Advisory Committee, Notre Dame University
- Editorial board for *International Journal of Older People Nursing*, *Nursing Older Person Journal*, *Austin Journal of Nursing and Health Care*

Dr Nicole Kochan

- Clinical Neuropsychologist, Neuropsychiatric Institute, Prince of Wales Hospital
- Honorary Associate, Department of Psychology, Macquarie University
- Approved supervisor, College of Clinical Neuropsychologists, Australian Psychological Society

Dr Teresa Lee

- Senior Clinical Neuropsychologist, Neuropsychiatric Institute, Prince of Wales Hospital
- Approved Supervisor, College of Clinical Neuropsychologists, Australian Psychological Society

Dr Karen Mather

- Visiting Research Fellow, Neuroscience Research Australia (NeuRA)

Dr Adith Mohan

- Consultant neuropsychiatrist, Neuropsychiatric Institute, Prince of Wales Hospital
- Member, Local Training Network Governance Committee (NGC) and site coordinator for Training for Psychiatry, Prince of Wales Hospital, South Eastern Sydney & Illawarra Psychiatry Training Network

Dr Anne Poljak

- Senior Research Scientist, Bioanalytical Mass Spectrometry Facility, Mark Wainwright Analytical Centre, UNSW
- Conjoint Lecturer, School of Medical Sciences, UNSW
- Post-Doctoral Fellow, School of Psychiatry, UNSW
- Member, Scientific Review Committee, NSW Brain Bank Network (NSWBBN)
- Member, Scientific Advisory Committee Member, Rebecca L. Cooper Medical Research Foundation

Dr Simone Reppermund

- Editorial board, *Advances in Medicine*

Professor Perminder Sachdev

- Clinical Director, Neuropsychiatric Institute, Prince of Wales Hospital, Sydney (1987-present)
- Chief Medical Adviser to Alzheimer's Australia (2014-present)
- Visiting Fellow, The Centre for Research on Ageing, Health and Wellbeing , Australian National University (2012-2014)
- Member of the F1000 Reports Advisory Board – Neuropsychiatry panel (2010-current)
- Member of the International Advisory Group for the Revision of ICD-10 Mental and Behavioural Disorders and the International Advisory Group for the Revision of ICD-10 Diseases of the Nervous System, WHO ICD-11 Expert Working Group on Neurocognitive Disorders, Mental Health and Substance Abuse Department (2011-present)
- President of the International College of Geriatric Psychoneuropharmacology (2012-2014)
- Executive Member of the International Society of Vascular Behavioural and Cognitive Disorders (VASCOG) (2012-present)
- Member, Neurocognitive Disorders Work Group, DSM-5 (2007-present)
- Founding Executive Committee Member of the Tourette Syndrome Association of Australia (1989-present)
- Scientific Advisory Committee Member of the Alzheimer's Association of Australia (1995-present)

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- Committee Member on Psychotropic Drugs and Other Physical Treatments, Royal Australian and New Zealand College of Psychiatrists (1996-present)
- Chair of the Medical Advisory Committee of the Tourette Syndrome Association of Australia (1996-present)
- Secretary & Treasurer of the Australian Consortium of Centres for Clinical Cognitive Research (1998-present)
- Chair of the Section of Neuropsychiatry, RANZCP (2005-present)
- Fellow of the NHMRC Academy 2011(2011-present)
- Member of the NHMC Assigner's Academy (2012-present)
- Chair of the Scientific Review Committee of the Division of Psychiatry, ESAHS Eastern Section (1996-present)
- Invited Member,Task Force of the International League Against Epilepsy (ILAE) Neuropsychobiology Commission (2011-present)
- Editorial board for *Neuropsychiatric Disorders and Treatment*, *Acta Neuropsychiatrica*, *Current Opinion in Psychiatry*, *Middle Eastern Journal of Ageing*, *Brain and Mind Matters*, *The Open Neuroimaging Journal*, *Middle Eastern Journal of Psychiatry and Alzheimer's*, *American Journal of Geriatric Psychiatry*

Hon. Associate Professor Kuldip Sidhu

- Member, Board of Directors, Society for Brain Mapping & Therapeutics, USA
- Member, Executive Committee, Australasian Society of Stem Cells & Research, Australia
- Editorial board for *Journal of Neurological Disorders*

Professor Julian Trollor

- Chair, Intellectual Disability Mental Health, School of Psychiatry, UNSW
- Senior Medical Practitioner (Academic), Professor in Neuropsychiatry and Intellectual Disability, South Eastern Sydney Local Health District, Sydney
- Visiting Senior Research Fellow, Neuroscience Research Australia (NeuRA)
- Member, NSW Institute of Psychiatry Board
- Executive member, Intellectual and Developmental Disability Special Interest Group, RANZCP
- Executive committee member, NSW Health Agency for Clinical Innovation, Intellectual Disability Health Network
- Executive member, NSW Ministry of Health; Department of Family and Community Services, Joint Committee Intellectual Disability Mental Health
- Member, Panel of Expert Advisers- Disability Deaths, NSW Ombudsman
- Executive Member & immediate past Secretary & Treasurer, International Neuropsychiatric Association
- International member, Neuroleptic Malignant Syndrome Information Service
- Member, Australasian Society for the Study of Intellectual Disability
- Member, National Association for the Dually Diagnosed
- Member, Joint Committee, NSW Health and Ageing Disability and Home Care, NSW Government Family and Community Services
- Member, NSW Council for Intellectual Disability
- Member, Research Advisory Committee, NSW Mental Health Commission
- Member, Society for the Study of Behavioural Phenotypes
- Vice President & Member, Australian Association of Developmental Disability Medicine
- Member, Neurocognitive Disorder Working Group, Diagnostic Manual for Intellectual Disability

