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Centre for Healthy Brain Ageing (CHeBA)

Annual Report 2017

research

big data

ageing

prevention

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CO-DIRECTORS' REPORT

The year 2017 has been a significant one for the Centre for Healthy Brain Ageing (CHeBA) toward our vision of healthier brain ageing for everyone and better clinical care for those in need. We saw an expansion of our group, steady research output, active engagement with the community and continued success with funding agencies.

The year also marked the fifth anniversary of CHeBA and recognition that our aspiration to bring together researchers from distinct disciplines under a collaborative focus of age-related brain disorders has been successful. We are delighted by the productivity levels of our various research groups both independently and collectively, and are grateful for the enduring support of so many organisations, individuals and grant funding bodies that have allowed us such accomplishments.

It is our belief that one of the major strengths of CHeBA is its multidisciplinary approach to age-related brain disorders and it remains our ambition for CHeBA to be an international leader in brain ageing research. Looking forward to 2018, we are thrilled to announce that we will finally be housed on one site which has been an ongoing challenge having been spread across multiple sites from the inception.

With dementia research continuing to be heavily underfunded despite its high burden on the community, we are enormously encouraged by the renewed funding from the Sir Moses Montefiore Jewish Homes following completion of our 5 year agreement, as well as noteworthy growth in our Members and Friends across The Dementia Momentum initiative. In total we have $6.3 million in received and committed funding toward a lofty goal of $10 million by 2020.

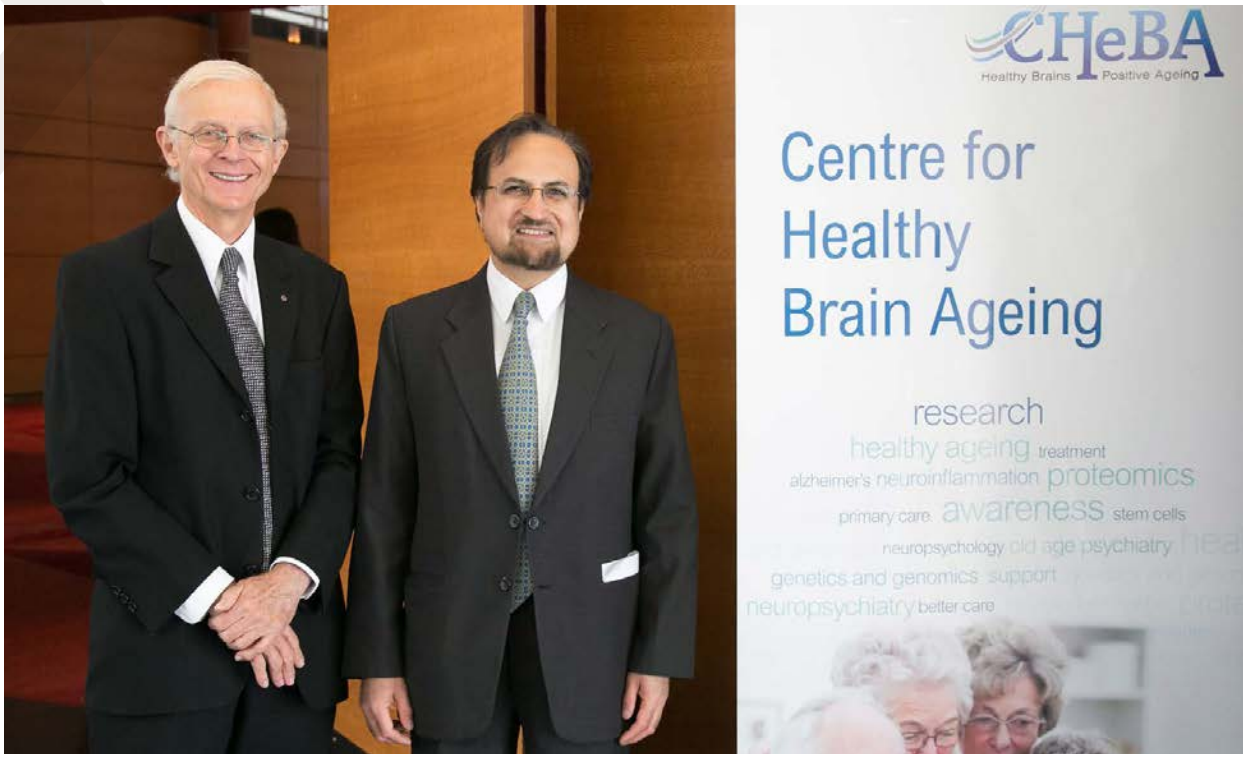
We are extremely fortunate to have the fervent and creative assistance of Richard Grellman AM, Spokesman for The Dementia Momentum and Ambassador for our Wipeout Dementia campaigns. The impact his staunch support of CHeBA's research has had upon the expansion of our Centre and his heavy involvement across fundraising campaigns to drive corporate contribution to dementia research cannot be underestimated.

We are also grateful for the continuing support of KPMG Sydney and ARIA Restaurant, both partners of The Dementia Momentum since its launch in 2015. Colliers International Residential once again demonstrated their extraordinary commitment to CHeBA, raising over $80,000 for Wipeout Dementia at their annual lunch.

With the ever-increasing funding and in-kind support for this initiative, we have had the opportunity in 2017 to expand its programs focusing on the pooling, harmonising and analysing of data from a number of international studies. We have also been able to expand funding across CHeBA's genetics research, particularly RNA sequencing and whole genome sequencing. This work is being done in collaboration with a nymber of research groups in Europe and North America, as part of the BRIDGET, EADB, CHARGE and ENIGMA consortia. Media coverage of The Dementia Momentum continues to be encouraging, with the initiative and its donors featuring once again in the *Australian Financial Review*.

We were also encouraged by a number of major funding grants in 2017 including a US$2.57 million National Institutes of Health, USA, grant to identify risk factors for dementia through CHeBA's COSMIC consortium. We are confident this research will make a lasting impact upon the epidemiology of cognitive ageing and dementia. CHeBA's Dr Nicole Kochan was awarded a $700,000 NNIDR Boosting Dementia Research grant for a world-first study, looking at computerised neuropsychological testing.

"We gratefully acknowledge our colleagues and other supporters for their enthusiastic connection to CHeBA."



This funding, along with continued significant funding from the Vincent Fairfax Family Foundation, the John Holden Family Foundation and the Yulgilbar Foundation will enable CHeBA to expand upon its record of pioneering research in the fields of ageing and the dementias.

In 2017, CHeBA published several noteworthy papers, including a major paper from the COSMIC consortium examining cognitive decline in several ethnoregional groups, an influential report on dementia registries which lays the groundwork for an Australian dementia registry, a comprehensive review of the use of lipidomics in Alzheimer's disease, results of the HALT trial to deprescribe antipsychotics in residential care facilities, several papers on genetics and proteomics, and novel data on the role of NAD+ in ageing.

We gratefully acknowledge our colleagues and other supporters for their enthusiastic connection to CHeBA, without which our work would not occur. Our highly skilled group of researchers continue to provide new insights into brain ageing and we thank them for their devotion to a valuable research cause. We would also like to thank our highly committed Centre Manager, Angie Russell and the administrative team for their assiduousness, and Heidi Douglass and her Marketing, Communications and Fundraising team for their extraordinary creativity and social connectedness.

2018 promises to be another big year for CHeBA. The pilot trial of **Maintain Your Brain**, of which Ita Buttrose is patron, has been completed. After showcasing this trial at the 2017 Alzheimer's Association International Conference (AAIC) held in London during 16-20 July, 16,000 people aged 55-75 years are now expected to be involved in this exciting research with formal recruitment intended to commence by second quarter 2018. We look forward to hosting the ICC Dementia conference in the Blue Mountains as well as the Living to 100 conference in Sydney. We will continue our collaboration with the Montefiore Homes focussing on improving the quality of life in residential care.

We look forward to continuing to deliver on these goals and working toward overcoming the challenge of cognitive decline globally in the year ahead.

Sincerely,

Scientia Professor Henry Brodaty AO

Scientia Professor Perminder Sachdev AM

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 in October 2012. It is headed by internationally acclaimed leaders in the field, Professors Henry Brodaty and Perminder Sachdev.

OUR PURPOSE

CHeBA is an international centre of excellence in multidisciplinary research into the ageing brain and various aspects of cognitive disorder, including dementia. 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 VISION

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

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.
- 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.

Professor Terry Campbell

Professor Philip Mitchell

GOVERNING 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. The Centre Steering Committee Members are:

- Professor Terry Campbell, Deputy 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

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.

Members of the CHeBA Advisory Committee are:

- Dagmar Schmidmaier AM – Chairperson
- John Gray – Deputy Chairperson
- Roger Layton AM
- Richard Matthews AM
- Imelda Roche AO
- Dr Sudarshan Sachdev
- John Thomas

DAGMAR SCHMIDMAIER AM

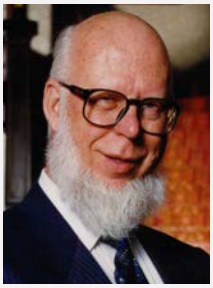
Chairperson, Chief Executive Women Leaders' Program

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 GRAY

Deputy Chairperson, 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 20 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.



ROGER LAYTON AM

UNSW Emeritus Professor of Marketing

Roger has been 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 AM MBBS

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.

IMELDA ROCHE AO

Co-Chairman
Roche Group Pty Ltd

Imelda Roche is internationally recognised for her outstanding achievements in business, which include an appointment by Prime Minister Paul Keating as Australia's representative to the Business Forum of the Asia-Pacific Economic Co-Operation (APEC) and subsequently by Prime Minister John Howard as representative to the successor organisation, the Business Advisory Council to APEC.

JOHN M THOMAS

KSS FAICD FIFS JP

Principal, JT Consultancy

John has been involved in banking, finance and funds management activities for over 42 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. JT was awarded a Papal Knighthood in 2011 for his extraordinary charitable work and he is also the Chairman of not-for-profits *Aftercare* and *River's Gift*.

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.

SIGNIFICANT HIGHLIGHTS

"If an impact is to be made on disability burden, we must understand the risk and protective factors for cognitive decline associated with ageing."

Professor Perminder Sachdev

MAINTAIN YOUR BRAIN

CHeBA Co-Directors Professors Henry Brodaty and Perminder Sachdev showcased CHeBA's *Maintain Your Brain* trial at the 2017 Alzheimer's Association International Conference (AAIC) held in London during 16-20 July.

Maintain Your Brain is the world's largest clinical trial for people aged 55-75 testing online tools designed to reduce participants' risk of dementia. Professor Brodaty said the study provides a critical contribution to the challenge of preventing dementia, which presents a rapidly rising economic and social burden particularly as there is no cure for the disease. Current estimates predict dementia costs will exceed $14 billion in Australia alone during 2017.

"Internet-based delivery of lifestyle interventions that can prevent or delay cognitive decline, are cost-effective and allow scalability at a population level," said Professor Brodaty. "The findings from *Maintain Your Brain* will provide crucial information for future clinical and policy guidelines, in line with CHeBA's vision of achieving healthier brain ageing through research."

Maintain Your Brain is a multimodal randomised-control trial, which is widely recognised as the gold-star standard for research methodology. The program will deliver exercise and cognitive training, nutritional advice, depression treatment and strategies for controlling cardiovascular health risks via the internet for 16,000 persons aged 55-75. Interventions will be conducted intensively for the first year, with boosters and follow-ups over four years.

Led by Professor Brodaty, *Maintain Your Brain* involves twenty specialists from around Australia, including experts in exercise, cognitive training, diet, IT platform design, general practice, research design and prevention, hypertension and depression and consumer representation. Ita Buttrose is the patron for the study.

> e-Health is coming of age and will be key to helping people change their lifestyle and maintain these changes.
> Professor Henry Brodaty

NIH PROVIDES $US2.57M FUNDING FOR COSMIC

CHeBA Co-Director Professor Perminder Sachdev was awarded US$2.57 million from the National Institutes of Health, USA, to identify risk and protective factors and biomarkers of cognitive ageing and dementia.

The grant will allow CHeBA to broaden their international research collaboration within COSMIC (Cohort Studies of Memory in an International Consortium), specifically to determine what factors are common for cognitive decline and dementia in all human populations irrespective of race, ethnicity and socioeconomic development.

"Ageing is intricately connected with cognitive decline and there is an increasing proportion of life lived with cognitive impairment as age increases," said Professor Sachdev.

"If an impact is to be made on this disability burden, we must understand the risk and protective factors for cognitive decline associated with ageing. The best approach to study this and develop early biomarkers is using population-based ageing cohorts," he said.

The priority objectives are to harmonise shared data from studies that longitudinally examine change in brain function and the development of dementia in those over 60 years of age. COSMIC uses a unique data harmonisation strategy which offers the potential to explore both existing and novel research questions by creating a single, large database.

> "This funding will make a lasting impact on the epidemiology of cognitive ageing and dementia.
> Professor Perminder Sachdev

Professor Perminder Sachdev AM

"COSMIC is truly an international effort," said Professor Sachdev. "It currently has 30 member studies from 5 continents and potentially data from more than 90,000 participants."

"The rules of COSMIC's engagement have been established and the success of its initial projects has demonstrated its feasibility."

"This funding will make a lasting impact on the epidemiology of cognitive ageing and dementia," he said.

Investigators on the grant include Professor Louisa Jorm, director of the UNSW Centre for Big Data Research in Health and CHeBA Co-Director Professor Henry Brodaty, as well as leading researchers from USA (Professors Mary Ganguli, Ron Petersen and Richard Lipton), France (Professors Karen Ritchie and Carole Dufouil) and South Korea (Prof Ki-Woong Kim).

DR KOCHAN RECEIVES BOOSTING DEMENTIA RESEARCH GRANT FOR WORLD-FIRST STUDY INTO COMPUTERISED NEUROPSYCHOLOGICAL TESTING

Dr Nicole Kochan, CHeBA Research Fellow and Co-Leader of the Neuropsychology Group, was awarded a Boosting Dementia Research Grant as part of a $40.1 million Australian Government initiative to improve understanding of the disease. Dr Kochan leads a world-first study to systematically evaluate and compare several prominent and widely-used computerised neuropsychological test batteries used for assessing cognition in older adults with and without dementia.

> "With an ageing population and associated increase in dementia there will be increased demand for neuropsychological assessment."
> Dr Nicole Kochan

Dementia is a major health problem with 200 Australians diagnosed every day and at least as many having mild cognitive impairment, which often precedes dementia. Early diagnosis is seen as critical for interventions yet many older adults do not receive timely diagnosis.

Objective assessment of cognitive abilities is essential for accurate diagnosis at mild or early stages.

"With an ageing population and associated increase in dementia there will be increased demand for neuropsychological assessment, however there are insufficient trained personnel and resources to meet this demand," said Dr Kochan.

Dr Nicole Kochan

"Computerised tests using tablet computers and internet delivery offer excellent opportunities for large scale implementation of cognitive screening and monitoring of older adults."

"Establishing the reliability and validity of these computerised tests is of critical importance before we can implement them into clinical practice. We anticipate that this study will move the field forward and have a major impact on the practice of cognitive testing in older adults with suspected cognitive decline," said Dr Kochan.

MONTEFIORE HOME RENEWS 5 YEAR PARTNERSHIP WITH CHEBA

Professor Henry Brodaty AO, David Freeman AM and Robert Orie

Montefiore Home has provided integral support to CHeBA since its inception in 2012. This year, Montefiore Home President David Freeman AM and CEO Robert Orie confirmed funding for a further five-year research partnership.

"We're proud to extend our support for the important work of Professor Henry Brodaty and the team at CHeBA," said Mr Orie. "The research projects Montefiore has funded since 2012 have had a direct impact on the quality of life of our residents and clients, and indeed people with dementia everywhere."

The latest agreement will address best practice in home care, residential aged care and dementia care, including promoting greater collaboration between families and staff. It builds on previous research into staff training, behavioural management of dementia and improved dental and oral health care.

CHeBA Co-Director Professor Henry Brodaty said research-industry partnerships were crucial for achieving excellence in care, with benefits for residents, families and staff.

> "The research projects Montefiore has funded since 2012 have had a direct impact on the quality of life of our residents and clients, and indeed people with dementia everywhere.
> Robert Orie, CEO Montefiore Home

RESEARCH HIGHLIGHTS

"Despite the staggering projections about the social and economic costs of dementia, there is enormous hope for change through research."

Professor Henry Brodaty

COSMIC IDENTIFIES DIFFERENT RATES OF COGNITIVE DECLINE INTERNATIONALLY

COSMIC, the international research consortium led by CHeBA, released its first findings into universal and demographic-specific risk factors for age-related cognitive decline. The study showed different rates of decline across twelve countries, but found several common risk factors associated with gender, ethnicity and genetics in a study published in the March 2017 edition of PLOS Medicine.

Dr Darren Lipnicki

Dr Darren Lipnicki, lead author and study co-ordinator of COSMIC (Cohort Studies of Memory in an International Consortium), said the findings provide an exciting insight into the global variation of dementia prevalence, as well as commonalities.

Cognitive test scores were analysed for over 42,000 elderly individuals from Australia, Brazil, France, Greece, Hong Kong, Italy, Japan, Singapore, Spain, South Korea, United Kingdom and the USA.

"We found that the 14 studies, conducted across 12 countries, showed different rates of cognitive decline. We also found that decline in some cognitive performance scores was faster for Asian than Caucasian populations, females than males, and *ApoE ε4*carriers," said Dr Lipnicki.Carrying the *ApoE ε4*allele has been previously associated with higher risk of late-onset Alzheimer's disease. Mini-Mental State Examination, and memory, processing speed, language, and executive functioning test scores all declined with age, and rates of decline accelerated with age.

"Now that we've identified differences in rates of decline, we will investigate whether specific factors like cardiovascular health, lifestyle or other risk factors have different associations with cognitive decline between ethno-cultural groups and geographic regions," said Dr Lipnicki.

"Identifying risk and protective factors will help to drive evidence-based intervention strategies to target, delay and potentially prevent dementia."

Publication: Lipnicki et al. 'Age-related cognitive decline and associations with sex, education and apolipoprotein E genotype across ethnocultural groups and geographic regions: A collaborative cohort study', PLOS Medicine, 2017; 14(3): e1002261.

"Identifying risk and protective factors will help to drive evidence-based intervention strategies to target, delay and potentially prevent dementia."
Dr Darren Lipnicki

OBJECTIVE MEASURES PROVIDE BEST PREDICTOR OF PROGRESSION FROM MCI TO DEMENTIA

CHeBA researchers found objective cognitive impairment measures provide the best predictor for progression from mild cognitive impairment (MCI) to dementia. The findings were published in the May 2017 edition of *The American Journal of Geriatric Psychiatry*.

Researchers are especially interested in MCI as it may provide an opportune time to try new drugs to prevent Alzheimer's disease, the most common form of dementia.

Lead author and CHeBA Co-Director, Professor Henry Brodaty, said the research aimed to clarify the impact of different applications of MCI diagnostic criteria on dementia incidence predictions. This is important because the wrong definition may mean trials of new drugs may not be choosing those people most likely to progress to Alzheimer's disease.

"We found the predictive accuracy of different definitions of MCI was poor," said Professor Brodaty.

Co-investigator Dr Liesbeth Aerts, calculated that according to which diagnostic criteria were applied, baseline MCI prevalence varied between 0.4% and 30.2% and progression to dementia ranged between 15.9% and 61.9%.

Surprisingly, the most accurate prediction was achieved by simply using performance on objective cognitive tests. Accuracy was not improved by including measures of subjective cognitive decline or mild functional impairment.