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Appendix C: Postgraduate Research Students

CURRENT

Anne-Nicole Casey

- Two degrees to social isolation: friendship schema & resident peer networks within a high-care residential aged care facility
- PhD student
- School of Psychiatry, Faculty of Medicine, UNSW
- Supervisors: Dr Lee-Fay Low, Associate Professor Yun-Hee Jeon, Professor Henry Brodaty

Sophie Chen

- The relationship of diet to neurocognitive health
- Masters by Research student
- School of Psychiatry, Faculty of Medicine, UNSW
- Supervisor: Professor Henry Brodaty, Dr Fiona O'Leary

Premilla Chinnappa-Quinn

- The effect of physical illness and hospitalisation on cognition in older adults
- PhD student
- School of Psychiatry, Faculty of Medicine, UNSW
- Supervisors: Associate Professor Michael Bennett, Professor Perminder Sachdev, Dr Nicole Kochan, Dr John Crawford

Tharusha Jayasena

- The role of polyphenolic compounds in modulating sirtuins and other pathways involved in Alzheimer's disease
- PhD student
- School of Psychiatry, Faculty of Medicine, UNSW
- Supervisors: Professor Perminder Sachdev, Dr Anne Poljak

Jiang Jiyang

- The association of macrophage inhibitory cytokine - 1 with ageing brains
- PhD student
- School of Psychiatry, Faculty of Medicine, UNSW
- Supervisors: Associate Professor Wei Wen, Professor Perminder Sachdev

Sri Chandana Kanchibhotla

- Investigating the genetics of the microstructure integrity of the corpus callosum in the ageing brain
- Master by Research student
- School of Psychiatry, Faculty of Medicine, UNSW
- Supervisors: Professor Perminder Sachdev, Dr Karen Mather, Professor Peter Schofield

Andrea Lammél

- Heritability of episodic memory and its neuroanatomical correlates: An extended twin-design study
- Macquarie University
- PhD student
- Supervisors: Professor Arthur Shores, Dr Jennifer Batchelor, Professor Perminder Sachdev

Jessica Lazarus

- Epigenetics and longevity
- PhD student
- Department of Anatomy, School of Medical Sciences, Faculty of Medicine, UNSW
- Supervisors: Dr Karen Mather, Associate Professor John Kwok

Aileen Lowe

- Advanced characterisation of skin derived neuroprecursors
- PhD student
- School of Psychiatry, Faculty of Medicine, UNSW
- Supervisors: Associate Professor Michael Valenzuela, Hon. Associate Professor Kuldip Sidhu
- *PhD submitted March 2014*

Janet Mitchell

- Service networks and their influence on the care of those with dementia in residential care
- Masters by Research student
- School of Psychiatry, Faculty of Medicine, UNSW
- Supervisor: Professor Henry Brodaty, Professor Jeoffrey Braithwaite

Claire O'Connor

- Understanding behaviour and function in frontotemporal dementia: Developing better assessments and intervention approaches
- PhD Student
- University of Sydney

- Supervisors: Professor Lindy Clemson, Professor Henry Brodaty

Amanda Olley

- Obsessive compulsive disorder: a decision making model
- PhD student
- School of Psychiatry, Faculty of Medicine, UNSW
- Supervisors: Professor Perminder Sachdev, Professor Gin Malhi
- *PhD submitted June 2014*

Alistair Perry

- Combined investigation of structural and functional connectivity in normal ageing and Alzheimer's disease
- PhD student
- School of Psychiatry, Faculty of Medicine, UNSW
- Supervisors: Associate Professor Wei Wen, Professor Perminder Sachdev, Professor Michael Breakspear

Mary Revelas

- The genetics of exceptional longevity and successful ageing
- PhD student
- School of Psychiatry, Faculty of Medicine, UNSW
- Supervisors: Dr Karen Mather, Dr Anbupalam Thalamuthu, Professor Perminder Sachdev

Katrin Seeher

- A study on psychosocial effects of becoming a carer: Predicting caregiver outcomes such as burden, psychological distress or quality of life
- PhD student
- Neuroplasticity in health, ageing and psychiatric disorders
- School of Psychiatry, Faculty of Medicine, UNSW
- Supervisors: Professor Henry Brodaty, Dr Lee-Fay Low, Dr Simone Reppermund

Gillian Stockwell-Smith

- A randomised controlled trial of a community based intervention for caregivers of people with dementia
- PhD student
- Centre for Health Practice Innovation, Griffith University
- Supervisors: Dr Ursula Kellett, Professor Wendy Moyle, Professor Henry Brodaty

Ruby Tsang

- Biomarkers of late-life depression
- PhD student
- School of Psychiatry, Faculty of Medicine, UNSW
- Supervisors: Dr Simone Reppermund, Professor Perminder Sachdev, Associate Professor Wei Wen, Dr Karen Mather

Jacqueline Wesson

- Evaluating functional cognition and performance of everyday tasks in older people with dementia – the validity, reliability and usefulness of the Allen's model of cognitive disability
- PhD student
- Faculty of Health Sciences, University of Sydney
- Supervisors: Professor Lindy Clemson, Professor Henry Brodaty, Dr Simone Reppermund

Zixuan Yang

- Age-associated structural brain changes on MRI from the eighth to eleventh decade of life
- PhD student
- School of Psychiatry, Faculty of Medicine, UNSW
- Supervisors: Professor Perminder Sachdev, Associate Professor Wei Wen

COMPLETED

Yanhong (Catherine) Dong

- Cognitive outcome after stroke: Detection of vascular cognitive impairment, prognosis, neuropsychological patterns, and the efficacy of revascularization
- PhD student
- School of Psychiatry, Faculty of Medicine, UNSW

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Appendix D: Awards

Dr Nady Braidy

- The Science and Industry Endowment Fund – Australian Academy of Science Fellowships to the 64th Lindau Nobel Laureate Meetings
- Chilean National Postdoctoral Prize

Professor Henry Brodaty & Professor Perminder Sachdev

- Joint Recipients: Dean's Award for Outstanding Achievement (Academic), UNSW -Outstanding contribution to research and reaching in the Faculty of Medicine

Hon. Associate Professor Kuldip Sidhu

- International Pioneer in Medicine, Society of Brain Mapping & Therapeutics, USA

Professor Julian Trollor

- Promoted from Associate Professor to Professor

Dr Karen Mather

- Yulgilbar Post-Doctoral Excellence Award

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Appendix E: Research Grants & Funding

Grants

Agilent 1290UHPLC equipment grant (Part 1)

Funding Source: National Health & Medical Research Council (NHMRC)
Project ID: RG134156-B
Investigator/s: Prof Perminder Sachdev, Dr Anne Poljak, Dr Nady Braidy, Dr Julia Müenchhoff, et al.
Duration: 1 year: 2014
Total Funds: $109,711

Agilent 1290UHPLC equipment grant (Part 2)

Funding Source: UNSW MREII Funds
Project ID: RG134854
Investigator/s: Prof Perminder Sachdev, Dr Anne Poljak, Dr Nady Braidy, Dr Julia Müenchhoff, et al.
Duration: 1 year: 2014
Total Funds: $18,039

A randomised controlled trial of cognitive remediation therapy for the obese: a preliminary investigation

Funding Source: Diabetes Australia Research Trust
Project ID: RG135112
Investigator/s: Dr Evelyn Smith
Duration: 1 year: 2014
Total Funds: $60,000

Biomarkers of late-life depression and associated cognitive impairment

Funding Source: Alzheimer's Australia Dementia Research Foundation – Postgraduate Scholarship
Project ID: RG134526
Investigator/s: Ms Ruby Tsang, Prof Perminder Sachdev
Duration: 3 years: 2014-2016
Total Funds: $90,000

Towards understanding the role of long non-coding RNA in age-related memory decline – an early marker of Alzheimer's disease

Funding Source: Yulgilbar Foundation
Project ID: RG141699
Investigator/s: Dr Karen Mather
Duration: 1 year: 2014-2015
Total Funds: $20,000

Improving clinical diagnosis of mild neurocognitive disorders

Funding Source: National Health & Medical Research Council (NHMRC) Early Career Fellowship
Project ID: RG123148
Investigator/s: Dr Nicole Kochan
Duration: 4 years: 2013-2016
Total Funds: $149,782
Amount per year: $37,445.50

Sirtuin single nucleotide polymorphisms in brain ageing

Funding Source: NHMRC Early Career Fellowship
Project ID: RG123293
Investigator/s: Dr Nady Braidy
Duration: 4 years: 2013-2016
Total Funds: $299,564
Amount per year: $74,891

The Older Australian Twins Study (OATS) of healthy brain ageing and age-related neurocognitive disorders

Funding Source: NHMRC Project Grant
Project ID: RG122225
Investigator/s: Prof Perminder Sachdev, Dr Margie Wright, Prof David Ames, A/Prof Julian Trollor, A/Prof Wei Wen, Prof Bernhard Baunes, Dr Teresa Lee, Dr John Crawford
Duration: 3 years: 2013-2015
Total Funds: $912,022

Computerised neuropsychological testing for early diagnosis of mild cognitive impairment and dementia

Funding Source: Dementia Collaborative Research Centre – Assessment & Better Care
Project ID: RG133185-C
Investigator/s: Dr Nicole Kochan
Duration: 1 year: 2013-2014
Total Funds: $50,000

Living with dementia in retirement villages: investigating the experiences of retirement village residents with dementia

Funding Source: Alzheimer's Australia NSW/IRT Research Foundation Research Grant
Project ID: RG141330
Investigator/s: Prof Lynn Chenoweth
Duration: 1 year: 2013-2014
Total Funds: $28,009

Genetic and epigenetic variation and early markers of late-onset Alzheimer's disease

Funding Source: Alzheimer's Australia Research / Postdoctoral Fellowship in Dementia
Project ID: RG123330
Investigator/s: Dr Karen A Mather
Duration 2 years: 2013-2014
Total Funds: $100,000