> "Clinical assessment procedures need to be refined in order to improve the identification of individuals with MCI and pre-dementia."
> Professor Henry Brodaty

Professor Henry Brodaty AO

"The major issue is that there are currently no standard operationalisations for MCI diagnosis, or guidelines around how each of the different components of the definition are strictly defined," said Professor Brodaty.

"Our findings highlight that clinical assessment procedures need to be refined in order to improve the identification of individuals with MCI and pre-dementia."

Publication: Brodaty et al. 'Operationalizing the Diagnostic Criteria for Mild Cognitive Impairment: The Salience of Objective Measures in Predicting Incident Dementia', The American Journal of Geriatric Psychiatry, 2017; 25(5): 485-497.

PREVALENCE OF INCIDENTAL FINDINGS ON MRIS ASSESSED

Dr Rebecca Koncz

CHeBA researchers assessed the prevalence of incidental findings, or unexpected abnormalities, on brain imaging scans from 400 twins over the age of 65. The findings were published in the July 2017 edition of *Brain Imaging & Behavior*.

The severity of abnormalities varies significantly and for a small proportion of individuals, the findings warrant further evaluation and potential treatment which can be costly and anxiety-provoking.

"Incidental brain findings are common, affecting approximately 2.7% of the population, but the rate significantly increases with age," said lead author and CHeBA PhD student Dr Rebecca Koncz. "Our study identified incidental findings in 11.75% of participants."

The most common finding was hyperostosis frontalis (a benign thickening of the frontal aspect of the skull) in 2% of participants, followed by meningiomas (a type of tumour; 1.5% of participants) and lipomas (a non-cancerous deposit of fatty tissue; 1.25% of participants). Four identical twin pairs had the same abnormality in their co-twin. A total of 12 (3%) participants needed to be referred for further evaluation.

Markers of cerebrovascular disease, or disease related to blood vessels in the brain, were also examined separately. Non-acute strokes (cortical infarcts) and mini-strokes (lacunes) were found in 2.75% and 5.5% of twins, respectively, which is at a rate that is comparable to the general population. White matter disease was found in more than two-thirds of participants.

Co-author, CHeBA Co-Director Professor Perminder Sachdev said the study had wider significance for practitioners, researchers and consumers.

"Given their prevalence, the development of clear guidelines for the management of incidental findings is recommended," said Professor Sachdev. "Clinicians and researchers should also be aware of the potential implications for the co-twin when ordering a brain scan for participants."

> "The development of clear guidelines for the management of incidental findings is recommended.
> Professor Perminder Sachdev

Publication: Koncz et al. 'Incidental findings on cerebral MRI in twins: the Older Australian Twins Study', Brain Imaging & Behavior, 2017; Jul 4. doi: 10.1007/s11682-017-9747-2. [Epub ahead of print].

SYDNEY MAS IDENTIFIES CORE RISK FACTORS FOR MCI, DEMENTIA AND MORTALITY IN LATE LIFE

CHeBA researchers identified a core group of late-life risk factors for mild cognitive impairment (MCI), dementia and mortality. The findings were published in the May 2017 edition of the *Journal of the American Medical Directors Association*.

The longitudinal study examined changes in cognitive status, particularly the development of MCI or dementia, as well as death, over a six year period for 873 community-dwelling individuals aged 70-90 years in CHeBA's Sydney Memory & Ageing Study (MAS). Baseline factors associated with having MCI and dementia after 6 years were: older age, MCI at baseline, poorer smelling ability, slower walking speed and being an *ApoE* ε4 carrier, a known genetic risk for Alzheimer›s disease. All factors except *ApoE* ε4 carrier-status were also associated with mortality.

Lead author CHeBA researcher Dr Darren Lipnicki said the findings provided exciting new insights into risk factors to inform early diagnosis and promote healthy ageing.

"Risk factors indicative of physical and mental frailty were significantly associated with dementia, MCI and mortality. This means that relatively straight-forward tests like walking speed and smelling ability may help screen for cognitive decline," explained Dr Lipnicki.

Dr Darren Lipnicki

> "Relatively straight-forward tests like walking speed and smelling ability may help screen for cognitive decline."
> Dr Darren Lipnicki

The study also highlighted the complex relationship between MCI and dementia, with 28% of participants with MCI at the start of the study reverting to being cognitively normal within two years. However, reverters were at greater risk of future MCI than those who were cognitively stable and showed different associations between baseline risk factors and outcomes.

Co-author and CHeBA Co-Director, Professor Perminder Sachdev, said that large, longitudinal studies like MAS are vital for determining risk factors over time.

Publication: Lipnicki et al. 'Risk factors for mild cognitive impairment, dementia and mortality: The Sydney Memory and Ageing Study', Journal of the American Medical Directors Association, 2017; 18(5): 388-395.

PROMOTE FINDS EUROPEAN INDICATORS PROBLEMATIC FOR ASSESSING ASIA-PACIFIC QUALITY OF CARE

A recent pilot study found that European quality indicators (QIs) are problematic for measuring quality of psychosocial care of people with dementia in Asia-Pacific countries, which account for over half of the global population with dementia. The study was undertaken by PROMOTE (Psychosocial Research Consortium), a group of international researchers led by Professor Brodaty and the University of Sydney's Professor Yun-Hee Jeon, and published in the July 2017 edition of *Aging & Mental Health*.

The research, undertaken at sixteen residential care facilities in seven Asia-Pacific countries (Australia, Hong Kong, mainland China, Malaysia, Singapore, South Korea, and Thailand), found that endorsement of each of the QIs varied considerably across sites, from 0 to 100%.

"Quality of medical records, family and cultural differences, definitions and scoring of some indicators, and the time consuming-nature of QI administration were major concerns for implementation," said lead author, Professor Yun-Hee Jeon, University of Sydney.

The European QIs are the only content- and face-valid tool for assessing person-centred care for people with dementia. Despite the high proportion of people living with dementia in Asia-Pacific countries and their rapidly ageing populations, psychosocial research about mental health in this area is poorly developed. This is the first collaborative study to evaluate quality of care for residents with dementia in long-term care settings in the area.

"Our findings provide crucial insights for future research and implementation of psychosocial dementia care quality indicators in our region," said co-author, CHeBA Co-Director Professor Henry Brodaty.

Publication: Jeon et al. 'Application of the European quality indicators for psychosocial dementia care in long-term care facilities in the Asia-Pacific region: A pilot study', Aging & Mental Health, 2017; July 17; 1-8 [Epub ahead of print].

> Our findings provide crucial insights for future research and implementation of psychosocial dementia care quality indicators in our region.
>
> Professor Henry Brodaty

FUNCTIONAL BRAIN NETWORK EXPLORES HEALTHY BRAIN AGEING

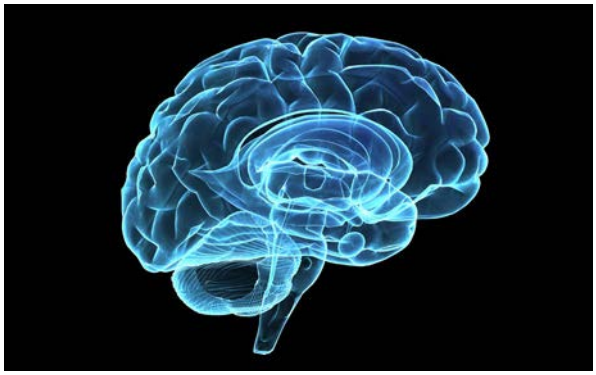
CHeBA PhD student Dr Alistair Perry studied the brain functional connectivity patterns of 101 healthy older adults aged 70-90 years to improve understanding of brain changes as we age. The research was published in the July 2017 edition of *Human Brain Mapping*.

Functional connectivity studies examine the neural interactions, or connections, between different regions of the brain and have been made possible by significant advances in neuroimaging technology in the last decade. This approach provides an invaluable resource for comparing and understanding the changes involved between healthy brain ageing and neuropathological conditions, such as dementia.

Dr Alistair Perry

"Healthy ageing is accompanied by a constellation of changes involved between healthy brain ageing and neuropathological conditions, such as dementia. How environmental factors in earlier life - such as educational history - provide a protective influence on ageing processes is also unknown."

> "Healthy ageing is accompanied by a constellation of changes."
> Dr Alistair Perry



Dr Perry said that the current research identified that age and educational attainment confer independent influences on brain patterns supporting cognitive processes. "It implies that age-related changes may be resistant to positive lifestyle factors that modify the risk of cognitive impairment such as educational attainment."

Co-author and CHeBA Co-Director Professor Perminder Sachdev said Dr Perry's research is a valuable contribution to understanding age-related cognitive changes and may have implications for behavioural interventions targeting healthy ageing.

Publication: Perry et al. 'The independent influences of age and education on functional brain networks and cognition in healthy older adults', Human Brain Mapping, 2017; 38: 5094-5114.

CHANGES IN APOLIPOPROTEIN LEVELS IDENTIFIED OVER LIFESPAN

CHeBA researchers examined age and sex-related differences in plasma levels of apolipoprotein to explore their potential contribution to physical and cognitive health in subjects aged over 50. The study was published in the July 2017 edition of *Neurobiology of Aging*.

The study suggested that levels of some apolipoproteins are associated with lifespan and cognitive function in exceptionally long-lived individuals, according to lead author Dr Julia Muenchhoff.

Prior to this study, it was unclear how levels of apolipoproteins differed with age, particularly in the 50+ age group, and whether these associations remain stable, diminish or increase with age. The research measured seven plasma apolipoproteins (ApoA1, ApoA2, ApoB, ApoC3, ApoE, ApoH and ApoJ) in over 1000 individuals aged from 56 to 105 years from the Sydney Centenarian Study and Sydney Memory & Study run by CHeBA, and the Hunter Community Study run by the University of Newcastle.

> "Higher levels of ApoE and ApoJ in exceptionally long-lived individuals seems related to an extended life span."
> Dr Anne Poljak

"We found that plasma levels of all seven apolipoproteins modestly decreased with age from mid-life in a linear manner, except for ApoE and ApoJ, for which we observed U-shaped curves, reflecting a trend to higher ApoE and ApoJ levels in those aged over 95 years. Higher levels of these two apolipoproteins in exceptionally long-lived individuals seems related to an extended life span." said co-author and leader of CHeBA's Proteomics group, Dr Anne Poljak. A number of sex-related differences were also identified.

Publication: Muenchhoff et al. 'Plasma apolipoproteins and physical and cognitive health in very old individuals', Neurobiology of Aging, 2017; 55: 49-60.

Dr Julia Muenchhoff

Dr Anne Poljak

EPIGENETIC FACTORS ACROSS LIFESPAN IDENTIFIED FOR HEALTHY AGEING

Dr Karen Mather

A study led by CHeBA has examined epigenetic factors across individuals aged 34-103 years to better understand the secrets to healthy ageing. The paper was published in the May 2017 edition of *Epigenomics*.

Dr Mather, co-author and leader of CHeBA's Genetics & Epigenomics Group, said this work investigates exceptionally long-lived individuals who can be seen as exemplars of successful ageing because many have escaped disease or delayed illness until very late in their lives.

While our DNA blueprint does not change with age, ageing and other factors can leave its mark on the DNA in the form of a chemical change called methylation that can alter the activity of our genes. DNA methylation is one example of an epigenetic marker. The biological age of an individual, known as the 'epigenetic clock,' can be calculated from these epigenetic markers.

There are a number of different epigenetic clocks described in the literature, depending upon which markers are used. The Horvath and Hannum epigenetic clocks are the best known and this study examined the relationships between these two clocks and exceptional ageing.

Co-author and CHeBA Co-Director Professor Perminder Sachdev said the epigenetic clocks under-estimated the ages of very old individuals (95 years and over) participating in CHeBA's Sydney Centenarian Study. "This finding supports the view that these individuals are biologically younger than their chronological ages would suggest," said Professor Sachdev.

> "The epigenetic clocks under-estimated the ages of very old individuals in CHeBA's Sydney Centenarian Study."
> Professor Perminder Sachdev

"Understanding the reasons for this may well reveal the secrets to their longevity," he said.

Publications: Armstrong et al. 'Aging, exceptional longevity and comparisons of the Hannum and Horvath epigenetic clocks', Epigenomics, 2017; 9(5): 689-700.

BRAIN METALS IN OCTODON DEGUS SHED NEW LIGHT ON ALZHEIMER'S DISEASE

The distribution of brain biometals using a natural animal model for Alzheimer's disease (AD) has been examined for the first time in a study led CHeBA. The findings provide new insights into the progression of Alzheimer's disease and may inform future drug developments to target the disease. The study was published in the March 2017 edition of *Frontiers in Aging Neuroscience*.

Researchers found a significant and age-dependent rise in levels of iron, calcium, zinc, copper and aluminium in the brains of *Octodon degus*, a rodent which shows naturally occurring neuronal, neuropathological and behavioural abnormalities associated with sporadic or late-onset AD. The innovative study methodology, combining a natural animal model with laser ablation inductively coupled plasma mass spectrometry (LA-ICPMS), overcomes current limitations in the research according to lead author and head of CHeBA's Molecular Biology group Dr Nady Braidy.

Dr Nady Braidy

"Currently, biometal accumulation can only be examined post-mortem in humans," said Dr Braidy. "Studies using transgenic mice models are problematic because the disease progression may differ and many discoveries have been lost in human translation. The ***Octodon degus*** model allows us to examine various brain regions over time to understand the progression from early to late-stage sporadic Alzheimer's, the most common form of the disease."

The researchers identified higher levels of iron, calcium, zinc and copper in the cortex and hippocampus, the regions where amyloid plaques and other brain changes associated with AD are most commonly reported. Aluminium was found to be higher in the hippocampus alone. Age-related deregulation of metal trafficking pathways was observed, as well as impaired lysosomal function which is associated with digestion and waste removal.

Better understanding of the trafficking pathways and micro-distribution of these biometals may help improved drug targeting.

> "Metal chelation may represent an important therapeutic strategy to prevent the onset or slow down the progression of Alzheimer's disease."
> Dr Nady Braidy

"Given the role of abnormal biometal accumulation, treatment that bonds and removes heavy metals from the body, called metal chelation, may represent an important therapeutic strategy to prevent the onset or slow down the progression of AD," said Dr Braidy.

Publication: Braidy et al. 'Identification of Cerebral Metal Ion Imbalance in the Brain of Aging Octodon degus', Frontiers in Aging Neuroscience, 2017; 9 (66): 1-16.

OUR GROUPS

"Internationally, there is a need for research across the full spectrum of dementia beyond drug treatments, to include early diagnosis and prevention strategies."

Professor Perminder Sachdev

GROUP SNAPSHOT

EPIDEMIOLOGY

Professor Perminder Sachdev

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.

NEUROPSYCHIATRY

Professor Perminder Sachdev

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.

GENETICS & EPIGENOMICS

Dr Karen Mather

The Genetics & Epigenomics group has grown out of our interest in the genetic and epigenetic factors involved in brain ageing and age-related disease. This group has many collaborations with national and international research groups and consortia. Large sample sizes are required for genetic and epigenetic studies to identify genetic and epigenetic variants that contribute to complex traits. Indeed, a recent consortia study used a sample size of over 280,000 participants recruited from around the world to identify novel genetic loci for cognitive performance. These collaborations have been productive, with many of the results published in well-known and distinguished journals, including Molecular Psychiatry and the Nature family of journals. The findings of this work have facilitated the identification of novel genes and pathways that contribute to a wide range of traits, including brain structure, and may lead to new insights into the underlying biology and suggest new treatments for age-related disease and decline. Dr Mather was promoted to Senior Lecturer in 2017.

MOLECULAR BIOLOGY & STEM CELLS

Dr Nady Braidy & Hon. Associate Professor Kuldip Sidhu

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).

NEUROIMAGING

Associate Professor Wei Wen

The Neuroimaging group is dedicated to researching the ageing of the human brain. By studying neuroimaging modalities, the group aims to improve understanding of brain ageing pathways, which in turn will lead to clinical advances in prediction, diagnosis and treatment. We are interested in computational neuroanatomy: the development of a comprehensive structural and functional model of the brain. Our neuroimaging studies address normal ageing, mild cognitive impairment (MCI) and dementia.

NEUROINFLAMMATION

Professor Julian Trollor

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.

NEUROPSYCHOLOGY

Dr Nicole Kochan & Dr Teresa Lee

The Neuropsychology group 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. The Neuropsychology group has 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. The group is also interested in establishing 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.

PROTEOMICS

Dr Anne Poljak

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.

HIGHLIGHTS FROM OUR GROUPS

- Mild cognitive impairment (MCI) is considered an intermediate stage between normal ageing and dementia. However, our research suggests that objective assessment of cognitive impairment alone is the best predictor of progression to dementia in a community sample. Clinical assessment procedures need to be refined to improve the identification of pre-dementia individuals (Brodaty et al., *The American Journal of Geriatric Psychiatry*).
- Reversion to normal cognition from MCI is common. We found up to 46.5% of individuals classified with MCI at baseline reverted to normal cognition at some point during follow-up (Aerts et al., *Neurology*).
- Intraindividual variability of reaction time (IIVRT) increases in old age, and has been associated with dementia and mortality. Based on performance on two computerised reaction time tasks, greater IIVRT but not mean reaction time predicted survival time after accounting for age, sex, global cognition score, cardiovascular risk index and apolipoprotein ε4 status. Our findings suggest that greater IIVRT uniquely predicts shorter time to death and that lower global cognition and prodromal dementia in older individuals do not explain this relationship (Kochan et al., *PLOS ONE).*
- Functional connectivity studies examine the neural interactions, or connections, between different regions of the brain. Our research has identified that age and educational attainment confer independent influences on brain patterns supporting cognitive processes. It implies that age-related changes may be resistant to positive lifestyle factors that modify the risk of cognitive impairment such as educational attainment (Perry et al., *Human Brain Mapping*).
- We examined the relationship between two epigenetic clocks, ageing and exceptional longevity. In the Sydney Centenarian Study cohort, the Hannum DNAmage underestimated the age of the long-lived participants by up to 11 years. This finding supports the view that centenarians are 'biologically younger' than their chronological age (Armstrong et al., *Future Medicine*).
- Our preliminary findings indicate that in more than half of the centenarian studies participating in ICC-Dementia, rates of cognitive and functional impairments increase with age. However, people with more years of education and who live in the community show better cognitive and functional performance, based on their scores in the mini-mental state examination and their independence in activities of daily living, such as traveling alone and dressing themselves. There are substantial variations in the prevalence of dementia between studies/across countries.
- We quantified levels of seven different apolipoproteins in 1067 individuals aged 56-105 years. Centenarians had the highest APOE levels and the lowest frequency of the APOE ε4 allele. The findings suggest that levels of some apolipoproteins, especially APOE, are associated with lifespan and cognitive function in the oldest old (Muenchhoff et al., *Neurobiology of Aging*).
- There is substantial age and sex-related variation in the plasma lipidome of healthy individuals during the second half of the human lifespan, especially among 'oldest old' subjects over 95 years. Most lipid classes are lower in older age, especially in subjects over 95 years. We observed a strong association of age and total cholesterol with lipid levels. Sex-related differences include higher LDL-C, HDL-C, total cholesterol, particular sphingomyelins, and docosohexanoic acid-containing phospholipid levels in females. Surprisingly few associations between lipids and body mass index were observed.
- Plasma Aβ levels and the Aβ1−42/1-40 ratio are related to cognition and hippocampal volumes, with differential associations of Aβ1-40 and Aβ1-42 in ε4 carriers and non-carriers. Our data support the Aβ sink model of Alzheimer's disease (AD) pathology, and suggest that plasma Aβ measures may serve as biomarkers of AD (Poljak & Sachdev, *Expert Review of Neurotherapeutics*).
- We observed dysregulation in a variety of protein functional clusters, including antioxidant proteins, metabolic enzymes and mitochondrial proteins. These were generally downregulated in Alzheimer's disease (AD), whereas the expression of several proteins involved in cell cycle regulation, neuronal remodelling or structural roles, were upregulated in AD compared with controls, suggesting possible mechanisms of cellular repair or regeneration (Poljak et al., *Alzheimer's Association International Conference, London*).