Plasma protein profiles in normal brain ageing and early stages of dementia

Funding Source: Australian Research Council (ARC) Discovery Project
Project ID: RM10093
Investigator/s: Prof Perminder Sachdev, Dr Anne Poljak, Prof Mark Duncan, Prof John Attia, Prof Peter W Schofield, Dr John Crawford
Duration: 3 years: 2012-2014*
Total Funds: $330,000

*Extension granted to 31 March 2015

Secondary analyses and archiving of social and behavioral databases in aging

Funding Source: National Institutes of Health (USA)
Project ID: RG114384
Investigator/s: Prof P Sachdev, Prof Henry Brodaty, Dr Kristan Kang
Duration: 1 year: 2012-2013*
Total Funds: $52,402

*Project acquitted and closed January 2014

Genetic and environmental determinants of brain networks in ageing: a diffusion tensor imaging based study of twins

Funding Source: NHMRC Seed Funding Project Grant
Project ID: RM10658
Investigator/s: A/Prof Wei Wen
Duration: 1 year: 2012-2013*
Total Funds: $144,708

*Project acquitted and closed September 2014

Genetic and environmental contributions to amyloid burden in older Australians: a PiB-PET imaging study of twins

Funding Source: NHMRC Seed Funding Project Grant
Project ID: RM01657
Awardee/s: Dr Melissa J Slavin
Duration: 1 year: 2012-2013*
Total Funds: $181,265

*Project acquitted and closed May 2014

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The prevention, early detection, and effective management of neurocognitive disorders in the elderly

Funding Source: NHMRC Program Grant
Project ID: RM06756
Investigator/s: Prof Perminder Sachdev, Prof Henry Brodaty, Prof Gavin Andrews
Duration: 5 years: 2010-2014*
Total Funds: $6,090,000

*Extend grant duration approved by NHMRC, 26 November 2014 - new end date 31 December 2015

A cognitive and neuroimaging study of exceptionally old age: Sydney Centenarian Study

Funding Source: NHMRC Project Grant
Project ID: RM07525
Investigator/s: Prof Perminder Sachdev, Prof Robyn Richmond, Dr Nicole Kochan, A/Prof Wei Wen, Dr John Crawford
Duration: 3 years: 2010-2014*

*Extend grant duration approved by NHMRC, 23 July 2014 – new end date 31 December 2014

Prevention and management of mental disorders in older Australians

Funding Source: NHMRC Capacity Building Grant
Project ID: RM06714
Investigators: Prof Perminder Sachdev, Prof Henry Brodaty, Prof Gavin Andrews, Prof Stephen Lord
Duration: 5 years: 2009-2013*
Total Funds: $2,352,525
Amount per year: $407,505

*Extend grant duration approved by NHMRC, 26 November 2014 - new end date 31 December 2015

Gene-environment interactions in healthy ageing and age-related neurodegeneration (the Older Australian Twins Study – OATS)

Funding Source: NHMRC/ARC Strategic Award
Project ID: RM04226
Investigators: Prof Perminder Sachdev, Prof David Ames, Prof Peter Schofield, Prof GA (Tony) Broe, Prof Henry Brodaty, A/Prof Julian Trollor, Dr Margie Wright, Dr Wei Wen, Dr Teresa Lee
Duration: 5 years: 2007-2011*
Total Funds: $2,000,000
Amount per year: $400,000

*Project acquitted and closed October 2014

Philanthropic

The Thomas Foundation Grant

Funding Source: The Thomas Foundation
Awardees: Prof Henry Brodaty, Prof Perminder Sachdev
Duration: 5 years: 2011-2015
Total Funds: $1,000,000

The Montefiore Chair of Health Brain Ageing at UNSW

Funding Source: The Sir Moses Montefiore Jewish Home
Awardees: Prof Henry Brodaty, Prof Perminder Sachdev
Duration: 5 years: 2011-2015
Total Funds: $665,000

Major Partner & Direct Donations 2014:

$150,538

Event & Sponsorship 2014:

$64,464

Appendix F: Statement of In-Kind Contributions

- ARIA Restaurant
- Breathe Fire Specialised Training
- HWL Ebsworth Lawyers
- Intellectual Ventures
- Rockdale City Council

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Appendix G: Statement of Financial Performance

Centre for Healthy Brain Ageing (CHEBA)

Statement of Financial Performance for the Year Ended 31 December 2014

	Notes	2014 $	2013 $
Funds			
Research Revenue		1,876,397	2,503,977
Donations		365,895	170,954
Fees		-	-
Faculty Funds	4	10,000	-
UNSW Contribution - Competitive	2	52,886	78,000
UNSW Contribution - Strategic	3	-	15,000
Sundry Other Revenue		1,709	3,513
Total Funds	**2,306,887**	**2,771,444**	
Costs			
People Costs		1,872,655	2,908,302
Scholarship Stipends		50,151	22,164
Contract & Consulting Services		222,061	402,298
Repairs and Maintenance		4,086	1,470
Consumables		35,928	60,036
Travel		63,443	136,364
Equipment		125,039	32,731
Other Expenses		24,308	22,196
Internal Expense		52,248	67,076
Total Costs	**2,449,919**	**3,652,637**	
Operating result	**(143,032)**	**(881,193)**	
Opening Balance	**1**	**749,341**	**1,630,535**
Closing Balance	**606,309**	**749,341**	

Notes to the Statement of Financial Performance

1. CHeBA was established as a centre in October 2012. As a result, the brought forward balance into 2013 is combination of new projects created in CHeBA and existing projects associated to the co-directors, Prof Perminder Sachdev and Prof Henry Brodaty, and other academics based in CHeBA. The 2013 brought forward balance of $1.630m includes funds relating to external research projects of $1.585m.
2. UNSW Contribution - Competitive relates to funding awarded to CHeBA from UNSW through various competitive schemes supporting research activities and infrastructure.
3. UNSW Contribution - Strategic relates to funding provided to CHeBA from UNSW as a strategic investment in the centre's research activities.
4. Faculty Funds - Operating funds provided by the faculty are budget allocations, with no revenue transferred to CHeBA.

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Appendix H: Publications

Journal Publications

Adams S, Teo C, McDonald KL, Zinger A, Bustamante S, Lim CK, Sundaram G, Braidy N, Brew BJ, Guillemin GJ. Involvement of the kynurenine pathway in human glioma pathophysiology. *PLoS One*. 2014 Nov 21; 9(11):e112945. DOI: 10.1371/journal.pone.0112945. PMID: 25415278 / PMCID: PMC4240539.

Al-Adawi S, Braidy N, Essa M, Al-Azri F, Hussain S, Al-Sibani N, Al-Khabouri J, Al-Asmi A, Al-Mashani A. Cognitive profiles in patients with multi-infarct dementia: an Omani study. *Dement Geriatr Cogn Dis Extra*. 2014 Jul 18; 4(2):271-82. DOI: 10.1159/000363621. PMID: 25202321 / PMCID: PMC4154192

Arcot J, Kim J, Trollor J, Brodaty H, Crawford J, Sachdev P. Anthropometric indices in a community-dwelling Australian population aged 70–90 years: the Sydney Memory and Ageing Study. *Nutr Diet*. 2014 Sep 11. DOI: 10.1111/1747-0080.12140. [Epub ahead of print].

Assareh AA, Mather KA, Crawford JD, Wen W, Anstey KJ, Easteal S, Tan X, Mack HA, Kwok JB, Schofield PR, Sachdev PS. Renin-angiotensin system genetic polymorphisms and brain white matter lesions in older Australians. *Am J Hypertension*. 2014 Sep; 27(9):1191-8. DOI: 10.1093/ajh/hpu035. PMID: 24622918. [Epub 12 Mar 2014].

Assareh AA, Piguet O, Lye TC, Mather KA, Broe GA, Schofield PR, Sachdev PS, Kwok JBJ. Association of SORL1 gene variants with hippocampal and cerebral atrophy and Alzheimer's disease. *Curr Alzheimer Res*. 2014; 11(6):558-63. DOI: 10.2174/1567205011666140618101408. PMID: 24938503.

Baldwin R, Chenoweth L, dela Rama M, Liu Z. Quality failures in residential aged care in Australia: The relationship between structural factors and regulation imposed sanctions. *Australasian J Age*. 2014 May 22. DOI: 10.1111/ajag.12165. PMID: 24854338. [Epub ahead of print].

Batouli SAH, Sachdev PS, Wen W, Wright MJ, Ames D, Trollor JN. Heritability of brain volumes in older adults: the Older Australian Twins Study. *Neurobiol Aging*. 2014 Apr; 35(4):937.e5-937.e18. DOI: 10.1016/j.neurobiolaging.2013.10.079. PMID: 24231518. [Epub 17 Oct 2013].

Batouli SAH, Trollor JN, Wen W, Sachdev PS. The heritability of volumes of brain structures and its relationship to age: a review of twin and family studies. *Ageing Res Rev*. 2014 Jan; 13(1):1-9. PMID: 24211464. DOI: 10.1016/j.arr.2013.10.003. [Epub 8 Nov 2013].

Boccardi M, Bocchetta M, Apostolova LG, …; EADC-ADNI Working Group on The Harmonized Protocol for Hippocampal Volumetry; Alzheimer's Disease Neuroimaging Initiative. Establishing magnetic resonance images orientation for the EADC-ADNI manual hippocampal segmentation protocol. *J Neuroimaging*. 2014 Sep-Oct; 24(5):509-14. DOI: 10.1111/jon.12065. PMID: 24279479 [Epub 26 Nov 2013].

Braidy N, Brew BJ, Inestrosa NC, Chung R, Sachdev P, Guillemin GJ. Changes in Cathepsin D and Beclin-1 mRNA and protein expression by the excitotoxin quinolinic acid in human astrocytes and neurons. *Metab Brain Dis*. 2014 Sep; 29(3):873-83. DOI: 10.1007/s11011-014-9557-9. PMID: 24833554. [Epub 16 May 2014].

Braidy N, Gai WP, Xu YH, Sachdev P, Guillemin GJ, Jiang XM, Ballard JW, Horan MP, Fang ZM, Chong BH, Chan DK. Alpha-synuclein transmission and mitochondrial toxicity in primary human foetal enteric neurons in vitro. *Neurotox Res*. 2014 Feb; 25(2):170-82. DOI: 10.1007/s12640-013-9420-5. PMID: 24026637. [Epub 12 Sep 2013].