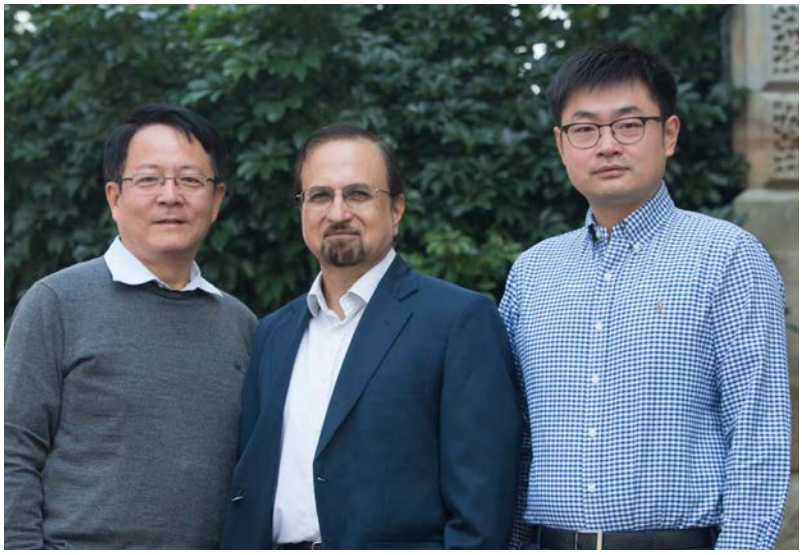
- We identified genetic variants affecting MIC-1/GDF15 blood concentration in the largest meta-analysis of genome-wide association studies examining this trait. The findings identified a significant locus on chromosome 19 and a putative locus on chromosome 1.
- Heritability of changes in global and subcortical brain volumes was estimated in five longitudinal twin cohorts from across the world (including OATS) and at different stages of the lifespan. Heritability of brain volume changes was generally higher in adults than in children. Modelling suggests that the gene variants influencing regional brain volume changes are not the same gene variants that explain brain volumes at baseline. It is thought that the former are more specific for brain plasticity and possibly important for disease characterised by altered developmental trajectories (Brouwer et al., *Human Brain Mapping*).
- Genetic data and MRI scans of brain structures from OATS participants contributed to a large study (total sample 33,536 individuals) of genetic contributions to hippocampal volume. Six independent genetic loci were associated with hippocampal volume, four of them novel. Genetic variants found to be associated with decreased hippocampal volume are also associated with increased risk for Alzheimer's disease (Hibar et al., *Nature Communications*).
- Incidental findings on structural cerebral magnetic resonance imaging (MRI) are common in healthy subjects, and the prevalence increases with age. Periventricular white matter hyperintensities were moderately heritable and deep white matter hyperintensities highly heritable (Koncz et al., *Brain Imaging & Behavior*).
- The Neuroimaging Group developed two sets of CHeBA Neuroimaging Software (CNS): UBO Detector and TOPMAL (TOolbox for Probabilistic MApping of Lesions). UBO Detector has been validated with: high segmentation and volumetric agreement between the UBO Detector-derived and manually traced white matter lesions (WML); highly correlated and a steady increase of WML volumes over time; and significant associations of periventricular and deep WML volumes generated by UBO Detector with Fazekas rating scores. It can be implemented using either graphic user interface (GUI) or command line. In addition to workstations with multi-core CPUs, UBO Detector has also been tested on PBS Pro-based clusters. Since November 2017, TOPMAL has been integrated into CNS as an extension of UBO Detector. TOPMAL is a toolbox to map cerebral small vessel disease-related lesions, including WML, lacunar infarcts, dilated perivascular space and microbleeds, to brain atlases, including John Hopkins University (JHU) WM Tractography Atlas and Harvard-Oxford Subcortical Structural Atlas. The output can be directly used for region of interest (ROI) lesion-symptom mapping analyses (Biesbroek et al., *Clinical Science*).

- We applied TOPMAL to Sydney Memory and Ageing Study (MAS) data and found that regional WML were associated with processing speed, executive function and global cognition, independent of total grey matter, white matter and WML volumes. Moreover, regional WML explained more variance in executive function, compared to total grey matter, white matter and WML volumes. The measurement of NAD+ and its related metabolites (the NAD+ metabolome) represents an important indicator of cellular function. We developed a sensitive, selective, robust, reproducible, and rapid method for the concurrent quantitative determination of intracellular levels of the NAD+ metabolome in glial and oocyte cell extracts using liquid chromatography coupled to mass spectrometry. This method provides a sensitive profiling tool, tailoring chromatography for metabolites that express significant pathophysiological changes in several disease conditions and is indispensable for targeted analysis (Bustamante et al., *Metabolomics*).
- We were the first to quantify changes in the NAD+ metabolome in plasma samples collected from consenting healthy human subjects across a wide age range (20-80 years). Our data cumulatively suggests that age-related impairments may also be associated with alterations in the NAD+ metabolome. Measurement of plasma levels of the NAD+ metabolome can be used as a biological index for niacin nutrition.
- We evaluated repeat dose intravenous (IV) NAD+ (1000 mg) for 6 days in a population of 8 healthy adults between the ages of 70 and 80 years. Our data is the first to show that IV NAD+ increases the blood NAD+ metabolome in elderly humans. IV NAD+ infusions also altered the plasma lipid profile in a favourable manner. The study shows that repeat IV dose of NAD+ is a safe and efficient way to slow down age-related decline in NAD+.
- Using whole brain extracts, we found that transition metals may be enriched with age in the brains of *O. degus* – a natural model for AD, and metal dyshomeostasis including alterations in the expression of lysosomal protein, major iron/copper transporters, and selected zinc transporters in specific brain regions is age-related (Braidy et al., *Frontiers in Aging Neuroscience*).
- Our data provides the first biochemical evidence that may explain the pathological similarities and differences between glaucoma and Alzheimer's disease. Identification of the overlapping pathways promises to provide renewed understanding of the aetiology and pathogenesis of age-related neurodegenerative diseases (Mirzaei et al., *Scientific Reports*).

Staff, Older Australian Twins Study

NEUROIMAGING GROUP PIPELINE IDENTIFIES WMHS IN BRAIN SCANS

CHeBA's innovative Neuroimaging Group pipeline, UBO Pipeline, has proven successful in identifying white matter hyperintensities (WMHs) in brain scans of older participants. Creation and testing of the pipeline was generously funded by The John Holden Family Foundation.



Associate Professor Wei Wen, Professor Perminder Sachdev AM and Dr Jiyang Jiang

White matter works as the brain's transport system, connecting and transmitting signals between different regions of grey matter. Believed to be the result of reduced blood supply or damage, WMHs are an important marker for brain disease and have been consistently associated with negative health outcomes including cognitive decline, dementia, neuropsychiatric disorders and motor deficits.

WMHs appear as bright spots (unidentified bright objects or UBOs) on brain scan images. The severity of WMHs has traditionally been assessed using visual inspection and a rating scale, which is time consuming and inaccurate for research purposes. By contrast, the automated pipeline improves consistency of findings and can process approximately 250 brain scans within two to three days. With parallel computing enabled in UBO Detector, the pipeline increases processing speeds by using multi-core central processing units (CPUs) that are commonly available in computer workstations.

CHeBA's UBO Detector pipeline is a fully automated, cluster-based system which extracts information from large numbers of brain scans (T1-weighted and FLAIR) to identify the locations of WMHs within the brain, as well as their regional and global volumes. The pipeline uses a supervised machine learning algorithm (k-nearest neighbours) to extract and calculate variables for regions of WMHs. The high performance of the UBO Detector has been validated against traditional manual tracing methods and brain scans over time.

The pipeline was made publically available and free of charge to researchers world-wide in August 2017 to boost research productivity and help improve understanding of the link between WMH and brain disease. It has already been downloaded and trialled internationally by over ten groups in four countries. Researchers from the University of Bordeaux are currently using it on a dataset of approximately 3000 older brain scans.

CHeBA's Neuroimaging Group is currently working on improving the capacity of the pipeline, so that in the future it will be able to:

detect WMH and other brain lesion burdens at the level of individual brain fibre tracts; and

more accurately detect WMH in young and healthy brains, where WMHs appear to be extremely subtle compared to older brains.

UBO is available for download at: https://cheba.unsw.edu.au/group/neuroimaging-pipeline

"CHeBA is thrilled to be leading international dementia research, which would not be possible without the generous spirit of collaboration we have encountered from fellow research groups around the world."
Professor Perminder Sachdev

CHEBA-LED CONSORTIA

CONSORTIA

COSMIC

About

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, India, Indonesia, Japan, Korea, Malaysia, Singapore), Australia, Europe (France, Germany, Greece, Italy, Spain, The Netherlands, UK), The Americas (Canada, USA, Cuba, Brazil), and the Middle East (Iran).

Highlights

- We published a paper in PLOS Medicine reporting on similarities and differences in cognitive decline across 14 cohorts from 12 different countries.
- COSMIC was awarded US$2.57 million (over 5 years to 2022) from the National Institutes of Health, USA, to identify risk and protective factors and biomarkers of cognitive ageing and dementia.
- We held a COSMIC symposium at the 16th Congress of the International Federation of Psychiatric Epidemiology Congress 2017, with presentations by members representing cohorts from Australia, France, India, Japan, and Singapore.
- We expanded the ethno-regional diversity of our membership by recruiting studies from countries that include Cuba, Iran, and Malaysia, as well as a cohort of Latinos from Sacramento.
- We began three new research projects: investigating cognitive decline across 20 cohorts from 15 different countries, the effects of sedentary behavior on late-life cognition, and the prevalence of subjective cognitive decline.

ICC-DEMENTIA

About

Combining eighteen different centenarian and near-centenarian studies from Australia, Germany, Hong Kong, Italy, Japan, Poland, Portugal, Sweden, The Netherlands, UK, and USA, ICC-Dementia seeks to harmonise these studies internationally to describe the cognitive and functional profiles of exceptionally old individuals and systematically explore the factors involved in dementia and longevity. ICC-Dementia aims to spearhead an international effort to promote successful brain ageing by identifying risk and protective factors into the 11th decade of life that are robust across cohorts.

Highlights

- We received ethics approval renewed until 26 November 2022.
- We collected additional cognitive (MMSE item-level scores) and sensory impairment data from members of the consortium.
- We are analysing international prevalence of dementia using combined data from 17 centenarian studies. Preliminary findings indicated that in more than half of the centenarian studies, rates of cognitive and functional impairments increase with

age. However, people with more years of education and who live in the community show better cognitive and functional performance, based on their scores in the mini-mental state examination and their independence in activities of daily living, such as traveling alone and dressing themselves. There are substantial variations in the prevalence of dementia between studies/across countries, with further analysis currently being undertaken to understand this phenomenon.

PROMOTE

PROMOTE

About

Launched in 2013, PROMOTE (Psychosocial Research Consortium to Advance Mental Health of Older People in the Asia Pacific region) is a consortium of psychosocial researchers in the Asia-Pacific region aiming to advance psychosocial research. In attempting to ensure quality and person centred dementia care, members of PROMOTE are working on the first regional collaborative study "Testing feasibility and face validity of Quality Indicators (QIs) for psychosocial interventions". This collaboration is a replication of a European multinational consortium project which was initiated and led by Alzheimer Europe. This project includes data from Hong Kong, South Korea, Malaysia, Australia, China, Singapore and Thailand.

Highlights

- *European indicators problematic for measuring quality of care in Asia-Pacific countries* was published in 2017 in Aging and Mental Health.
- Professors Jeon and Brodaty met with representatives of 14 Asia-Pacific Regional national members of Alzheimer's Disease International in November 2016 who endorsed the concept of PROMOTE and agreed to help foster collaborations in Asia-Pacific psychosocial research.
- At the Alzheimer's Disease International Conference in Kyoto, Japan in April 2017, proposals for new research projects were put forward and voted. Five countries agreed to undertake a qualitative study of the experiences of people with dementia, (and their family carers and their health professionals), from the time of their first symptoms through diagnosis and over the following 12 months.
- The qualitative research approach adopted in this application uniquely positions each country member to inform their policy, education, practice and service development. One of the strengths of qualitative research is its power to tell individual stories in a cohesive way that reflects the overall experience of living with dementia with and without diagnosis, from the perspectives of people with dementia and their family carers. We have planned to have sufficient numbers of participants to reach data saturation for each country. This will enable individual country members to use their data to tell the stories of people with dementia and family carers in their own language to educate future and current health professionals, and inform service providers and policy makers. Comparing the experiences from different participating countries across the region will further help health professionals, service providers, and policy makers understand where the gaps and strengths are in their effort to provide care and support for people with dementia and their family carers. Furthermore the findings will identify knowledge gaps and generate further research areas in each of the participating countries.
- Currently the logistics, support required and funding are being explored.

STROKOG

STROKOG

About

STROKOG is a consortium of longitudinal studies of cognitive disorders following stroke, TIA or small vessel disease. Developed under the auspices of VASCOG (Society for the Study of Vascular Cognitive and Behavioural Disorders), it is the first international effort to harmonise work on post-stroke dementia. The consortium brings together 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=28; total sample approximately 16,600 individuals, representing 17 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.

Highlights

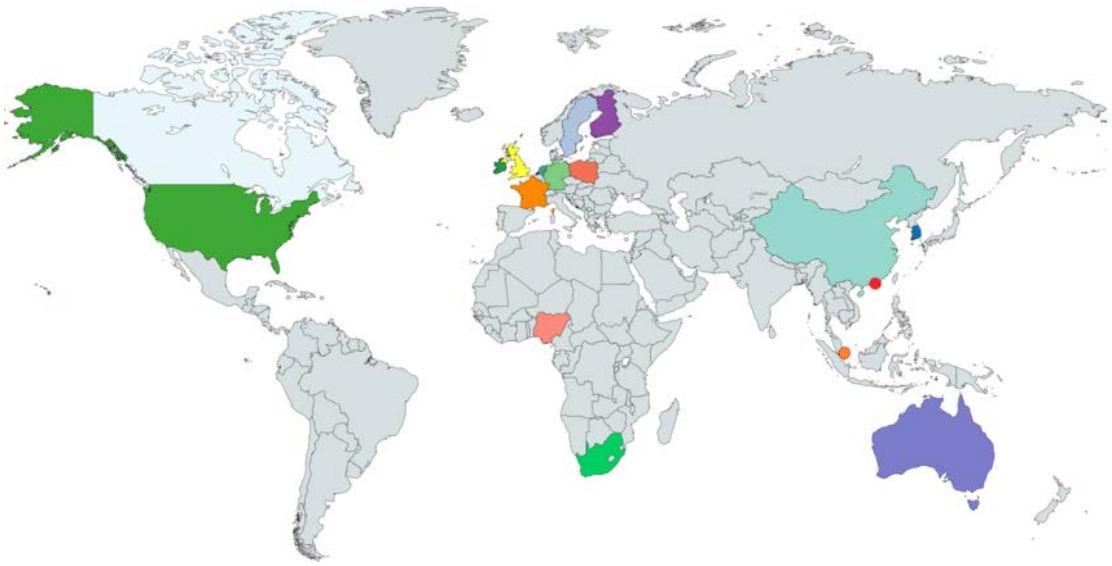
- We have completed the labour-intensive task of harmonising data from 13 studies.
- We completed analyses for our first project, "Profile and risk factors of post-stroke cognitive impairment in diverse geographical and ethno-racial groups: An individual participant data meta-analysis from the STROKOG consortium". From our combined sample of 10 hospital based studies from Africa, Asia, Australia, Europe and USA, we found that 2-6 months after stroke or TIA 45% of participants were impaired in global cognition and 30-35% were impaired in different cognitive domains. The degree of impairment was similar in the five cognitive domains (attention & processing speed, memory, language, perceptual motor and frontal executive function). Overall Koreans had the highest rate of impairment and Singaporean Chinese the lowest, compared to whites in Australia/Europe/USA. Diabetes and a history of past-stroke had significant negative effects on cognitive function in all domains; these effects were independent of stroke, age and gender.
- We received the first four project proposals from external investigators and PhD students in the UK, all of which the Scientific Steering Committee reviewed and approved. We have released STROKOG data for two PhD students who are now using them to validate risk models for dementia and cognitive impairment in stroke patients.

CHEBA CONSORTIA COLLABORATIONS

In addition to the CHeBA-led consortia (COSMIC, ICC-Dementia, PROMOTE and STROKOG), CHeBA is a member of the following:

- BRIDGET (Brain imaging, cognition, Dementia and next generation GEnomics: a Transdisciplinary approach to search for risk and protective factors of neuro-degenerative disease)
- CHARGE (Cohorts for Heart and Ageing Research in Genetic Edpidemiology)
- DIAN (Dominantly Inherited Alzheimer Network)
- EADB (European Alzheimer's Disease DNA BioBank)
- ENIGMA (Enhancing Neuro Imaging Genetics through Meta-Analysis)
- EuroDiscoTWIN (European Discordant Twin Study)
- IALSA (Integrative Analysis of Longitudinal Studies on Aging and Dementia)
- IGEMS (Consortium on Interplay of Genes and Environment across Multiple Studies)
- PERADES (Defining Genetic, Polygenic and Environmental Risk for Alzheimer's disease)

- Presentation at the Vascular Factors in Dementia and Neurodegeneration Symposium, 13-14 July in London.
- Presentation at the Vascular Neurodegeneration Symposium, 2 March in Melbourne.
- Three additional studies joined STROKOG. These include the very large South London Stroke Registry (n>6000) and a Chinese study, extending our international coverage to include Europe, Australia, Asia, USA and Africa.



STROKOG members around the world

DR YVONNE LEUNG: ICC-DEMENTIA COORDINATOR

Post-doctoral research fellow Dr Yvonne Leung joined CHeBA as the study co-ordinator of ICC-Dementia (International Consortium of Centenarian studies of Dementia) in July 2017, bringing experience in computer programming, experimental design and data analysis.

"With a background in social work, psychology and interdisciplinary research on human-machine interaction, I look forward to contributing a different skill-set to ICC-Dementia to gain insights into healthy ageing and dementia in centenarian populations," said Ms Leung.

ICC-Dementia combines international centenarian and near-centenarian studies to describe the cognitive and functional profiles of exceptionally old individuals. CHeBA researchers are systematically exploring the risk and protective factors involved in dementia and longevity, as well as providing real-life models of healthy brain ageing to develop strategies for escaping or delaying the onset of dementia.

Currently, Ms Leung is conducting statistical analysis on studies contributed by international collaborators to estimate the prevalence of dementia in centenarians globally. Data mining is involved which seeks to discover patterns and anomalies in large data sets using interdisciplinary methods from the fields of statistics, machine learning and database systems.

"The greatest strength of ICC-Dementia research is that it is very applicable and closely related to people's lives," said Ms Leung. "Our research seeks to inform clinical intervention and health policies, which would potentially improve quality of life for all Australians in the long-term, as well as diagnosis of the dementias in the centenarian population in the shorter term."

"The greatest strength of ICC-Dementia research is that it is very applicable and closely related to people's lives."
Dr Yvonne Leung

Ms Leung is encouraged by experiences of positive brain ageing in her family, with her grandparents and great-grandparents enjoying good physical and mental health into late life.

"Ultimately, I am optimistic that the general population will be proactive about sourcing information to improve their cognitive ageing, once it is made available," said Ms Leung. "To facilitate this, we need strong resource allocation and support from government and corporate philanthropists."