Braidy N, Matin A, Rossi F, Chinain M, Laurent D, Guillemin GJ. Neuroprotective effects of rosmarinic acid on ciguatoxin in primary human neurons. *Neurotox Res*. 2014; 25(2):226-234. DOI: 10.1007/s12640-013-9429-9. PMID: 24097334 [Epub 5 Oct 2013].

Braidy N, Poljak A, Grant R, Jayasena T, Mansour H, Chan-Ling T, Guillemin GJ, Smythe G, Sachdev, P. Mapping NAD(+) metabolism in the brain of ageing Wistar rats: potential targets for influencing brain senescence. *Biogerontology*. 2014 Apr; 15(2):177-98. DOI: 10.1007/s10522-013-9489-5. PMID: 24337988. [Epub 17 Dec 2013].

Braidy N, Poljak A, Marjo C, Rutlidge H, Rich A, Jayasena T, Inestrosa NC, Sachdev P. Metal and complementary molecular bioimaging in Alzheimer's disease. *Front Aging Neurosci*. 2014 Jul 15; 6:138. PMID: 25076902 / PMCID: PMC409812. DOI: 10.3389/fnagi.2014.00138.

Braidy N, Subash S, Essa MM, Al-Buraiki Z, Vaishnav R, Al-Adawi S, Al-Asmi A, Al-Senawi AAR, Alobaidy H, Lakhtakia R, Guillemin GJ. Neuroprotective effects of a variety of pomegranate juice extracts (PJE) against the excitotoxin quinolinic acid in human primary neurons. *J Prev Alz Dis*. 2014; 1(2):84-90. DOI: 10.14283/jpad.2014.3

Brodaty H, Low L-F, Liu Z, Fletcher J, Roast J, Chenoweth L. Successful ingredients in the SMILE study: Resident, staff and management factors influence the effects of humor therapy in residential aged care. *Am J Geriatr Psychiatry*. 2014 Dec; 22(12):1427-37. DOI: 10.1016/j.jagp.2013.08.005. PMID: 24119859 [Epub 8 Oct 2013].

Brodaty H, Mothakunnel A, de Vel-Palumbo MD, Ames D, Ellis KA, Reppermund S, Kochan NA, Savage G, Trollor, JN, Crawford J, Sachdev PS. Influence of population versus convenience sampling on sample characteristics in studies of cognitive aging. *Ann Epidemiol*. 2014 Jan; 24(1):63-71. DOI: 10.1016/j.annepidem.2013.10.005. PMID: 24211070. [Epub 12 Oct 2013].

Callisaya ML, Srikanth VK, Lord SR, Close JC, Brodaty H, Sachdev PS, Phan T, Beare R, Trollor J, Wen W, Zheng JJ, Delbaere K. Sub-cortical infarcts and the risk of falls in older people: combined results of TASCOG and Sydney MAS studies. *Int J Stroke*. 2014 Oct; 9(Suppl A100):55-60. DOI: 10.1111/ijs.12279. PMID: 24712920. [Epub 8 Apr 2014].

Casey AN, Low LJ, Goodenough B, Fletcher J, Brodaty H. Computer-assisted direct observation of behavioral agitation, engagement and affect in long-term care residents. *J Am Med Dir Assoc*. 2014 Jul; 15(7):514-20. DOI: 10.1016/j.jamda.2014.03.006. PMID: 24755476 [Epub 20 Apr 2014].

Chen C, Upton C, Braidy N, Khalil J, Fang ZM, Xu YH, Chan DK. Association between leukocyte telomere length and vascular dementia and cancer mortality in an elderly population. *J Am Geriatr Soc*. 2014 Jul; 62(7):1384-6. DOI: 10.1111/jgs.12910. PMID: 25039510.

Chenoweth L, Forbes I, Fleming R, King M, Stein-Parbury J, Luscombe G, Kenny P, Haas M, Brodaty H. PerCEN: a cluster randomised controlled trial of person-centred environment outcomes for people with dementia. *Int Psychogeriatr*. 2014 Jul; 26(7):1147-60. DOI: 10.1017/S1041610214000398. PMID: 24666667 [Epub 26 Mar 2014].

Chenoweth L, Low L-F, Goodenough B, Liu Z, Brodaty H, Casey A-N, Spitzer P, Bell J-P, Fleming R. Something to SMILE about: potential benefits to staff from humour therapy with nursing home residents. *J Gerontol Nurs*. 2014; 40(2):47-52. DOI: 10.3928/00989134-20130930-01. PMID: 24102103 [Epub 8 Oct 2013].

Chenoweth L, Jeon Y-H, Duffield C, Tait F, Merlyn T. Attracting and retaining qualified nurses in aged and dementia care: outcomes from an Australian study. *J Nurs Manag*. 2014 Mar; 22(2):234-47. DOI: 10.1111/jonm.12040. PMID: 23465290 [Epub 7 Mar 2013].

Cherbuin N, Kumar R, Sachdev PS and Anstey KJ. Dietary mineral intake and risk of mild cognitive impairment: the PATH through life project. *Front Aging Neurosci*. 2014 Feb; 6:4. DOI: 10.3389/fnagi.2014.00004. PMID: 24550825 / PMCID: PMC3912433.