Ms Leung holds a Bachelor of Arts with Honours and a PhD from the MARCS Institute for Brain Behaviour and Development, and a Master of Arts from the University of Sheffield, UK.

COLLABORATIVE RESEARCH: EFFECT OF BLOOD GLUCOSE ON BRAIN ATROPHY

Higher blood glucose levels, even within the 'normal' range, may have a significant impact on total brain volume and grey matter atrophy in later life. Findings from the PATH Through Life Study by the Centre for Research on Ageing, Health & Wellbeing (CRAHW) at ANU, with which CHeBA collaborates, were published in *Diabetes & Metabolism* in July 2017.

Lead author, CRAHW's Dr Erin Walsh said the research provided valuable new insights into the role of blood glucose levels beyond the effects associated with type-2 diabetes.

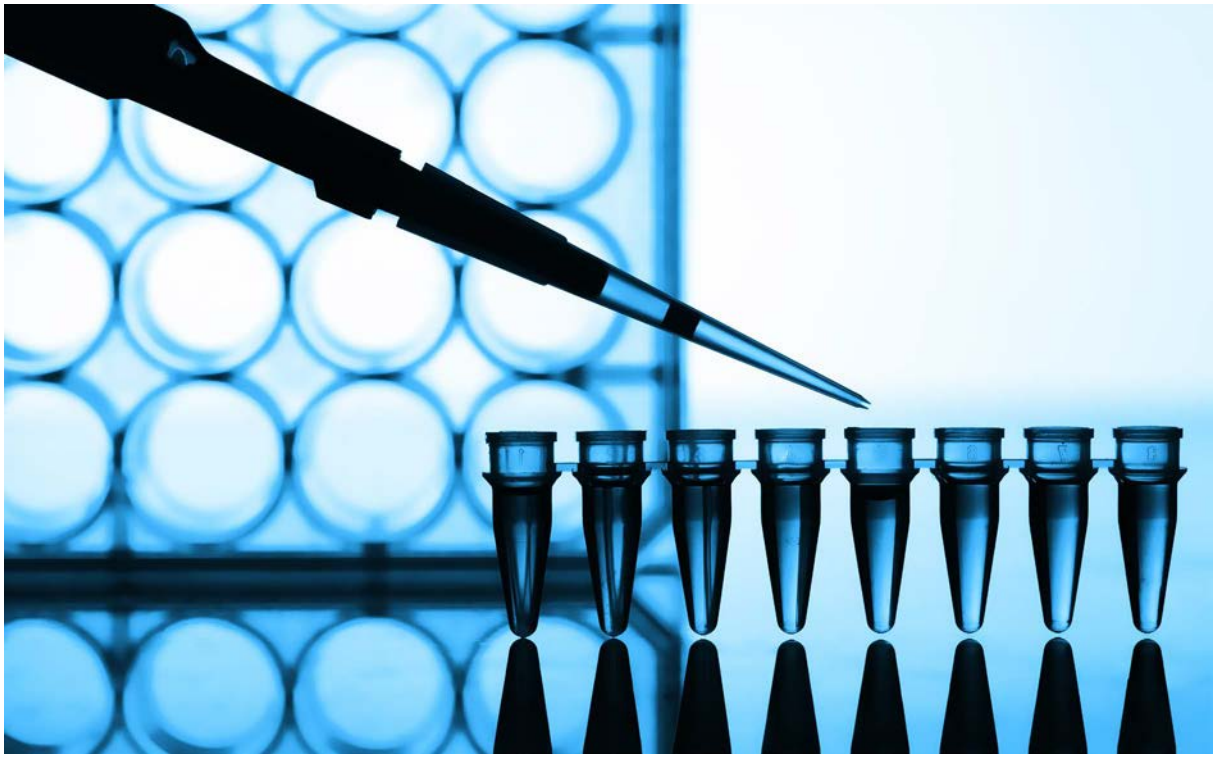
"This study showed that the impact of blood glucose on the brain is not exclusive to type-2 diabetes and that blood glucose levels even in the normal range can have a significant impact on total brain and grey matter atrophy," said Dr Walsh.

"In combination with typical age-associated changes in brain volume, additional atrophy of this magnitude may be associated with an increased risk of mild cognitive impairment and Alzheimer's disease."

> "Blood glucose levels appear to be important even in non-diabetic individuals."
> Professor Perminder Sachdev

Co-author Professor Perminder Sachdev, said that if further research can replicate these findings, they could have important implications for clinical interventions.

"Blood glucose levels appear to be important even in non-diabetic individuals, and we need to consider the role of higher normal levels as a risk factor for brain health."



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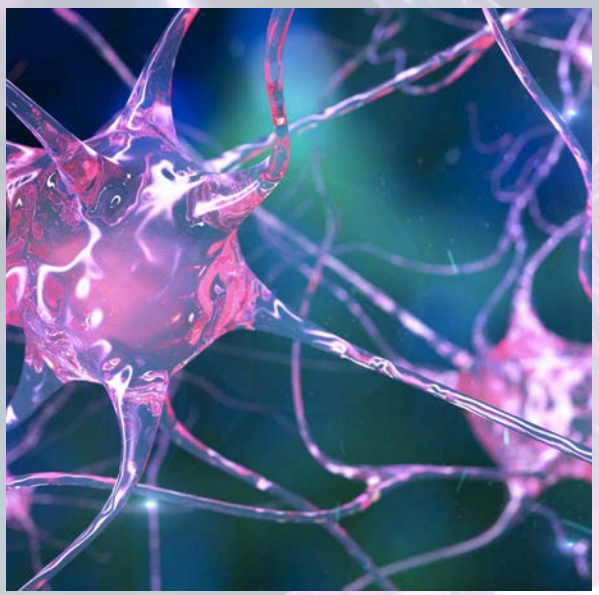

SOCIALISATION & DEMENTIA

CHeBA research students Dr Anne-Nicole Casey and Mr Ross Penninkilampi investigated the significance of socialisation for brain health, including effects on quality of life for people with dementia and the potential protective effect of socialisation for cognition.

For her PhD (co-supervised by Professor Henry Brodaty), awarded in 2017, Dr Casey examined the role of friendship and relationship interactions for people in residential aged care. Her findings suggest a pressing need to focus on residents' social health and develop individually tailored interventions.

"People with dementia who live in residential aged care, including people with more severe cognitive-functional impairment, are able to clearly articulate what friendship means to them," said Dr Casey.

"Despite multiple barriers to relationships, residents with dementia wish to reach-out to co-residents to connect in positive and meaningful ways. However, interactions that began positively often ended in rejection and disconnection, few friendships existed and observations indicated negative relationships were common."

Dr Casey has since been appointed as a CHeBA post-doctoral research fellow on the Sydney Memory & Ageing Study (MAS) Social Network project, funded by the Thomas Foundation. The project will examine the protective effects of socialisation against cognitive decline, including associations between social-network size and cognitive-functional ability, using 10 years' worth of MAS data.

The project is also informed by a systematic literature review about the risk and protective factors of socialisation for cognitive decline and dementia conducted by Mr Penninkilampi for his Medicine Honours degree in 2017.

Mr Penninkilampi is also investigating the effects of loneliness on cognition with ageing, the effects of socialisation on exercise and cognition benefits, and whether benzodiazepine use (tranquilisers to treat anxiety and sleep disorders) is a risk factor for cognitive decline.

DR THARUSHA JAYASENA

Thesis: The roles of sirtuins and polyphenols in brain ageing and neurodegeneration

Sirtuins, or "silent information regulators" of gene transcription, are enzymes found in all life. Evidence suggests that they are key regulators of stress resistance, cell division and repair, and cell death. My research involved developing and validating a mass spectrometry-based method to quantify all seven mammalian sirtuins in the brain and cerebrospinal fluid. I examined proteomic changes in neurons exposed to Alzheimer's disease plasma and found changes to glycolysis, the process which converts glucose to extract energy. I also tested polyphenolic plant compounds for their ability to aggregate amyloid and reduce oxidative stress, which are associated with age-related cognitive disorders such as dementia.

At CHeBA, I received great mentorship and supervision, expanded my skills, and developed collaborations with other research groups.

Dr Jayasena is continuing her research with the Proteomics Group as a CHeBA post-doctoral fellow.

DR CLAIRE O'CONNOR

Thesis: Understanding behaviour and function in frontotemporal dementia: developing better intervention approaches

A key outcome from my thesis was highlighting that apathy, a common behavioural symptom, is a strong contributor to limitations in everyday function in people with frontotemporal dementia. My research also demonstrated the potential for using an activity-based intervention to address some of the behavioural symptoms and everyday functional limitations associated with frontotemporal dementia.

I benefitted from the wealth of knowledge of my supervisor Professor Brodaty, who was able to provide a great perspective on the bigger picture.

Dr O'Connor is a research fellow at the Centre for Positive Ageing, HammondCare, and conjoint lecturer at the School of Public Health and Community Medicine, UNSW Sydney.

DR ALISTAIR PERRY

Thesis: Brain networks in healthy ageing and psychiatric conditions

My research explained large-scale brain network connectivity associated with cognitive and behavioural changes in normal ageing and psychiatric conditions. In particular, I found connectivity patterns with age in brain-regions supporting lower-level functions are most susceptible to the influence of ageing. Furthermore, changes in structural connectivity patterns were identified in individuals at high-genetic risk for bipolar disorder, which are suggestive of developmental abnormalities which pre-empt illness onset.

Working with CHeBA increased my awareness of how brain changes, both normal and abnormal, are integral to the ageing population and the costs incurred on society and family members.

Dr Perry has since completed a six month post-doctorate position at the Queensland Institute of Medical Research and will be starting a post-doctoral position at the Max Planck Institute for Human Development in Berlin.

BRAIN BANK DONATION PROGRAM

Dr Kristan Kang is CHeBA's Data Manager and Co-ordinator of the Brain Donation Program and the CHeBA Research Bank. He provides guidance to CHeBA on research governance and ethics and ensures the safe handling of CHeBA's research collections.

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. 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.

In 2017, 6 new brains were donated to the CHeBA Brain Donation Program, while an additional 4 research participants signed up.

OUR COMMUNITY

"One of the most effective strategies we can adopt to reduce the risk of cognitive decline and dementia later in life is to become physically active from an early age, and remain active throughout our lives."

Professor Henry Brodaty

THE DEMENTIA MOMENTUM

SPOKESMAN'S REPORT

As the third anniversary of The Dementia Momentum rapidly approaches, it is timely to reflect on how this initiative has evolved. This anniversary is also an excellent opportunity to acknowledge the many donors, Members and Friends, fundraisers, sponsors and in-kind supporters who have come on board. The breadth of research that has been possible as a result of our collective efforts is terrific.

Although there are many individuals and organisations worthy of mention, I would particularly like to extend my thanks to KPMG Sydney, ARIA Restaurant, Colliers International Residential, Morgans, Cunninghams, Kennards Hire and Anchorage Capital.

To date, we have generated $6.3 million for CHeBA's large-scale 'big data' research toward a goal of $10 million by 2020.

This year bore witness to the property industry boasting the most successful Wipeout Dementia to date - with $120,000 raised in November at Bondi Beach. Not far behind was $100,000 raised at the event in May held at Queenscliff. I commend the surfers, sponsors and donors of this campaign which has become a prominent feature of The Dementia Momentum and indicative of an extraordinary level of support across individuals and organisations. I would like to thank all participants for their enthusiastic involvement and their generosity in driving new interest to the competition.

Special thanks this year must go to our highest fundraisers Peter Chittenden, Simon Liddy, Steve Watson and Andrew Wilson as well as those that kindly assisted with CHeBA's media coverage for this campaign: Geoff Nesbitt, Rob Gillespie, Chris Clarke and Steve Watson.

Additional media coverage supported the cause in September when Peter Chittenden and his team at Colliers International Residential held their annual developers' lunch on World Alzheimer's Day, 21 September 2017, raising over $80,000 in auction bids. I am humbled by the efforts of so many individuals like Peter, whose opinion piece in the Australian Financial Review acknowledged the extraordinary increase in

"Looking back, part of my hope as Spokesman of this initiative was not just to help drive fundraising to CHeBA but to start a movement that alters the prejudice largely still existing around dementia. "

> CHeBA's focus on international collaboration inspires significant promise for future outcomes in dementia research.
> Richard Grellman AM

construction on 120 aged care homes in Australia and recognised the need for collaborative behaviour between the property industry and dementia researchers. I'm extremely pleased to see that philanthropic partnership with CHeBA forging ahead.

Looking back, part of my hope as Spokesman of this initiative was not just to help drive fundraising to CHeBA but to start a movement that alters the prejudice largely still existing around dementia. I want dialogue increased about the disease, people encouraged to see a specialist sooner, and of course, resources directed in the right way to help alter the future of this crippling disease. It remains my view that the right direction is CHeBA.

There is no denying that the number of people with dementia is increasing rapidly, with figures estimated to rise to 135 million worldwide and to almost 1 million in Australia in just a couple of decades. The reality is that this disease is going to impact more and more people. We are going to continue to live longer and the costs of providing appropriate care to an increasing number of people points to an enormous economic impact. This cannot be something we sit back and watch happen.

I am sure that many of you reading this have ageing parents who were or are suffering from dementia. If so, you will be familiar with the debilitating and unstoppable impact of this condition on those affected and indeed the whole family as the disease takes hold and worsens. I ask you to reflect on how it would be if something very similar to old age dementia were to strike you in your prime; during that period of your life when you would normally hope to be enjoying the fruits of your hard work, the successes of your children and the joy of having grandchildren. My wife, Suellen, is one such person. In the last three years since this initiative commenced, Suellen's condition has deteriorated significantly. In fact, she is now in need of direct assistance for every daily function and activity, having been in residential care for the last four years. She now cannot walk, has lost the ability to speak and even needs family or the carers where she lives to feed her at meal times. She has just turned 67.

It is my great hope that The Dementia Momentum will allow CHeBA to achieve strong advances in understanding the causes, preventative measures, earlier diagnosis and new and sustainable treatment options in order to turn the tide on this confronting social issue.

Richard Grellman AM

Chairman, IPH Limited & AMP Foundation

THE DEMENTIA MOMENTUM TWO YEAR ANNIVERSARY AT KPMG

The Dementia Momentum marked its two year anniversary in 2017, with a lunch hosted by ongoing supporter KPMG Sydney on 29 March and coverage in the *Australian Financial Review*.

> "With a current annual cost to the Australian community of $14 billion, dementia is the costliest of all diseases."
> Professor Henry Brodaty

CHeBA Co-Director Professor Henry Brodaty informed the 130 corporate attendees it is predicted there will be 1.1 million Australians with Alzheimer's disease and other dementias by 2056, with a current annual cost to the community of $14 billion - the ***costliest*** of all diseases. Professor Brodaty and Spokesman for The Dementia Momentum, Richard Grellman AM, urged the corporate and government sectors to increase funding support for research to change the future of dementia incidence and reduce the staggering social and economic burden it poses.

The lunch provided an opportunity to thank many of the key supporters involved in the success of the initiative, which raised $2.4 million over two years and $6.2 million by the end of 2017.

COLLIERS INTERNATIONAL RESIDENTIAL SUPPORT THE DEMENTIA MOMENTUM ON WORLD ALZHEIMER'S DAY

Colliers International Residential continued their incredible track record of support for CHeBA on World Alzheimer's Day 2017. Colliers donated the proceeds of their annual residential developer lunch charity auction, totalling $74,500, to CHeBA's research into dementia incidence. In an opinion piece published on the same day in the ***Australian Financial Review***, Mr Peter Chittenden, Managing Director, Colliers International – Residential, highlighted the need for stronger linkages between the property industry and researchers.

Facing an ageing population, growing demand for residential care, and dementia projections, Mr Chittenden said improved understanding of the disease and care requirements is both an ethical and business imperative.

"We have acknowledged the need for collaborative behaviour between the property industry and dementia researchers and as such are proud to have formed a philanthropic partnership with leading experts at CHeBA," said Mr Chittenden.

Dementia is now the second leading cause of death in Australia. With more than 413,000 Australians with the disease, it is projected that there are 244 new cases diagnosed each day. By 2056 the figure is set to increase to a total of 1.1 million with a prediction of 650 new cases per day. As the numbers increase, so do costs: from an estimated $14 billion a year in 2017 to $36.8 billion in 2056. Of these costs 61% are direct, including factors such as residential care. Currently, around 52% of all permanent residents in care have a diagnosis of dementia.

To date, Platinum Member of The Dementia Momentum, Colliers International – Residential, has raised over $150,000 for CHeBA's research into dementia, including sponsorship of both property industry Wipeout Dementia campaigns in November 2016 and 2017, respectively.

Richard Grellman AM

Richard Grellman AM and Peter Chittenden

> Improved understanding of the disease and care requirements is both an ethical and business imperative.
>
> Peter Chittenden, Managing Director, Colliers International – Residential

MEMBERS OF THE DEMENTIA MOMENTUM

DIAMOND MEMBERS

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Vincent Fairfax Family Foundation

PLATINUM MEMBERS

Colliers International

Sachdev Foundation

Judy Harris & Phil Cave AM

GOLD MEMBERS

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Peter & Yvonne Halas

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WIPEOUT DEMENTIA 2017

Wipeout Dementia held its two most successful campaigns to date in 2017, collectively raising over $216,000. Since its launch in May 2015, Wipeout Dementia has raised over $600,000, at a time when high profile corporate support for dementia is increasing internationally.

"I am extremely encouraged by the enhanced awareness and attention Wipeout Dementia is generating throughout the Australian corporate community," said Spokesman for The Dementia Momentum Mr Richard Grellman AM, Chairman of IPH Limited and AMP Foundation and former Chairman of The Association of Surfing Professionals (International) Limited. "There is a critical need for partnerships between research and business in order for us to tackle the extraordinary challenge posed by dementia."

The fifth campaign held in May at Queenscliff Surf Life Saving Club exceeded its fundraising target, raising $96,000. The custom Mark Richards 1982 replica twin fin '*Gnarly Award'* for highest fundraiser was taken by Managing Director of Colliers International Residential, **Peter Chittenden**, who raised over $15,000 in the event and who has also generated significant company support for the cause in recent years. Participants included Warringah Federal Liberal MP **Tony Abbott** and former NSW Premier **Mike Baird.**

In November, the sixth campaign brought together 24 heavy hitters from across the property industry at Bondi Beach for the second year. In an incredible display of dedication, Steve Watson, Managing Director of Steve Watson & Partners, personally raised over $17,000, for which he was awarded the prestigious *'Gnarly Award*'.

> "There is a critical need for partnerships between research and business in order for us to tackle the extraordinary challenge posed by dementia."
>
> Richard Grellman AM, Spokesman for The Dementia Momentum

Fittingly, in the week of Bill Gates announcing his decision to join the fight against dementia, Wipeout Dementia November raised the highest funds to date, with $120,000 directed to dementia research at CHeBA.

CHeBA Co-Director Professor Perminder Sachdev said Bill Gates' announcement is another shot in the arm for dementia research, coming only a few years after David Cameron, the then Prime Minister of the UK, put dementia research on the global agenda. What Cameron did for public funding for dementia research could be replicated in the private sector and philanthropy after Gates' bold initiative.

"Internationally, there is a need for research across the full spectrum of the disease beyond

drug treatments, to include early diagnosis and prevention strategies in mid-life to reduce modifiable risk factors associated with dementia," he said.

Wipeout Dementia aims to increase awareness about the modifiable risk factors of Alzheimer's disease and other dementias while driving research funds to harness global research to prevent dementia.

Wipeout Dementia Ambassador and 1978 World Surfing Champion Wayne 'Rabbit' Bartholomew AM congratulated all participants for their enthusiasm and involvement.

"The knowledge that this will be injected into the research coffers of Professor Henry Brodaty and Professor Perminder Sachdev and their team is very reassuring. It was definitely sobering to hear the stats on the coming tsunami for this country, so to be involved in some way warms the heart," said Rabbit.

Wipeout Dementia is held in honour of Richard's wife Suellen who has advanced young onset Alzheimer's disease and requires full time high level care and attention at age 67.

Morgans and Kennards Hire were the major sponsors for Wipeout Dementia in May and November 2017.

Cunninghams and SkiJapan were secondary sponsors in May. Ray White Commercial and Colliers International were secondary sponsors in November.

Hurley, Queenscliff Surf Life Saving Club and The Bucket List provided in-kind support.

GNARLY AWARD WINNERS

May 2015 Gnarly Award: John Cunningham

November 2015 Gnarly Award: Phil Butt

May 2016 Gnarly Award: John Cunningham

November 2016 Gnarly Award: Mark Gross

May 2017 Gnarly Award: Peter Chittenden

November 2017 Gnarly Award: Steve Watson

HALL OF FAME

2015

May

Winning Team: Grellman's Evergreens

Gnarly Award – John Cunningham

Players' Player – Chris Clarke

Best Wipeout – Peter Chittenden

Wave of the Day – Rob Gillespie

November

Winning Team: Grellman's Evergreens

Gnarly Award – Phil Butt

Players' Player – Ian Freestone

Best Wipeout – Mark Westfield

Wave of the Day – Andy Kennard

2016

May

Winning Team: Gillespie's Grommets Forever

Gnarly Award – John Cunningham

DHD Runner Up – Ben Grellman

Players' Player – Andy Kennard

Best Wipeout – Shawn Hobbs

Wave of the Day – Austin Ware

Coach's Award – Stephen Westfield

Most Valuable Players – Chris Clarke, Peter Murphy & Ian Freestone

November

Winning Team: Rodgers' Forget-Me-Nots

Gnarly Award – Mark Gross

DHD Runner Up – Peter Clemesha

Best Wipeout – John Morgan

Wave of the Day – Nick Ebrill

Highest Wave Scorers – Nick Ebrill & Philip Vivian

2017

May

Winning Team: Cunningham's Cruisers

Gnarly Award – Peter Chittenden

DHD Runner Up – Simon Liddy

Players' Player – Rob Gillespie

Best Wipeout – Andy Kennard

Wave of the Day – Austin Ware

Coach's Award – Ian Freestone

Highest Wave Scorers – Austin Ware, Dylan Norman & Heath Sims

November

Winning Team: Cliff's Carvers

Gnarly Award – Steve Watson

DHD Runner Up – Andrew Wilson

Players' Player – John L'Estrange

Best Wipeout – Andrew Wilson

Wave of the Day – Anthony Scotts

Coach's Award – Nic George

Highest Wave Scorers – 'Rabbit', Anthony Scotts & Guy Lake

WIPEOUT DEMENTIA 2017 PARTICIPANTS

- Tony Abbott
- Scott Anderson
- Mike Baird
- Wayne 'Rabbit' Bartholomew (Ambassador)
- Darren Beasley
- Michael Beggs
- Phil Butt
- Tony Camphin
- Peter Chittenden (Gnarly Award for highest fundraiser, May)
- Chris Clarke
- Peter Clemesha (Team Captain, November)
- John Cunningham (Team Captain, May)
- Brett Eichhorn
- Matthew Faddy
- Ian Freestone (Coach's Award, May)
- Nic George (Coach's Award, November)
- Robert Gillespie (Team Captain, May; Player's Player Award, May)
- Ben Grellman
- Richard Grellman (Team Captain, May)
- Mark Gross
- Andy Kennard (Wipeout Award, May)
- Graham Kittle
- Peter Kleijn
- Guy Lake
- John L'Estrange (Player's Player Award, November)
- Simon Liddy
- Chris Meehan
- Peter Murphy
- Stephen Neille
- Stephen Newey
- Brett Newman
- Geoff Nesbitt
- Dylan Norman
- Karl Riedel
- Nicholas Roche
- Clive Rodell
- Craig Rodgers (Team Captain, November)
- David Scardoni
- Anthony Scotts (Wave of the Day Award, November)
- George Sharpe
- Simon Smart
- Heath Sims
- Philip Vivian (Team Captain, November)
- Austin Ware (Wave of the Day Award, May)
- Steve Watson (Gnarly Award for highest fundraiser, November)
- Phillip Wicks
- Sam Wicks
- Andrew Wilson (Wipeout Award, November)

CHeBA CHAMPIONS

The CHeBA Champions are Fitness Ambassadors for CHeBA in their 20s, 30s and 40s; all striving for optimal brain health in late life by adopting evidence-based, risk-reducing lifestyle strategies early.

With studies indicating that physically inactive individuals have an 80% increased risk of dementia, the Champions provide much-needed advocacy for incorporating more routine physical activity in daily life. Simultaneously, they raise funds for research to change the future of dementia incidence.

WARREN KING

A CHeBA Champion since the program's inception in 2012, Warren King tackled two Ironman 70.3km events in two months to raise dementia awareness and funds for CHeBA's research.

Inspired by the experience of friends who have been affected by the disease, as well as a desire to protect his own brain health in later life, Warren completed the Port Macquarie Ironman on May 7and the Hawaii Ironman on June 3.

> I have two very good friends whose fathers are both suffering with dementia so I really feel the need to help out more. I'm happy to support the amazing work being done in the battle against Alzheimer's disease and dementia by CHeBA.
>
> Warren King, CHeBA Champion

ARIA RESTAURANT SYDNEY HOSTED CORPORATE LUNCH

ARIA Restaurant Sydney held its fourth annual senior executives' corporate luncheon to support CHeBA and drive awareness for The Dementia Momentum initiative on 16 June. Ita Buttrose AO OBE, Patron of CHeBA's Maintain Your Brain Study, was MC for the event which she said was an important opportunity for connecting the corporate community with leading international researchers.

"Enormous social and economic change will soon be upon us if, as a nation, we don't act now," said Ms Buttrose. "We want to set the scene for positive change in ageing through the research being conducted at CHeBA."

Spokesman for The Dementia Momentum Richard Grellman AM, CHeBA Co-Director Professor Perminder Sachdev AM and renowned science journalist Robyn Williams AM also delivered talks.

> "Enormous social and economic change will soon be upon us if, as a nation, we don't act now."
> ITA Buttrose AO OBE, Patron of Maintain Your Brain

PUBLIC FORUMS

I'M OLDER, BUT NOT OLD

In a joint initiative of the Aged Care Psychiatry Service, Eastern Suburbs Mental Health Service and CHeBA, a free public forum was held on 24 October: "I'm older, but not old". The forum addressed ways lifestyle changes contribute to healthy ageing, including suggesting a range of practical strategies to implement in everyday life. Rugby legend Ron Coote AM gave a guest speech on healthy ageing, while clinicians and researchers spoke about falls prevention, mindfulness, pain management and memory fitness.

SENIORS & HEALTHY BRAIN AGEING

The Uniting War Memorial Hospital held its free annual public lecture in conjunction with CHeBA in September. CHeBA research fellow and leader of the Neuropsychology Group, Dr Nicole Kochan, ran a highly informative session for seniors about how to maximise memory and improve memory fitness.

NNIDR LECTURE TOUR

Two of the world's leading names in dementia research, CHeBA Co-Director Professor Henry Brodaty and CEO and President of Alzheimer's Association USA Harry Johns, undertook a national public lecture tour during March and April.

The tour was launched by the NHMRC National Institute of Dementia Research (NNIDR) as part of the Australian Government's Boosting Dementia Research initiative and was supported by Alzheimer's Australia and the J.O. and J.R. Wicking Trust.

With dementia now the second leading cause of death in Australia and with over 25% of the population set to be aged 65+ by 2050, Professor Brodaty stressed the need to target early life to reduce the risk of dementia. He also stressed the potential of implementing internet based interventions - such as CHeBA's Maintain Your Brain study - to prevent or delay the onset of Alzheimer's disease and other dementias.

He said that despite the projections there is enormous hope through research and his intention was to use this tour to share his knowledge.

Professor Henry Brodaty AO, Janice Besch and Harry Johns

AUSTRALIAN MENTAL HEALTH PRIZE

L to R: Henry Brodaty AO with fellow Committee Members Jessica Rowe AM, Ita Buttrose AO OBE, Perminder Sachdev AM

CHeBA Co-Directors Professor Henry Brodaty and Professor Perminder Sachdev, both members of the Australian Mental Health Prize Committee, attended the 2017 ceremony where dual winners Janet Meager, a champion for the rights of people with mental health issues and Professor Allan Fels, Chairman of the National Mental Health Commission, were awarded this prestigious prize. Federal Health Minister Greg Hunt presented the two outstanding winners with their awards at an event held at UNSW Sydney on 20 November 2017.

NEUROPSYCHIATRY TRAINING WEEKEND

CHeBA and the Neuropsychiatric Institute co-hosted the third neuropsychiatry training weekend on 17-18 March. The event, attended by junior and senior clinicians and researchers, provided a rewarding professional development experience for all levels of proficiency.

The 2017 theme was: "Clinical neuropsychiatry in the 21st century: New developments, new challenges" and covered a wide range of cutting edge topics including: pharmacogenetics, genomic medicine, newer drugs and treatments such as ketamine and medical cannabis, lifestyle prescriptions, brain inflammation, advances in brain connectivity and neuroplasticity, and movement and seizures.

Speakers at the 2017 training weekend were: Professor Perminder Sachdev, Professor Andrew Somogyi, Professor Iain McGregor, Professor Cyndi Shannon Weickert, Professor Colleen Loo, Professor Katherine Samaras, Professor Maria Fiatarone Singh, Professor Michael Breakspear, Associate Professor Clement Loy, Associate Professor David Brown, Associate Professor Ernest Somerville, Associate Professor Michael Valenzuela, Associate Professor Greg de Moore, Dr Adith Mohan, Dr Rebecca Koncz, Dr Lauren Taylor, Dr Stephen Tisch and Dr Anna Takacs.

CHeBA IN THE MEDIA

CHeBA continued to improve public awareness about brain ageing, health and disease through broad media outreach in 2017, including articles in the Australian Financial Review and the Sydney Morning Herald and coverage on ABC Radio and 2UE Radio.

ABC TV's Catalyst program "It's a twin thing" showcased CHeBA's Older Australian Twin Study, the findings of which may help us to live a longer, healthier life.

KIDS4DEMENTIA IN THE SYDNEY RUNNING FESTIVAL

CHeBA partnered with Kensington Public School to raise money for the Kids4Dementia program through the Sydney Running Festival on 17 September. Thirteen (13) families joined the team and participated in either the 3.5km Family Fun Run or the 10km Bridge Run, raising $15,000.

Currently a third of young people know someone living with dementia, and with 1.1 million Australians expected to be living with dementia by 2050, their exposure to this chronic disease will only increase.

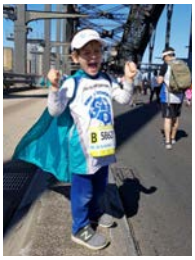
Kids4Dementia is a classroom-based dementia education program designed for young people where students learn that a person with dementia is "still a person", and not someone to fear, laugh at or ignore.

Founder and Program Developer of Kids4Dementia, Dr Jess Baker, said educating children about dementia is the foundation to a dementia-friendly society.

A dementia-friendly society is a vision shared by many researchers, practitioners, educators and consumers. It is a society where people with dementia are recognised as valued citizens and supported to remain meaningfully engaged with the community and in daily life.

CHeBA's immediate vision is to support Dr Baker roll out the program across 30 schools in NSW. Ultimately Dr Baker's goal is for this program to become part of the primary school curriculum.





MAJOR SUPPORTERS

DONORS SUPPORT FUTURE OF RESEARCH THROUGH PHD SCHOLARSHIPS

CHeBA donors are helping to foster a new generation of dementia researchers by funding PhD scholarships. The Kwan Fung & Yuet Ying Fung Scholarship and the Josh Woolfson Memorial Scholarship will enable promising students to advance understanding of the disease and build their skills as future research leaders.

The **Kwan Fung & Yuet Ying Fung Award** was established by Ms Mabel Cheng and will honour Mrs Yuet Ying Fung, who suffers from stroke-induced dementia, and the late Mr Kwan Fung who had Alzheimer's disease. The award supports research into the diagnosis, prevention and cure of Alzheimer's disease and other dementias, as well as improved care of patients with these disorders.

The first recipient, Ms Annette Spooner, commenced her PhD in 2017 and is investigating prediction of dementia onset in older individuals using machine learning techniques. Ms Spooner will explore the poorly understood transition from normal cognitive function to mild cognitive impairment, with the aim of diagnosing dementia onset before clinical signs become manifest. This innovative research employs advanced computer science techniques to identify patterns in complex sets of clinical data using different modalities, which is essential given the varied range of factors involved in abnormal, age-related cognitive decline.

The **Josh Woolfson Memorial Scholarship** was established by Mrs Liz Woolfson in honour of her late husband, who had advanced Alzheimer's disease. The scholarship will support research looking at the modifiable risk factors of Alzheimer's disease, identifying and targeting at-risk groups and individuals, and developing intervention strategies for risk reduction. Applications opened in November, with the successful recipient to begin study in mid-2018.

CHeBA Co-Directors Professors Henry Brodaty and Perminder Sachdev expressed their gratitude to Mrs Cheng and Mrs Woolfson. They said that scholarship opportunities are a vital component of building research capacity to tackle the challenges of the disease.

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- Montefiore Home

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- 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)
- RANZCP Faculty of Psychiatry of Old Age
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CURRENT PROJECTS

A study of the effect of acute physical illness requiring hospitalisation on the long-term cognitive and functional trajectory of two elderly cohorts: the Sydney Memory and Aging Study (MAS) and the Older Australian Twins Study (OATS)

CHeBA staff: Lucia Chinnappa-Quinn (PhD student), Perminder Sachdev, Nicole Kochan, John Crawford, Steve Makkar.

Other investigators: Professor Michael Bennett (Prince of Wales Clinical School, UNSW), Lara Harvey (NeuRA).

Aims:

- Observe the effect of acute physical illness requiring hospitalisation on cognitive and functional trajectory over several years in longitudinal cohort studies of cognitive ageing.
- Examine whether variables describing the nature of the illness and hospitalisation influence the level of decline in cognition and function over time.
- Explore whether a number of risk-factor variables, such as APOE4 carrier status or mild cognitive impairment (MCI), act as moderator variables to increase the effect of acute physical illness requiring hospitalisation on cognitive and functional decline.

Findings: Findings to be reported in 2018.

Funding: Australian Society of Anaesthetists, DCRC-ABC.

Amyloid-beta blood levels as an early marker of neurodegenerative disease, using data from multiple studies, including Sydney MAS, DIAN, AIBL, ADNI and OATS

CHeBA staff: Anne Poljak (conjoint), John Crawford, Henry Brodaty, Perminder Sachdev.

Other investigators: Professor Randall J. Bateman (Washington University), Professor Anne Fagan (Washington University), Professor Ralph Martins (Edith Cowan University), Professor Colin Masters (University of Melbourne), Professor John Morris (Washington University).

Aims:

- Explore covariates for correlation with Aβ levels across all cohorts. Covariates to explore include: comorbidities, therapeutic drugs, blood biochemistry, as well as lifestyle choices.
- Compare corrected Aβ levels (all cohorts) across neurodegenerative diseases: Alzheimer's disease, Parkinson's disease and Mild Cognitive Impairment (MCI).
- Identify effects of soluble Aβ levels on brain volumetric parameters, across the neurodegenerative conditions tested.

Findings: Analysis underway.

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

Anatomical mapping of white matter hyperintensity - TOPMAL (Toolbox for probabilistic mapping of lesions)

CHeBA staff: Jiyang Jiang, Wei Wen, Perminder Sachdev, Matthew Paradise.

Other investigators: Dr Wanlin Zhu (Beijing Normal University) (CHeBA Hon. Research Fellow), Associate Professor Tao Liu (Beihang University, China) (CHeBA Hon. Research Fellow).

Aim: Investigate whether associations between regional white matter lesions (WML) and cognition are independent of global grey matter (GM) and white matter (WM) volumes, which have also been linked to cognition.

Findings:

Emerging evidence from lesion-symptom mapping (LSM) studies suggests that regional WML on strategic WM fibre tracts are significantly associated with specific cognitive domains, independent of global WML burden. We performed a region of interest

(ROI) LSM study to examine the relationship between regional WML on strategic WM tracts and cognitive performance in a large community-based cohort of older individuals. We extracted WML measures using a publicly available pipeline created by CHeBA, UBO Detector. WML were mapped to the Johns Hopkins University WM atlas using an automated TOolbox for Probabilistic MApping of Lesions (TOPMAL), which maps cerebral small vessel disease-related lesions, including WML, lacunar infarcts, dilated perivascular space and microbleeds, to brain atlases. The output can be directly used for ROI lesion-symptom mapping analyses and TOPMAL has been integrated into CHeBA neuroimaging software as an extension of UBO Detector since November 2017.

Different patterns of brain structural volumes in the ageing brain were associated with different cognitive domains. Regional WML were associated with processing speed, executive function and global cognition, independent of total GM, WM and WML volumes. Moreover, regional WML explained more variance in executive function, compared to total GM, WM and WML volumes. The current study highlights the importance of studying regional WML in age-related cognitive decline. A journal paper is currently under review.

Funding: NHMRC, John Holden Family Foundation.

Apolipoproteins in plasma (particularly APOA1, APOD, APOJ and APOH)

CHeBA staff: Anne Poljak (conjoint), Nady Braidy, Nicole Kochan, Wei Wen, John Crawford, Fei Song, Julian Trollor (conjoint), Henry Brodaty, Perminder Sachdev.

Other investigators: Dr Julia Muenchhoff (CHeBA Hon. Research Fellow), Professor John Attia (University of Newcastle), Professor Mark Duncan (University of Colorado), Professor Ralph Martins (Edith Cowan University), Associate Professor Mark McEvoy (University of Newcastle), Associate Professor Peter W. Schofield (University of Newcastle), Dr Tamar Ziehm (visiting research fellow from Forschungszentrum Jülich, Germany), Professor Dieter Willbold (collaborating researcher from Forschungszentrum Jülich, Germany).

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.
- Interactions between APOH and Aß peptides, and binding partners of APOH in plasma and cerebrospinal fluid (CSF).

Findings: We quantified 7 apolipoproteins in the plasma of 1067 individuals aged 56-105 years using immunoassays and explored relationships with APOE polymorphism E2/3/4, vascular health, frailty, and cognition. All seven apolipoproteins decreased from mid-life. Centenarians had the highest APOE levels and the lowest frequency of APOE4 allele. Apolipoprotein levels trended lower in APOE4 homozygotes and heterozygotes compared with non-carriers, with APOE and APOJ being significantly lower. Levels of all apolipoproteins except APOH were higher in females. This work was published in the journal *Neurobiology of Aging 55*, 49-60.

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.

Brain proteomics: Differential expression of the proteome in AD brain

CHeBA staff: Anne Poljak (conjoint), Nady Braidy, Tharusha Jayasena, Perminder Sachdev.

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

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.

Findings: We observed dysregulation in a variety of protein functional clusters, including antioxidant proteins, metabolic enzymes and mitochondrial proteins. These were generally downregulated in AD, whereas the expression of several proteins involved in cell cycle regulation, neuronal remodeling or structural roles, were upregulated in AD compared with controls, suggesting possible mechanisms of cellular repair or regeneration. By immunohistochemistry we validated the following proteomics based observations: Translocase of outer mitochondrial membrane (TOMM70) and Solute Carrier Family 25 Member 11 (SLC25A11) were both upregulated in AD vs control occipital lobe, possibly as a protective response to the burden of pathology. These findings were presented at the *2017 Alzheimer's Association International Conference* in London.