Cherbuin N, Mortby ME, Janke AL, Sachdev PS, Abhayaratna WP, Anstey KJ. Blood pressure, brain structure, and cognition: opposite associations in men and women. *Am J Hypertens*. 2014 Feb; 28(2):225-31. DOI: 10.1093/ajh/hpu120. PMID: 25159080. [Epub 26 Aug 2014].

Chan C, Upton C, Braidy N, Khalil J, Fang ZM, Xu YH, Chan DKY. Association of leukocyte telomere length with vascular dementia and cancer mortality in an elderly population. *J Am Geriatr Soc*. 2014; 62:1384-6. DOI: 10.1111/jgs.12910. PMID: 25039510.

Debette S, Ibrahim Verbaas CA, Bressler J, …, Mather KA, …, Armstrong NJ, …, Assareh A, Kochan NA, …, Sachdev PS, et al. Genome-wide studies of verbal declarative memory in non-demented older people: the CHARGE consortium. *Biol Psychiatry*. 2014 Nov 25. DOI: 10.1016/j.biopsych.2014.08.027. [Epub ahead of print].

Dong YH, Slavin MJ, Chan BPL, Venketasubramanian N, Sharma VK, Collinson SL, Sachdev PS, Chen CLH. Improving screening for vascular cognitive impairment at 3–6 months after mild ischemic stroke and transient ischemic attack. *Int Psychogeriatr*. 2014 May; 26(5):787-93. DOI: 10.1017/S1041610213002457. PMID: 24423626. [Epub 15 Jan 2014].

Essa MM, Braidy N, Bridge W, Subash S, Manivasagam T, Vijayan RK, Al-Adawi S, Guillemin GJ. Review of natural products on Parkinson's disease pathology. *J Age Res Clin Prac*. 2014; 3(3):127-136. DOI: 10.14283/jarcp.2014.23.

Fiatarone Singh MA, Gates N, Saigal N, Wilson GC, Meiklejohn J, Brodaty H, Wen W, Singh N, Baune BT, Suo C, Baker MK, Foroughi N, Wang Y, Sachdev PS, Valenzuela M. The study of mental and resistance training (SMART) study – resistance training and/or cognitive training in mild cognitive impairment: a randomized, double-blind, double-sham controlled trial. *J Am Med Dir Assoc*. 2014 Dec; 15(12):873-80. DOI: 10.1016/j.jamda.2014.09.010. PMID: 25444575. [Epub 23 Oct 2014].

Fleming R, Low L-F, Goodenough B, Chenoweth L, Brodaty H. The relationship between the quality of the built environment and the quality of life of people with dementia in residential care. *Dementia*. 2014 May 5. DOI: 10.1177/1471301214532460. PMID: 24803645. [Epub ahead of print].

Fry M, Arendts G, Chenoweth L, Gallagher P. Cognitive impairment is a risk factor for delayed analgesia in older people with long bone fracture: a multicentre exploratory study. *Int Psychogeriatr*. 2014 Aug 27; 1-6 DOI: 10.1017/S1041610214001732. PMID: 25162158 [Epub ahead of print].

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Appendix I: Conference Presentations

Allen B, Chenoweth L, Cope S, Evans A, Lancaste, C. Management of pain and agitation experienced by people with advanced dementia in residential aged care. Panel presentation and discussion. *5th Biennial Palliative Care Nurses Conference. Building a bridge to the future - the wide span of palliative care nursing*. Sydney, Australia; 7 Apr 2014.

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Brodaty H. 14 essentials in the practice & art of diagnosis & management of dementia. *General Practitioner Conference and Exhibition*. Melbourne, Sydney; 14-16 Nov 2014.

Brodaty H. A global view of dementia from the primary care perspective. *Alzheimer's Association International Conference*. Copenhagen, Denmark; 12-17 Jul 2014.

Brodaty H. Can Alzheimer's disease be prevented? *Alzheimer's Auckland Symposium*. Auckland, New Zealand; 31 Aug 2014.

Brodaty H. Dementia in Australia. *Alzheimer's Disease Conference*. Prague, Czech Republic; Mar 2014.

Brodaty H. Dementia: where are we now? [Keynote address]. *Alzheimers New Zealand Biennial Conference: Dementia: The Future Is Now*. Rotorua, New Zealand: 14-15 Nov 2014.

Brodaty H. Good practice in management of behavioural and psychological symptoms of dementia: knowledge is only the first step. *29th International Conference of Alzheimer's Disease International*. San Juan, Puerto Rico; 1-4 May 2014.

Brodaty H. Non-pharmacological interventions in patients with behavioural symptoms. *Alzheimer's Association International Conference*. Copenhagen, Denmark; 12-17 Jul 2014.

Brodaty H. Physical comorbidity of dementia. *6th Biennial Australian and New Zealand Falls Prevention Conference*. Sydney, Australia; 16-18 Nov 2014.

Brodaty H. Symposium: Psychosocial Research Consortium to advance mental health of older people in the Asia Pacific region (PROMOTE). *16th International Congress of the International Psychogeriatric Association: Towards Successful Aging: Harmony of Mental, Physical and Social Life*. Seoul, Korea: 1–4 Oct 2013. *International Psychogeriatrics*, 25 (Supplement 1), S10 (SY02-06) [Abstract].