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

BRIDGET Consortium: Brain imaging, cognition, Dementia and next generation GEnomics: A transdisciplinary approach to search for risk and protective factors of neuro-degenerative disease

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

Other investigators: Dr Nicola Armstrong (Murdoch University) (CHeBA Hon. Research Fellow), BRIDGET Consortium members.

Aims:

- Identify rare and common genetic variants influencing brain structure in older adults.
- Explore the determinants of brain ageing from a life-course perspective, including genomic, epigenomic and environmental factors.
- Examine whether identified genes predict decline in memory performance and an increased risk of Alzheimer's disease.

Findings: This work comprises a number of ongoing collaborative genetic and epigenetic projects, with a current focus on neuroimaging traits, such as perivascular spaces and cerebral small vessel disease. In 2017, CHeBA researchers attended the second Annual BRIDGET Meeting in Germany.

Funding: NHMRC National Institute for Dementia Research (NNIDR) (administered by CHeBA), European Union Joint Programme for Neurodegenerative Disease (not administered by CHeBA).

Collaboration between family members and direct care staff in quality improvement of residential care services

CHeBA staff: Lynn Chenoweth, Henry Brodaty.

Other investigators: Tracey Clarke, Megan Mills and Jeanine Lew (Montefiore Home), Janet Cook (DCRC, UNSW).

Aim: Develop and pilot test a protocol which promotes collaboration and positive relationships between family and direct care staff for the purpose of improving the quality of residential care services.

Findings: Pilot study participants included 43 nurses, direct care staff and allied health staff; 38 family carers of aged care residents; 6 staff trainers, 6 family liaison staff personnel, and an advisory group ofv 10 managerial, clinical, policy and consumer experts. The train-the trainer approach to staff education and culture change helped with team building and staff cooperation, and helped to improve family/staff relationships and communication regarding carer services in selected care units in three ways: 1) cognitive (the knowledge gained in relationship development, conflict resolution, power relationships, negotiation techniques and reflective techniques, including verbal knowledge and strategies); 2) skills (the behavioural changes involving active listening, improved response and reporting procedures); and 3) affective (attitudes reflecting greater awareness of family and staff needs, self-efficacy for improved relationship-building, and motivation to learn and change behaviour). The focus and emphasis placed on the different services, mainly by management systems, were found to impact on family/staff relationships and collaboration in achieving quality service through:

- The overarching service philosophy/mission as developed and interpreted by administrators, managers and senior staff, and operationalised by direct care staff.
- The service delivery orientation of individual managers and staff within different departments and within different roles.
- The political positions of the different departments and staff roles, and the competition for limited resources and staff positions.

These structural factors are being addressed through a recently integrated holistic organisational model.

Funding: Montefiore Home.

Deprescribing guidelines for people with dementia: Cholinesterase inhibitors and Memantine

CHeBA staff: Lynn Chenoweth.

Other investigators: Professor Sarah Hilmer (University of Sydney), Professor Ken Rockwood (Dalhousie University), Professor Parker Magin (University of Sydney), Tara Quirke (consumer), Barbara Farrell, Mary Gorman, Nathan Herrmann, Dr Graeme Bethune, Wade Thompson, Professor Ingrid Sketris (Dalhousie University), Ms Christina McNamara (Dalhousie University), Dr Emily Reeve (NHMRC/ARC Dementia Research Fellow, University of Sydney).

Aims:

- Provide recommendations regarding in what situations it might be suitable to withdraw the dementia medications cholinesterase inhibitors and Memantine.
- Provide guidance on how to conduct withdrawal, and to develop additional materials to provide information to people with dementia and their family members.

Findings: The guideline was produced following a systematic review using the GRADE process to assess the quality of the evidence and to convert the evidence into recommendations. The Guideline is registered on the NHMRC guideline register (https://www.clinicalguidelines.gov.au/portal/2588/evidence-based-clinical-practice-guideline-deprescribing-cholinesterase-inhibitors-and), with recommendations only applying to individuals already taking one of the described medications (donepezil, rivastigmine, galantamine and/or memantine).

The main points of this guideline are as follows:

- There is considerable uncertainty in the benefits and harms of both prescribing and deprescribing in the individual who has used these medications for over 12 months. Cessation may have minimal, clinically relevant negative consequences, but in some individuals discontinuation of ChEIs and/or memantine may lead to a worsening of cognitive function. In regard to quality of life and function, these outcomes may not be altered by discontinuation.
- Good communication between clinicians and people with dementia and/or carers/family on the benefits and harms of continuing versus discontinuing, in the context of their values and preferences, is necessary when discussing a potential trial of deprescribing, since individuals may feel that deprescribing is 'giving up', or a signal that they are no longer worth treating.
- The cost implications of deprescribing may include reduced medication costs, reduced costs of treating adverse drug effects, and an uncertain benefit or cost if there is a change in function that increases or decreases health service utilisation.

Funding: NHMRC and ARC (administered by University of Sydney).

Determinants of cognitive performance and decline in diverse ethno-regional groups: The COSMIC collaboration

CHeBA staff: Darren Lipnicki, John Crawford, Steve Makkar, Anbupalam Thalamuthu, Nicole Kochan, Henry Brodaty, Perminder Sachdev.

Other investigators: Study leaders and associates from 19 COSMIC member studies representing 15 countries.

Aims:

- Investigate how cognitive performance and decline is affected in different ethno-regional groups by various risk factors: sex, educational attainment, apolipoprotein E4 allele (APOE4) status, body mass index, general health, current anxiety, current and past depression, hypertension, blood and pulse pressure, diabetes, high cholesterol, peripheral vascular disease, atrial fibrillation, cardiovascular disease, stroke, smoking, alcohol use, and physical activity.
- More thoroughly investigate associations between cognitive decline and body mass index (BMI), as well as other anthropometric measures, in diverse ethno-regional groups, giving consideration to how BMI values correspond to different weight categories (obese, underweight etc.) in different racial groups.
- Investigate the extent to which the effects of the APOE4 allele on cognitive decline are influenced by interactions between age and sex in various ethno-regional groups.

- Conduct a more in-depth investigation of the influence of education on cognitive decline, by looking at differences in the effects of education between males and females, APOE4 carriers and non-carriers, and in different ethno-regional groups.

Findings: Preliminary findings suggest that being an APOE4 carrier and having poor health are both associated with lower performance and faster decline on multiple cognitive measures. Lower performance is also associated with anxiety, depression, diabetes, and stroke, and faster decline is also associated with depression, past smoking, and higher pulse pressure. There are also indications that effects of the APOE4 allele on cognitive decline are influenced by interactions between sex and age. Physical activity and light or moderate alcohol use were both associated with better cognition. Alcohol use was also associated with slower cognitive decline. To put this in perspective while there have been several studies claiming light-moderate alcohol be protective against dementia, others have disputed this. The debate hinges on how the studies are done. For example, comparisons where the risk of cognitive decline is higher in people who are tee-total may be because they abstain because of other health problems, which increase their risk rather than the lack of alcohol. A safe message is that for those who drink alcohol, light-moderate consumption (up to two standard drinks per day with some alcohol free days) may have some benefit but everyone agrees heavy use is harmful. For those who do not drink alcohol, there is no evidence to recommend you should take this up.

Funding: Direct donations to The Dementia Momentum Fund, NIH grant.

Dysregulation of lipids in the ageing brain and Alzheimer's disease: A novel biomarker approach

CHeBA staff: Anne Poljak (conjoint), Nady Braidy, Perminder Sachdev, Matthew Wong (PhD student), Yue Liu (MSc candidate), Maboobeh Hosseini (MSc candidate – to enrol in 2018).

Other investigators: Dr Russ Pickford (BMSF, UNSW), Dr Fatemeh Vafaee (BABS, UNSW), Professor Daniel Chan (Department of Aged Care and Rehabilitation, Bankstown-Lidcombe Hospital).

Aims:

- Identify lipid biomarkers in plasma to assist in diagnosis of MCI and/or Alzheimer's disease (AD).
- Explore the possibility that plasma lipids are correlated with brain volumetric and cognitive changes.
- Compare plasma lipidomics profiles across dementia subtypes (AD, vascular dementia) and stroke.
- Compare fatty acid levels in control vs AD, using plasma from MAS and OATS subjects.

Findings: There is substantial age and sex-related variation in the plasma lipidome of healthy individuals during the second half of the human lifespan, especially among 'oldest old' subjects over 95 years. Most lipid classes are lower in older age, especially in subjects over 95 years. We observed a strong association of age and total cholesterol with lipid levels. Sex-related differences include higher LDL-C, HDL-C, total cholesterol, particular sphingomyelins, and docosohexanoic acid-containing phospholipid levels in females. Surprisingly few associations between lipids and body mass index were observed. A journal manuscript is currently in preparation.

Funding: NHMRC, Australian Postgraduate Award PhD Scholarship to Matthew Wong.

EADB Consortium: A European DNA bank for deciphering the missing heritability of Alzheimer's disease

CHeBA staff: Perminder Sachdev, Karen Mather, Wei Wen, Anbupalam Thalamuthu, Henry Brodaty.

Other investigators: Dr Nicola Armstrong (Murdoch University) (CHeBA Hon. Research Fellow), EADB Consortium members.

Aim: Identify common and rare novel genetic variants for Alzheimer's disease by collecting a very large data set of individuals who are cognitively normal, have mild cognitive impairment or Alzheimer's disease and have genetic data available.

Findings: This large international consortium plans to undertake genetic studies examining Alzheimer's disease and related phenotypes. Planned genetic studies include a large genome-wide association study (GWAS) on mild cognitive impairment and the largest Alzheimer's disease GWAS to date.

Funding: NHMRC National Institute for Dementia Research (NNIDR) (administered by CHeBA), European Union Joint Programme for Neurodegenerative Disease (not administered by CHeBA).

Epigenetic and genetic factors and AD development

CHeBA staff: Karen Mather, Helen Wu (PhD student), Perminder Sachdev, Henry Brodaty, Anbupalam Thalamuthu.

Other key investigators: Dr Nicola Armstrong (Murdoch University) (CHeBA Hon. Research Fellow), Professor Bernhard Baune (University of Adelaide), Associate Professor John Kwok (NeuRA, UNSW), Professor Peter Schofield (NeuRA, UNSW).

Aim: Understand the relationships between DNA methylation, microRNAs (miRNAs), genome variation and gene expression in Alzheimer's disease (AD).

Findings: This work is currently underway using samples and data from CHeBA studies and the Australian Imaging Biomarker and Lifestyle Study (AIBL). Identical twins discordant for brain amyloid imaging have been selected for miRNA and gene expression studies, seeking to identify differentially expressed genes that may be linked to an early marker of AD, brain amyloid. Cognitively normal controls, individuals diagnosed with mild cognitive impairment and Alzheimer's disease have also been selected from AIBL for miRNA studies using small RNA sequencing. This work aims to find differentially expressed genes between these groups. All of these assays will be completed in 2018.

Funding: The Mason Foundation, Henroth Investments, NHMRC, Thomas Foundation.

Evaluating the effectiveness and cost-effectiveness of DCM to enable person centred care training: A cluster randomised trial

CHeBA staff: Lynn Chenoweth.

Other investigators: Professor Claire Surr (Leeds Beckett University, UK), Professor Clive Ballard (King's College London, UK), Professor Murna Downs (University of Bradford, UK), Dr Anne Corbett (King's College London,UK), Sue Fortescue (Alzheimer's Society Research Network), Kirsty Nash (Oxford Health NHS Foundation Trust), Professor Louise Robinson (University of Newcastle, UK), Professor Graham Stokes (Bupa Care Services, Leeds, UK), Professor Amanda Farrin (University of Leeds, UK), Alison Ferguson (University of Leeds, UK), Dr Jane Fossey (University of Oxford, UK), Lucy Garrod (Oxford Health NHS Foundation Trust), Ms Liz Graham (University of Leeds, UK), Dr Alys Griffiths (University of Bradford, UK), Madeline Harms (University of Leeds, UK), Ivana Holloway (University of Leeds, UK), Steph Jones (University of Bradford, UK), Amanda Lilley-Kelly (University of Leeds, UK), Dr Najma Siddiqi (University of Leeds, UK), Dr Daphne Wallace (University of Bradford, UK).

Aims:

- Evaluate the clinical and cost-effectiveness of Dementia Care Mapping (DCM) in supporting the implementation of person-centred care training (PCCT).
- Evaluate its effectiveness as a process for improving care quality and quality outcomes for people with dementia, compared with usual dementia care.

Findings: The EPIC trial was conducted with 725 people with a formal diagnosis of dementia, scoring 4+ on FAST and with capacity to give consent from 50 screened, randomly allocated UK aged care homes which met the inclusion criteria. The trial was completed in December 2017. Two staff from each intervention home were trained to use the Dementia Care Mapping (DCM™) method via the standard four-day training course provided by the University of Bradford. Control group homes had no exposure to recent DCM training. Trained DCM 'mappers' undertook three cycles of DCM™ intervention at 5-month intervals. They were supported by an expert mapper who was experienced in use of DCM™ in care homes, during their first implementation cycle. Primary outcomes included resident agitation and quality of life. Framework Data Analysis was used, assessing staff experiences of utilising and implementing DCM™, with a focus on identifying patterns and variations in implementation, barriers and facilitators to implementation, and the impacts of DCM™ implementation on residents. The mean resident age was 85.3 years (control), 86.0 years (intervention), with similar FAST scores in each arm (range 4-7). There were 272 (37.5%) deaths reported between randomisation and the end of 16-month follow-up, 111 (36%) in the control and 161 (39%) in the intervention group. A two-level heteroscedastic linear regression model was fitted to the multiply imputed datasets (assuming data were missing at random), adjusting for differential clustering at the site level between arms, and for minimisation factors (site level: type and size of care home, provision of dementia awareness training and hub) and for site-level average characteristics at baseline (dementia severity measured by CDR, age and CMAI score). The mean difference in agitation (CMAI) score at 16 months was -2.11 points (95% CI -4.66 to 0.44) lower in the intervention group than the control. The

adjusted intraclass correlation coefficient (ICC) was estimated to be 0.001 in the intervention and 0.000 in control. The treatment effect was not statistically significant (p=0.104). The mean quality of life (EQ-5D) scores declined over 16 months in all residents, with the decline greater in the control group than in intervention group. The total cost of the DCM intervention was estimated to be £421.07 per resident (£9,290.30 per care home). Control group costs were assumed to be zero, indicating that in relation to outcome effects, DCM is not cost-effective. The only significant predictors of net benefit were baseline EQ-5D (higher QoL leads to higher net benefit) and CDR (lower values lead to higher net benefit). Secondary data are still being analysed.

Funding: National Institute for Health Research, UK (administered by Leeds Beckett University; contract between CHeBA, UNSW and Leeds Beckett University, UK. for L. Chenoweth's contribution).

Genetic and environmental contributions of amyloid deposition using amyloid-PET imaging in the Older Australian Twins Study cohort

CHeBA staff: Perminder Sachdev, Rebecca Koncz (PhD student), Wei Wen, Anbupalam Thalamuthu, Teresa Lee, Vibeke Catts, Suzy Forrester, Tanya Duckworth, Kristan Kang, Karen Mather, Anne Poljak (conjoint).

Other investigators: Professor Christopher Rowe (Austin Hospital, Victoria), Associate Professor Victor Villemagne (University of Melbourne), Professor David Ames (National Ageing Research Institute), Ms Christel Lemmon (National Ageing and Research Institute), Dr Eva Wegner (Prince of Wales Hospital, NSW).

Aims:

- Determine the heritability of amyloid deposition in the brain using amyloid PET imaging in the Older Australian Twins Study (OATS) cohort, as a potential endophenotype of Alzheimer's disease.
- Determine the genetic and environmental risk (and protective) factors associated with amyloid deposition in older individuals.
- Investigate the relationship between amyloid burden and aspects of cognitive function.

Findings:

- OATS Wave 4 and 1P recruitment, assessment and scanning now complete (total n=207; PiB-PET n=60; NAV-PET: VIC - n=67, NSW n=80).
- Preliminary findings from July 2017 for n=194 (59 MZ and 38 DZ pairs) revealed moderate heritability for global amyloid burden (h2= 0.36), with a range of 0.18–0.52 across cortical regions of interest.
- These findings suggest that amyloid deposition is under strong environmental influences (to be investigated).
- Presented by Sachdev et al. in poster format at the 2017 Alzheimer's Association International Conference, London.

Funding: NHMRC.

Genetic and epigenetic markers of late-life depression

CHeBA staff: Ruby Tsang (PhD student), Perminder Sachdev, Karen Mather, Anbupalam Thalamuthu.

Other key investigators: Dr Simone Reppermund (UNSW Medicine) (CHeBA Hon. Research Fellow), Professor David Ames (National Ageing Research Institute, Royal Melbourne Hospital), Dr Nicola Armstrong (Murdoch University) (CHeBA Hon. Research Fellow), Associate Professor John Kwok (NeuRA, UNSW), Professor Peter Schofield (NeuRA, UNSW), Professor Naomi Wray (Queensland Brain Institute, University of Queensland), Associate Professor Margaret J. Wright (QIMR Berghofer Institute, Brisbane, Australia).

Aims:

- Estimate heritability for late-life depression and depressive symptoms.
- Calculate bivariate genetic correlations between measures for depression and related phenotypes, such as anxiety.
- Identify differentially methylated regions of the genome associated with depression in late-life

Findings: Heritability has been estimated using the Older Australian Twins Study cohort, with depression in late life under moderate to high genetic influence. There was also a significant bivariate genetic correlation observed between depression and anxiety. This work is currently being written up for publication. Suggestive differentially methylated regions were identified using the twin sample but require replication in independent cohorts.

Funding: NHMRC, Thomas Foundation, Viertel PhD Scholarship – Ruby Tsang (Alzheimer's Australia Dementia Research Foundation).

Genetic influence on human hippocampal atrophy

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

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

Aim: Examine whether and how genetics influence ageing-related hippocampal atrophy.

Findings: We performed size and shape analyses separately on both left and right hippocampi. The genetic patterning of hippocampal surface, calculated using the differences in shapes and sizes, demonstrated a remarkable variability in the different subfields of this important subcortical structure. The pattern of genetic correlations for the surface of the hippocampus largely corresponded to hippocampal atrophy in the ageing brain. The patterns of heritability and genetic correlations of the right and left hippocampi were similar, but not bilaterally symmetrical on the vertex level. A journal manuscript is currently in preparation.

Funding: NHMRC.

Genetic influence on white matter fibre tracts between brain regions – is genetic correlation and fibre tract connectivity associated?

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

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

Aims:

- Test the hypotheses that:
  - White matter fibre connection between two brain regions that are genetically similar will be stronger than those which are genetically less similar.
  - This pattern will be symmetric in both hemispheres.
- Investigate whether the connections between network hub regions are genetically stronger than those of non-hub regions, including feeders and non-feeders.

Findings: We established a mathematical model which summarises and analytically represents the geometry of the density, shape and flow of brain fibre tracts. Computations of the scans are to start in 2018.

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

Genetic influences on cerebral blood perfusion using arterial spin labelling (ASL) data

CHeBA staff: Jiyang Jiang, Forrest Koch, Wei Wen, Perminder Sachdev.

Aim: Examine the heritability of cerebral blood flow (CBF) using a community-based cohort of twins.

Findings: Arterial spin labelling (ASL) is a non-invasive MRI technique to investigate CBF. CBF has been linked to various pathologies including neurodegenerative diseases such as Alzheimer's disease (AD), cerebrovascular disease, mild traumatic brain injury, and psychiatric disorders such as depression. The genetic contribution to the variability of CBF using ASL has not been previously studied. We used ASL scans of 182 OATS (Older Australian Twins Study) participants for initial data analysis. The CBF in the whole brain and grey matter (GM) regions was moderately heritable with the heritability of the whole brain being 0.34 *($p = 0.0168$)*, and that of GM being 0.411 *($p = 0.0026$)*.

Funding: John Holden Family Foundation

Genetics and epigenetics of longevity

CHeBA staff: Perminder Sachdev, Karen Mather, Anbupalam Thalamuthu, Mary Revelas (PhD student), Jessica Lazarus (PhD student), Julian Trollor (conjoint).

Other key investigators: Dr Nicola Armstrong (Murdoch University) (CHeBA Hon. Research Fellow), Professor John Attia (University of Newcastle), Associate Professor John Kwok (NeuRA, UNSW), Dr Chris Oldmeadow (University of Newcastle), Professor Peter Schofield (NeuRA, UNSW); Professor David Ames (National Ageing Research Institute; Royal Melbourne Hospital), Associate Professor Margaret J. Wright (QIMR Berghofer Institute, Brisbane, Australia).

Aim: Identify genetic and epigenetic variation associated with longevity and longevity-related phenotypes, such as markers of healthy longevity (e.g. intact cognitive functioning).

Findings: Meta-analyses examining commonly studied genetic polymorphisms with exceptional longevity have been completed, including using data from the Sydney Centenarian Study. Several variants in genes such as *APOE* and *FOXO3A* were significantly associated with exceptional longevity. A manuscript has been completed and submitted for review. The epigenetic clock is proposed as a biomarker of ageing and is calculated based on the amount of DNA methylation at a number of sites across the genome. We explored the relationship between the epigenetic clock and exceptional longevity using data from three studies including the Sydney Centenarian Study and the Older Australian Twins Study. Exceptionally long-lived participants from SCS had a young epigenetic clock age compared with their chronological age. This work has been published (Armstrong, Mather et al., 2017, *Epigenomics*).

Funding: Sachdev Foundation, NHMRC, Thomas Foundation.

Genetics of growth differentiation factor 15 (GDF-15/MIC-1)

CHeBA staff: Jiyang Jiang, Anbupalam Thalamuthu, Karen Mather, Perminder Sachdev, Wei Wen, Julian Trollor (conjoint).

Other key investigators: Dr Nicola Armstrong (Murdoch University) (CHeBA Hon. Research Fellow), Associate Professor John Kwok (NeuRA, UNSW), Professor Peter Schofield (NeuRA, UNSW), Professor D Brown (St Vincents Hospital, UNSW), Professor SN Breit, (St Vincents Hospital, UNSW), Dr Jennifer E. Ho (Massachusetts General Hospital, Harvard Medical School, USA), Professor Andrew Morris (University of Liverpool, UK), Dr Weronica Ek (Uppsala University, Sweden).

Aim: Identify genetic variants associated with GDF-15 in mid to late life using community-based cohorts.

Findings: Genetic variants located in a locus on chromosome 19, containing the GDF-15 gene, were significantly associated with GDF-15 blood concentration in Sydney MAS and three other international cohorts. A manuscript describing this work is currently under review.

Funding: NHMRC, Thomas Foundation.

Genetics of white matter hyperintensities

CHeBA staff: Karen Mather, Wei Wen, Anbupalam Thalamuthu, Perminder Sachdev, Amelia Assareh.

Other key investigators: Dr Paul Nqyuist (NIH, USA), Dr Nicola Armstrong (Murdoch University) (CHeBA Hon. Research Fellow), Professor David Ames (National Ageing Research Institute, Royal Melbourne Hospital), Associate Professor John Kwok (NeuRA, UNSW), Professor Peter Schofield (NeuRA, UNSW), Associate Professor Margaret J. Wright (QIMR Berghofer Institute, Brisbane, Australia), and other external collaborators.

Aim: Identify genetic variants associated with deep and periventricular white matter hyperintensities (WMHs).

Findings: This project uses data from over 12,000 participants from around the world and has identified a number of genetic variants significantly associated with deep and periventricular WMHs. Replication of the results is currently being undertaken and the results will be written up for publication.

Funding: NHMRC, Thomas Foundation.

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

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

Other key investigators: Dr Nicola Armstrong (Murdoch University) (CHeBA Hon. Research Fellow), Professor David Ames (National Ageing Research Institute, Royal Melbourne Hospital), Associate Professor John Kwok (NeuRA, UNSW), Professor Peter Schofield (NeuRA, UNSW), Associate Professor

Margaret J. Wright (QIMR Berghofer Institute, Brisbane, Australia).

Aim: Identify single nucleotide polymorphisms (SNPs) for various brain measures, such as subcortical volume.

Findings: Include novel loci for hippocampal volume, this work was published in *Nature Communications* in 2017 (Hibar et al). The genetics of intracranial volume was also investigated in the ENIGMA consortium in collaboration with the CHARGE consortium, with five new loci identified (Adams et al., *Nature Neuroscience,* Dec, 2016). A number of other genetic and epigenetic projects are underway, including examining copy number variants and neuroimaging traits.

Funding: NHMRC, Thomas Foundation.

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)

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

Other key investigators: Dr Nicola Armstrong (Murdoch University) (CHeBA Hon. Research Fellow), Professor David Ames (National Ageing Research Institute, Royal Melbourne Hospital), Associate Professor John Kwok (NeuRA, UNSW), Professor Peter Schofield (NeuRA, UNSW), Associate Professor Margaret J. Wright (QIMR Berghofer Institute, Brisbane, Australia).

Aim: Identify single nucleotide polymorphisms (SNPs) associated with cognitive performance and other measures, such as brain imaging traits.

Findings: CHeBA studies (Sydney MAS, OATS) have contributed to a number of projects on a variety of phenotypes using not only genetic data but also epigenetic data (e.g. DNA methylation). A recent CHARGE project utilised a very large population sample of over 280,000 participants and investigated the genetics of general cognitive ability, with many hits observed. This work has been submitted for publication. Brain infarcts are a marker of cerebral small vessel disease and are associated with high risk of stroke and dementia. The CHARGE consortium has just completed a study using over 20,000 participants to examine the genetics of brain infarcts and found two novel loci that require confirmation in independent cohorts.

Funding: NHMRC, Thomas Foundation.

Heritability of Gene Expression

CHeBA staff: Karen Mather, Anbupalam Thalamuthu, Sri Chandana Kanchibhotla, Perminder Sachdev.

Other key investigators: Professor Bernhard Baune (University of Adelaide), Liliana Ciobanu (University of Adelaide).

Aim: To estimate the heritability of gene expression.

Findings: This work is ongoing with analyses using gene expression data from the Older Australian Twins Study. Preliminary results suggests that there are many heritable and well as non-heritable gene transcripts, suggesting that genetics as well as environmental factors are important in the regulation of gene expression.

Funding: NHMRC

ICC-Dementia (International Centenarian Consortium - Dementia): An international consortium to determine the prevalence, incidence and trajectories of decline for dementia in centenarians

CHeBA staff: Perminder Sachdev, Henry Brodaty, Yvonne Leung, John Crawford, Nicole Kochan.

Other investigators: Study leaders and their colleague from among 18 ICC-Dementia member cohorts.

Aims:

- Examine the incidence and prevalence of neurocognitive disorders and their determinants in people over the age of 95 years internationally.
- Compare the incidence and prevalence of dementia and precursor conditions such as mild cognitive impairment in different countries and ethnic groups.
- Identify and examine commonality and differences in risk and protective factors for dementia and cognitive decline.
- Identify and examine biological markers of cognitive disorders common to the different cohorts.

Findings: Preliminary findings indicated that in more than half of the centenarian studies, rates of cognitive and functional impairments increase with age. However, people with more years of education and who live in the community show better cognitive and functional performance, based on their scores in the mini-mental state examination and their independence in activities of daily living, such as traveling alone and dressing themselves. There are substantial variations in the prevalence of dementia between studies/ across countries, with further analysis currently being undertaken to understand this phenomenon.

Funding: Direct donations to The Dementia Momentum.

Identifying expression quantitative trait loci (eQTLS) in older adults

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

Other key investigators: Professor Bernhard Baune (University of Adelaide), Liliana Ciobanu (University of Adelaide), Dr Nicola Armstrong (Murdoch University) (CHeBA Hon. Research Fellow), Associate Professor John Kwok (NeuRA, UNSW), Professor Peter Schofield (NeuRA, UNSW).

Aim: Identify genetic variants associated with gene expression

Findings: Expression quantitative trait locus (eQTL) analysis has been completed in Sydney MAS and OATS, with many eQTLs identified. This work will be written up for publication.

Funding: NHMRC, Thomas Foundation.

Improved accessibility and long-term storage of biospecimens from the Centre for Healthy Brain Ageing's (CHeBA) longitudinal studies

CHeBA staff: Maboobeh Hosseini (Biobank Officer), Kristan Kang, Anne Poljak (conjoint), Karen Mather, Henry Brodaty, Perminder Sachdev.

Aims:

- Inventory and aliquot samples for ready distribution to researchers.
- Improve the safety of sample storage by aliquoting and transferring samples into -80°C and vapour phase storage.
- Setup of a biobanking subcommittee and preparation of a Biobank Ethics submission.

Findings: Aliquoting of MAS samples (all three waves which have plasma) has been completed. OATS samples aliquoting is currently in progress (W1 completed).

Funding: NHMRC and UNSW MREII 2015.

Improving clinical diagnosis of mild neurocognitive disorders using neuropsychological assessment

CHeBA staff: Nicole Kochan, Perminder Sachdev, Henry Brodaty, 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), Ms Claudia Woolf (University of Sydney).

Aims:

- 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.
- Facilitate interpretation of neuropsychological test performance in persons from CALD backgrounds by investigating the influence of cultural, linguistic and educational factors.
- 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.
- Evaluate the potential of a computerised tneuropsychological test battery as a more culture-fair measure of cognition compared to traditional neuropsychological measures in older adults from CALD backgrounds.

Findings:

- Normative data tables for a commonly used cognitive screening test – *The Addenbrooke's Cognitive Examination – Revised (ACE-R)* have been developed using data collected from the Sydney Centenarian Study. These normative scores are drawn from an extraordinary group of individuals,

aged 95-104 years of age who remain cognitively well (non-demented). We expect the ACE-R normative data will be useful in clinical practice to evaluate cognitive function in the oldest-old. The paper is being written up for publication.

- We have a number of projects examining the clinical utility of a simple computer-administered cognitive measure. Previously we have shown that *intra-individual reaction time variability* defined as an individual's variation in reaction times when completing a single cognitive task across several trials, is associated with the development of dementia in older adults and may be an important cognitive marker of neurobiological disturbance (American Journal of Geriatric Psychiatry 2016). In our most recent study, we observed that higher reaction time variability (greater inconsistency in speed) rather than overall slowing provides independent information about risk of death in older people even after accounting for signs of cognitive decline and dementia, and other mortality risk factors such as cardiovascular risk, older age and genetic markers of Alzheimer's disease (PLoS One 2017). Our findings suggest that simple computerised measures may be useful to identify individuals who are at highest risk for age-related neurodegenerative disorders. This project has been completed in 2017.

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

Longevity, ageing and transcriptomics

CHeBA staff: Karen Mather, Anbupalam Thalamuthu, Perminder Sachdev, Adith Mohan (PhD student).

Other key investigators: Dr Nicola Armstrong (Murdoch University) (CHeBA Hon. Research Fellow), Dr Michael Janitz (School of Biotechnology and Biomolecular Sciences, UNSW), Associate Professor John Kwok (NeuRA, UNSW), Professor Peter Schofield (NeuRA, UNSW).

Aims:

- Identify RNAs, including long non-coding RNAs associated with longevity.
- Identify transcriptomic changes in the ageing brain.

Findings: More than 2000 RNA transcripts were differentially expressed in exceptionally long-lived adults compared to controls, including genes previously associated with ageing. This work is currently being prepared for publication. For the ageing brain transcriptomics project, samples have been collected from national and international brain banks. RNA sequencing on these brain samples will be undertaken in 2018.

Funding: NHMRC, Thomas Foundation.

Metabolomic screening for discovery of low molecular weight blood-based biomarkers

CHeBA staff: Nady Braidy, Anne Poljak (conjoint), Perminder Sachdev.

Other investigators: Dr Julia Muenchhoff (CHeBA Hon. Research Fellow), Dr Sonia Bustamante (BMSF, UNSW), Dr Donald Thomas (NMR Facility, UNSW).

Aims:

- Develop gas chromatography (GC-MS) and nuclear magnetic resonance (NMR) methods for detection and quantitation of metabolites in blood samples.
- Identify blood metabolites that differ in healthy individuals and patients with MCI or AD.

Findings: We observed a significant age-dependent increase in the levels of D-serine, L-serine and glycine in the hippocampus of *O. degus* and APPsw/Tg2576 mice, along with a significant age-dependent decline in the levels of L-alanine, and L-threonine. In human plasma, concentrations of L-alanine, methylserine, glycine, D-serine and L-serine were significantly higher in plasma from participants with dementia. Using a series of NMR based plasma metabolite measures (48 compounds identified in 30 subjects), principle components analysis showed a clear separation of dementia from normal control subjects based on features in the NMR spectra. Separation of subjects with mild cognitive impairment vs normal controls was much less pronounced and did not reach statistical significance. We have a current manuscript in draft reporting the results of this work.

Funding: Thomas Foundation.

Maintain Your Brain

CHeBA staff: Henry Brodaty, Perminder Sachdev, Gavin Andrews, Megan Heffernan (Coordinator), Tiffany Chau, JC San Jose

Other investigators:

- Professor Kaarin Anstey (Australian National University), Professor Nicola Lautenschlager (Melbourne University), Professor Louisa Jorm (UNSW), Professor John McNeill (Monash

Univeristy), Professor Anthony Maeder (Western Sydney University), Professor Maria Fiatarone Singh (University of Sydney), Professor Michael Valenzuela (University of Sydney).

Aims:

- Determine the efficacy of a multi-modal targeted intervention delivered on the internet to reduce the rate of cognitive decline in non-demented community-dwelling persons aged 55-75 years and in the long-term to delay the onset of dementia.
- Examine the cost-effectiveness of the program with a view to making this a national and potentially a globally suitable program.

Findings: Validation of outcomes measures study partially complete and now being analysed. Pilot study underway. IT platform is being refined. Main study to commence soon.

Funding: NHMRC Dementia Team Research Grant.

MINDSED: The effects of sedentary behaviour on cognitive function and cognitive decline in older persons without dementia

CHeBA staff: Darren Lipnicki, Perminder Sachdev.

Other investigators:

- Workgroup from the Radboud Medical Center (The Netherlands): René Melis, Carlijn Maasakkers.
- Contributing COSMIC study leaders and associates: Representing cohorts from four countries.

Aim: Determine if sedentary behaviour is associated with poorer cognition, or predicts future poorer cognition, in older persons without dementia.

Findings: Participating studies currently planning and undertaking analyses.

Funding: Direct donations to The Dementia Momentum Fund.

Nursing competencies in care of the older person

CHeBA staff: Lynn Chenoweth.

Other investigators: Kristine Rice and Tracey Osmond (Anglican Retirement Villages), Mary McConochie (Anglicare), Carolyn Moir and Donna Lennon (BaptistCare), E. Roy and D. Donaghy (Uniting Care), Elaine Griffin and Fiona Kendall (Scalabrini Villages), Jolan Stokes and C. Carter (HammondCare), Dr Victoria Traynor (University of Wollongong).

Aim: Develop an evidence-based set of nurse competencies in care of the older person.

Findings: The initial Nursing Aged Care Competencies (NACC) group consisted of 80 senior registered nurses working in the partner organisations. The e-Delphi included volunteer nurses working across 10 countries (90% in Australia). Participation rate ranged from 409 in round 1 to 139 in round 5: registered nurses (57%), nurse managers (30%) and nurse academics (13%). Over half of the participants had postgraduate qualifications (56%). A final set of core competencies generated a 98% (SD ±2) level of agreement: 1. Living Well for Older People across Communities and Groups; 2. Maximising Health Outcomes; 3. Communicating Effectively; 4. Facilitating Transitions in Care; 5. Facilitating Choices; 6. Partnering with Family Carers; 7. Promoting Psychological Well-being and Mental Health; 8. Providing Evidence-Based Dementia Care; 9. Providing Optimal Pain Management; 10. Providing Palliative Care; 11. Enabling Access to Technology. Participants also agreed that the domains of practice within the GerNurs Competencies described two levels of practice for registered nurses working with older people and their families in nursing home and community care settings: essential and enhanced (60-88% levels of agreement). The next stage of the study is to undertake a final round of face-to face consultation with an expert panel made of representations to finalise the content of the GerNurs. These experts will be from relevant government, professional and peak body organisations and aged care nurse academics. This final stage of consultation will provide endorsement from influential organisations to increase the likelihood of uptake of the GerNurs Competencies in residential and community care settings. We are now planning a pilot implementation of the competencies across the NACC organisations. The last stage of the study will be making the GerNurs Competencies and supporting guidelines available on an accessible central website for use by individuals for their professional development and organisations to support implementation of their strategic plans.

Funding: Anglican Retirement Villages (now Anglicare), Uniting Care, BaptistCare, Scalabrini Villages, Hammond Care, University of Wollongong (none administered by CHeBA).

Olfactory ability and language test performance in Indonesian and Australian cohorts

CHeBA staff: Darren Lipnicki, Perminder Sachdev, Nicole Kochan, Henry Brodaty.

Other investigators: Workgroup from the Atma Jaya Catholic University, Indonesia: Yuda Turan, Yvonne Handajani, Tara Sani, Josephine Widayanti, Ika Suswanti.

Aim: Investigate associations between olfactory ability and language function and Mini-Mental State Examination (MMSE) scores in Indonesian and Australian cohorts.

Findings: Preliminary findings suggest that worse olfactory ability is associated with older age and lower language function and MMSE scores in Australians and Indonesians, but that there are different patterns of risk factors for olfactory impairment in the cohorts.

Funding: Direct donations to The Dementia Momentum Fund.

Oxidative stress in AD

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

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

Aims:

- Determine if protein oxidation and/or glycation changes in mild cognitive impairment (MCI) and Alzheimer's disease (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.

Findings: Oxidative stress to proteins can impair their function and shorten their half-life, and is a process often associated with disease. The ortho and meta isomers of tyrosine are specific products of oxidative stress and we have identified elevated levels of *o*- and *m*-tyrosine in plasma proteins of AD subjects relative to normal controls in a small cross-sectional study. Future work will also assess oxidative stress levels in MCI subjects and longitudinally in subjects progressing from normal control to MCI and AD.

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

Personality and Total Health (PATH) Through Life project

CHeBA staff: Perminder Sachdev, Wei Wen.

Other key investigators: Australian National University: Associate Professor Nicholas Cherbuin, Professor Kaarin Anstey, Dr Moyra Mortby, Dr Erin Walsh, Dr Marnie Shaw, Dr Sid Chopra; Dr Elizabeth Luders (UCLA).

Aims: The original aims were to investigate the causes of three classes of common mental health problems: (1) anxiety and depression (2) alcohol and other substance abuse (3) cognitive functioning and dementia. The project investigates a wide range of risk and protective factors from biological and psychosocial domains, as well as the impacts of cognitive impairment and common mental disorders. Data on health service use are also collected.