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Brodaty H. Understanding, preventing and remedying behavioural and psychological symptoms of dementia [Keynote address]. *BaptistCare: Dementia and Diversity Forum*. Sydney, Australia; 23 Sep 2014.

Brodaty H, Heffernan M, Kochan NA, Reppermund S, Mather K, Assareh A, Xu J, Draper B, Trollor J, Sachdev PS. The effect of alcohol consumption and apolipoprotein E (ApoE) 4 status on incident dementia over 4-years in the Sydney Memory and Ageing Study. *Alzheimer's Association International Conference (AAIC) 2014*. Copenhagen, Denmark; 12-17 Jul 2014. *Alzheimers Dement*. 2014 July; 10(4):P591. DOI: 10.1016/j.jalz.2014.05.986 [Abstract P2-307].

Brodaty H, Jessop T. Halting antipsychotic use in long term care – the HALT study. *Alzheimers New Zealand Biennial Conference: Dementia: The Future Is Now*. Rotorua, New Zealand: 14-15 Nov 2014.

Callisaya M, Srikanth V, Lord S, Close J, Brodaty H, Sachdev P, Thanh P, Beare R, Trollor J, Wen W, et al. Subcortical infarcts and the risk of falls in older people: combined results of TASCOG and Sydney MAS studies. *Australian and New Zealand Society for Geriatric Medicine Annual Scientific Meeting*. Melbourne, Australia; 28-30 May 2014. *Australasian Journal on Ageing*. 2014; 33: 37-38 [Abstract].

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Chenoweth L. Person-centred care implementation in the aged care setting: application and issues. *Inaugural Montessori Dementia Conference 2014*. Novotel-Brighton Beach, Sydney; 11-12 Nov 2014.

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Jayasena T, Poljak A, Zhong L, Braidy N, Smythe G, Raftery M, Sachdev PS. Development of a targeted mass spectrometry method for accurate quantification of human sirtuins in biological samples. *Alzheimer's & Parkinson's Disease Symposium 2014*. UNSW, Australia; 25-26 Sep 2014.

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Jeon Y-H, Low L-F, Chenoweth L, O'Connor D, Beattie E, Brodaty H. Best practice in assessing depression in nursing homes. *16th International Congress of the International Psychogeriatric Association: Towards Successful Aging: Harmony of Mental, Physical and Social Life*. Seoul, Korea: 1–4 Oct 2013. *International Psychogeriatrics*, 25 (Supplement 1), S60 (FC04-01) [Abstract].

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Appendix J: Workshops & Invited Lectures

International

Sachdev P [Presidential lecture]. A new approach to diagnosing vascular cognitive disorders: the VASCOG criteria. *14th Annual meeting of the International College of Geriatric Psychoneuropharmacology (ICGP)*. Tsukuba, Japan; 2-4 Oct 2014.

Sachdev P. Brain networks. *11th Annual World Congress of the Society of Brain Mapping and Therapeutics*. Sydney, Australia; 17-19 Mar 2014.

Sachdev P [Plenary Speaker]. Changing lifestyle to prevent Alzheimer's disease: examining the evidence. *17th Asia Pacific regional conference of Alzheimer's Disease International (ADI)*. New Delhi, India; 7-9 Nov 2014.

Sachdev P. Neuroimaging for early diagnosis of Alzheimer's disease. *BCS Colloquium*. Seoul National University, South Korea; 4 Jul 2014.

Sachdev P [Plenary Speaker]. The centenarian subjects as a model of successful ageing. *XIX Brazilian Congress of Geriatrics and Gerontology (CBGG)*. Belem, Para State, Brazil; 29 Apr – 3 May 2014.

Sachdev P [Plenary Speaker]. What twins have contributed to the understanding of aging and dementia? The Older Australian Twins Study. *XIX Brazilian Congress of Geriatrics and Gerontology (CBGG)*. Belem, Para State, Brazil; 29 Apr – 3 May 2014.

National

Reppermund S. Depression in old age – the first step to dementia? (Invited Keynote Speech). *Society for Mental Health Research Conference*. Adelaide, Australia; 3-5 December 2014.

Sachdev P. Biomarkers for Alzheimer's disease: the road to discovery. *Collaborative Research Network (CRN) on Mental Health and Well-being in Rural and Regional Communities Meeting:* "Minds Matter – promoting and researching rural, regional and remote mental health and well-being". Coffs Harbour, Australia; 3-5 Apr 2014.

Sachev P. Deep brain stimulation for Tourette Syndrome. *10th Annual ANZ DBS User Group Meeting*. Sydney, Australia; 28 Feb – 2 Mar 2014.

Local

Sachdev P. Toward promoting healthy brain ageing and preventing dementia: an overview of research at the Centre for Healthy Brain Ageing (CHeBA). *University of Wollongong Seminar Series*. Wollongong, Australia; 20 Mar 2014.

Sachdev P. What's new in Tourette's? *Tourette's Syndrome Association of Australia (TSAA) Annual Meeting* "Tourettes – It's not what you think". Burwood, Australia; 10 May 2014.

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