Findings:

- A thinner corpus callosum, important for inter-hemispheric connections, is related to symptoms of ADHD in older adults (Luders et al., *Psychiatry Research*).
- Higher plasma glucose levels (measured on up to three occasions) were associated with increased cortical thinning in individuals with type 2 diabetes (T2D) as well as those with impaired fasting glucose (IFG), with a similar trend for individuals with normal fasting glucose (NFG) levels. Across groups, a 1 mmol/l increase in plasma glucose (above 5 mmol/l in NFG and IFG and above 6.1 mmol/l in T2D) resulted in a 10-13% increase in annual cortical thinning. Increased cortical thinning was detected in the insular cortex, as well as the posterior cingulate, parahippocampus and medial orbitofrontal cortex. Our results provide support for the idea that raised plasma glucose levels, even in the normal range, are associated with accelerated age-related cortical atrophy (Shaw et al., *Brain Topography*).

- The impact of type 2 diabetes and body mass index on cerebral structure is modulated by brain reserve (Walsh et al., *Diabetes & Metabolism*).
- Body mass index is associated with cortical thinning with different patterns in mid- and late-life (Shaw et al., *International Journal of Obesity*).
- Validated Alzheimer's Disease Risk Index (ANU-ADRI) is associated with smaller volumes in the default mode network in the early 60s (Cherbuin et al., *Brain Imaging & Behavior*).
- More highly myelinated white matter tracts are associated with faster processing speed in healthy adults. (Chopra et al., *NeuroImage*).

Funding: NHMRC (administered by ANU).

Plasma proteomics biomarkers

CHeBA staff: Anne Poljak (conjoint), Tharusha Jayasena, Fei Song, Nicole Kochan, Julian Trollor (conjoint), Henry Brodaty, Perminder Sachdev, Gurjeet Kaur Virk (PhD student).

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

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.
- Investigate the plasma proteome in Dominantly Inherited Alzheimer's Disease (DIAN) samples, using iTRAQ and improved plasma fractionation methodology.

Findings: To date our iTRAQ proteomics studies have identified differential expression in a number of protein family groups, including complement components, apolipoproteins, inflammation related proteins, coagulation pathways and vitamin carrier proteins. Dysregulation of protein members from these same protein family groups (though not always identical proteins) has been observed across a number of independent cohorts (Sydney MAS, Hunter Community Study and a preliminary study of the DIAN cohort).

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.

Prediction of the Onset of Dementia in Older Individuals Using Machine Learning Techniques

CHeBA staff: Perminder Sachdev.

Other investigators: Annette Spooner (PhD student), Professor Arcot Sowmya (Computer Science & Engineering, UNSW), Professor Claude Sammut (Comupter Science & Engineering, UNSW).

Aim: Develop techniques, using artificial intelligence and machine learning, to identify patterns in the data from the Sydney Memory and Ageing Study and the Older Australian Twins Study that could identify a set of biomarkers to predict the onset of dementia in its early stages.

Findings: Traditional machine learning techniques operate only on numerical data from a single source, with small numbers of variables. Given the data that CHeBA has collected, new methods are needed that can explore large amounts of heterogeneous data from multiple sources, that is longitudinal in nature and contains missing values, in order to uncover new information about the onset of dementia, and in particular Alzheimer's disease. A systematic review of the literature on the latest machine learning techniques for analysing heterogeneous data, longitudinal data and incomplete data plus dimensionality reduction methods, combined with the latest theories on the causes of Alzheimer's disease, has been largely completed and some promising ideas identified. Ethics approval has been granted and initial exploration of the datasets has begun.

Funding: Kwan Fung & Yuet Ying Fung Scholarship.

Profile and risk factors of post-stroke cognitive impairment in diverse geographical and ethno-racial groups: An individual participant data meta-analysis from the STROKOG consortium (Formerly called: Profile of cognitive impairment at 3 to 6 months post-stroke or TIA in diverse geographical and ethno-cultural settings as represented by the STROKOG member cohorts)

CHeBA staff: Perminder Sachdev, Jessica Lo, John Crawford, Darren Lipnicki, Nicole Kochan.

Other investigators: STROKOG collaborators.

Aims:

- Harmonise shared data from STROKOG studies.
- Perform joint analyses using combined, harmonised data to estimate prevalence of post-stroke cognitive impairment.
- Compare prevalence estimates and profile of post-stroke cognitive impairment across geographical regions and ethnic groups.
- Perform individual participant data (IPD) meta-analysis on harmonised data to investigate the relationship between putative risk factors and cognitive function with greater statistical power.

Findings:

- From our combined sample of 10 hospital based studies from Africa, Asia, Australia, Europe and USA, overall 45% of post-stroke or TIA participants were impaired in global cognition, and 30-35% in different cognitive domains, at 2-6 months after stroke or TIA.
- The degree of impairment was similar in the five cognitive domains (attention & processing speed, memory, language, perceptual motor and frontal executive function).
- Overall Koreans had the highest rate of impairment and Singaporean Chinese the lowest, compared to whites in Australia/Europe/USA.
- Diabetes and a history of past-stroke had significant negative effects on cognitive function in all domains; these effects were independent of stroke, age and gender.

Funding: Vincent Fairfax Family Foundation, NHMRC.

Proteomics of natural and non-natural animal models for AD

CHeBA staff: Anne Poljak (conjoint), Nady Braidy, Tharusha Jayasena, Perminder Sachdev.

Other investigators: Professor Nibaldo Inestrosa (Pontificia Universidad Católica de Chile) (conjoint).

Aims:

- Determine if there are brain regional differences in the proteome profile comparing brain sections from APPSwe, 3xTG mice and *O. degus.*
- Determine if proteomic expression correlates with level of brain pathology (Braak stage).
- Identify age-related changes in the brain proteome profile.

Findings: We have demonstrated a significant age-dependent increase in the levels of D-serine, L-serine and glycine in the hippocampus of *O. degus* and APPsw/Tg2576 mice, parallel to an increase in the expression of SR and TUNEL expression. By contrast, we observed a significant age-dependent decline in the levels of L-alanine, and L-threonine. The expression of phosphorylated JNK increased with age, although no increase in total JNK was detected. Treatment with a custom mixed diet (pellets) containing 4% pomegranate for 15 months ameliorated the alterations to SR and JNK protein, and the levels of selected amino acids in APPsw/Tg2576 mice brain.

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

Social Orientation of Care in Aged Living (SOCIAL) Study (Formerly: Meaningful relationships for people with dementia in long term care)

CHeBA staff*:* Janet Mitchell (PhD student), Henry Brodaty, Lynn Chenoweth.

Other investigators*:* Professor Jeffrey Braithwaite (Australian Institute of Health Innovation and Centre for Healthcare Resilience and Implementation Science, Macquarie University), Dr Janet Long (Australian Institute of Health Innovation, Macquarie University).

Aim: Identify the occurrence of and factors associated with meaningful relationships among people expressing dementia-associated neuropsychiatric symptoms in long-term care.

Findings:

- Staff have little time to spend with residents other than for core items of residents' physical care, including making beds and keeping rooms tidy. On average across five long-term care homes, staff spend 31.6 paid hours per week per resident, with two care homes spending less than 24 paid hours per resident per week.
- Staff spend little time being social with residents. Out of 210 hours observing the interactions of purposively-selected residents over a 15 hour period per resident, residents were only involved in any type of interaction – positive or negative - for 18.5% of the time. Of this, 43% was with staff and 57% was spent with other residents, friends or family members. Of the total number of interactions, 59% were with staff; of which only 12% were positive social interactions.
- Physical design and layout of the care home, including bed capacity and current occupancy, are associated with residents' incidence of neuropsychiatric symptoms.
- The number of paid staff hours per week and the number of staff resignations are associated with residents' incidence of neuropsychiatric symptoms.

Funding: Thomas Foundation.

Superparamagnetic iron oxide nanoparticles (SPIONs) as contrast agents for MRI of neurodegenerative pathology

CHeBA staff: Perminder Sachdev, Wei Wen, Nady Braidy.

Other investigators: Professor Richard Tilley (ARC Centre for Excellence in Convergent Bio-Nano Science and Technology (CBNS), UNSW), Scientia Professor Justin Gooding (CBNS, UNSW), Dr Andre Bongers (Biological Resources Imaging Laboratory (BRIL)/ National Imaging Facility, UNSW).

Aims:

- Develop and test a series of novel SPIONs that can penetrate the blood-brain barrier (BBB) and provide a superparamagnetic signal for MRI with limited toxicity. If successful, these can be used as vehicles for specific ligands to penetrate the brain and bind to amyloid and other abnormal brain proteins, which can then be imaged with MRI. The SPIONs, developed by Professor Tilley in the School of Chemistry, UNSW Sydney, have already been subjected to characterisation studies to determine their size, morphology, structure, and chemistry.
- Demonstrate BBB permeability of the nanoparticles.
- Examine neuronal and glial cell toxicity of the nanoparticles.
- Investigate cellular internalisation and membrane transport of the nanoparticles.
- Examine the paramagnetic properties of the nanoparticles using MRI.

Findings: We have identified optimal SPIONs for pre-clinical and clinical MRI of the brain. In the future, we plan to develop suitable ligands that bind to SPIONs and can be used to image brain pathology such as amyloid deposition in the brain.

Funding: Sachdev Foundation.

The additive and interactive effects of cerebrovascular and Alzheimer-type pathology in the aetiology of neurocognitive disorders

CHeBA staff: Perminder Sachdev, Nady Braidy, Anne Poljak (conjoint), Yue Liu (MSc candidate).

Other investigators: Professor Daniel Chan (Department of Aged Care and Rehabilitation, Bankstown-Lidcombe Hospital).

Aims:

- Develop a greater understanding of vascular factors that contribute to the aetiology and heterogeneity of Alzheimer's and related dementias, by examining both the additive and interactive effects of cerebrovascular and Alzheimer-type pathologies in humans and animal models, using a cross-disciplinary and integrative approach.
- Establish animal models for both AD (transgenic) and cerebral vessel disease (hypoperfusion, small vessel disease, transgenic) to examine the interaction of the two pathologies, and the role of inflammation, oxidative stress, mitochondrial dysfunction, permeability of the blood-brain barrier, and stress response in the genesis of either pathology.
- Discover peripheral markers of vascular risk and/or cerebral vessel disease which alone, or in combination with markers of AD, can predict the onset of clinical symptoms and disease progression.

Findings:

- Cerebral small vessel diseases were significantly associated with AD pathology and may be associated with Aβ/tau pathology.
- White matter hyperintensities and microinfarcts are associated with increased risk of AD. It remains unclear whether they precede or follow AD pathology.

Funding: ARC.

The effects of intravenous NAD+ on Ageing and Metabolic Syndrome

CHeBA staff: Nady Braidy.

Other investigators: James Clement (Better Humans Inc.).

Aims:

- Investigate the safety and tolerability of intravenous NAD+ as well as its efficacy in elevating NAD+ levels in healthy elderly people between the ages of 70 and 80.
- Determine whether intravenous NAD+ will significantly increase cellular concentrations of NAD+, improve the NAD+/NADH ratio, favourably change metabolic biomarkers, and upregulate expression of anti-ageing genes in elderly individuals.

Findings: We developed a method for the quantification of NAD+ and 11 other related metabolites (hereafter the NAD+ metabolome) using liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) in human plasma, cells, and tissue. To illustrate this method, we quantified changes in the NAD+ metabolome in plasma samples collected from consenting healthy human subjects across a wide age range (20-80 years). Our data cumulatively suggests that age-related impairments may also be associated with alterations in the NAD+ metabolome. Measurement of plasma levels of the NAD+ metabolome can be used as a biological index for niacin nutrition. NAD+ infusions also altered the plasma lipid profile, oxidative stress and inflammatory markers in a favourable manner. No major adverse effects were reported in this study.

Funding: Better Humans Inc., ARC.

The expression and distribution of sirtuins in the brain and CNS and their role in AD

CHeBA staff: Tharusha Jayasena, Anne Poljak (conjoint), Nady Braidy, Perminder Sachdev.

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

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 cerebrospinal fluid (CSF) and variation with age and in AD and MCI.

Findings: A reliable and sensitive mass spectrometry based MRM method has been established in our laboratory for the quantification of all seven mammalian sirtuins and has detected all seven sirtuins in the human brain, with SIRT2 being the most abundant. Sirtuins were also detected in human CSF and plasma, and guinea pig and mouse tissues. We have previously identified differential expression of the sirtuins in several regions of the rat brain during ageing.

Funding: NHMRC, Rebecca L. Cooper Medical Research Foundation, UPRA PhD Scholarship.

The neural correlates of memory improvement following transcranial direct current stimulation combined with cognitive training (tDCS + CT) in patients with amnestic mild cognitive impairment

CHeBA staff: Adith Mohan, Henry Brodaty, Perminder Sachdev.

Other investigators: Professor Colleen Loo (Black Dog Institute), Dr Donel Martin (Black Dog Institute), Associate Professor Marcus Meinzer (University of Queensland), Professor Caroline Rae (NeuRA).

Aim: Investigate the neural correlates for improved memory in people diagnosed with amnestic mild cognitive impairment (aMCI) receiving cognitive

training (CT) combined with mild non-invasive brain stimulation (transcranial direct current stimulation (tDCS)) using functional magnetic resonance imaging (fMRI). Participants are a subset of a larger cohort drawn from a randomised control trial investigating tDCS combined with CT in aMCI.

Findings: On receipt of funding from the AADRF, we undertook to recruit a further 20 participants for the neuroimaging arm of the larger RCT (Transcranial direct current stimulation (tDCS) combined with cognitive training to enhance memory in patients with amnestic mild cognitive impairment (aMCI)). This increased the total sample size, in addition to adding a functional neuroimaging component. We currently have complete pre- and post-treatment MRI data for 15 out of an expected total of 20 participants and the analysis of this data is planned for mid-2018.

Funding: Alzheimer's Australia Dementia Research Foundation.

The transcriptomic profile of normal ageing in the human brain: An RNA sequencing (RNAseq) study using non-pathological, human post mortem brain tissue from two brain regions

CHeBA staff: Adith Mohan, Perminder Sachdev, Karen Mather, Anbupalam Thalamuthu.

Other investigators: Professor Cynthia Shannon Weickert (NeuRA), Dr Madhav Thambisetty (National Institute on Aging, USA).

Aims:

- Undertake a discovery driven RNA sequencing (RNAseq) study to examine age-associated changes in the gene expression profiles of two distinct human brain regions, the dorsolateral prefrontal cortex (DLPFC), and the posterior cingulate cortex (PCC).
- Identify changes in cortical gene expression that may drive changes in neocortical plasticity, as well the excitation-inhibition imbalance known to occur in the ageing human brain.

Findings: Post mortem tissue cohort assembled, RNA sequencing to commence in February 2018.

Funding: NHMRC.

The Older Australian Twins Study (OATS)

CHeBA staff:

Investigators: Perminder Sachdev, Henry Brodaty, Julian Trollor (conjoint), Wei Wen, Teresa Lee, Karen Mather, John Crawford, Anbupalam Thalamuthu

Study Coordinator: Vibeke S. Catts

NSW Research Assistant: Tanya Duckworth (until 30 August 2017)

NSW Administrative Assistant: Suzy Forrester

Data Manager: Kristan Kang

Other Researchers: Anne Poljak (conjoint), Jiyang Jiang, Jessica Lazarus (PhD student), Ruby Tsang (PhD student), Helen Wu (PhD student), Annette Spooner (PhD student), Rebecca Koncz (PhD student), Liliana Ciobanu (PhD student).

Other investigators and staff:

Investigators: Professor David Ames (National Ageing Research Institute), Professor Nick Martin (QIMR Berghofer Medical Research Institute, Qld), Dr Margaret J. Wright (QIMR Berghofer Medical Research Institute/ University of Queensland), Professor Bernhard Baune (University of Adelaide), Professor Peter Schofield (NeuRA, UNSW), Professor Katherine Samaras (Garvan Institute, NSW), Professor Christopher Rowe (Austin Hospital, Victoria), Dr Eva Wegner (Prince of Wales Hospital, NSW); *Research Assistants:* Christel Lemmon (National Ageing Research Institute – until 30 August 2017)

Other Researchers: Dr Michelle Lupton (QIMR Berghofer Medical Research Institute)

Aims:

- Maintain a well-characterised cohort of identical (MZ) and non-identical (DZ) twin pairs for longitudinal study.
- Follow-up the OATS cohort for the relative genetic and environmental contributions to mild cognitive impairment and dementia.
- Characterise endophenotypes of dementia, including amyloid plaque build-up.
- Explore the genetic basis of cognitive decline and brain changes in old age, as part of international consortia.
- Determine the heritability of amyloid deposition in the brain as an endophenotype of Alzheimer's disease (AD).

- Determine the shared genetic and environmental variance between amyloid build-up and i) cognition, ii) cardiovascular disease, and iii) cerebral atrophy.
- Investigate the genetic and environmental risk (and protective) factors associated with amyloid build-up in older individuals.
- Investigate the relationship between amyloid build-up and memory function.

Findings:

- We completed data acquisition for the amyloid imaging project which investigates the deposition of amyloid plaques in the brain using positron emission tomography (PET) scans. We performed scans on a total of 207 individuals, the majority of whom also provided a blood sample for genetics analysis and had a structural MRI scan of their brain. Preliminary analysis of data from 194 participants was presented at the Alzheimer's Association International Conference in London in 2017.
- The OATS online project aims to give OATS access to more participants, particularly those in non-metropolitan areas. The online questionnaires have been conducted for most of our amyloid imaging project participants and we are modifying delivery to make it the best possible experience for our research volunteers. We have agreement to use computerised cognitive tests from Cogstate and Cambridge Brain Sciences, which will be incorporated into the online delivery of our assessments. We anticipate starting recruitment for the next wave of OATS in early 2018.
- Incidental findings on structural cerebral magnetic resonance imaging (MRI) are common in healthy subjects, and the prevalence increases with age. We examined brain MRI data from 320 twins participating in the OATS study and observed a total of 47 (11.75%) incidental abnormalities (excluding infarcts and white matter hyperintensities). Concordance rates of incidental abnormalities was low, with no dizygotic and only four monozygotic twin pairs having concordant lesions. Periventricular white matter hyperintensities were moderately heritable and deep white matter hyperintensities highly heritable.
- Six PhD projects used OATS samples/data. PhD student Liliana Chiobanu investigated the molecular factors involved in the pathophysiology of depression. Previous transcriptomic studies investigating the mechanisms of depression have applied genome-wide and targeted approaches to identify individual genes under a cross-sectional framework, but these studies did not look at these genes at the systems-level. Ms Chiobanu applied an unsupervised gene-network based approach to a prospective experimental design using microarray genome-wide gene expression from peripheral whole blood of elderly individuals. She utilised the Sydney Memory and Aging Study (MAS) and the Older Australian Twin Study (OATS) as discovery and replication cohorts, respectively.
- DNA methylation is an epigenetic modification of the genome, which changes with exposure to various environmental factors. Recently, age-related methylation of particular genetic regions has been identified. Data obtained from DNA in blood and other body tissues have been used to develop epigenetic clocks, which predict an individual's chronological and biological age based on their DNA methylation profile. Blood samples from OATS participants were used in a study evaluating two epigenetic clocks and their precision in older individuals, including those with exceptional longevity.
- Heritability of changes in global and subcortical brain volumes was estimated in five longitudinal twin cohorts from across the world (including OATS) and at different stages of the lifespan. Heritability of brain volume changes was generally higher in adults than in children. Modelling suggests that the gene variants influencing regional brain volume changes are not the same gene variants that explain brain volumes at baseline. It is thought that the former are more specific for brain plasticity and possibly important for disease characterised by altered developmental trajectories.
- DNA samples from OATS participants were used as controls in a whole exome sequencing and DNA methylation analysis of a clinical amyotrophic lateral sclerosis (ALS) cohort. While the study confirmed a number of ALS-associated genetic variants, it was unable to identify specific DNA methylation signatures associated with the known rare single-nucleotide variants.
- Genetic data and MRI scans of brain structures from OATS participants contributed to a large study (total sample 33,536 individuals) of genetic contributions to hippocampal volume. Six independent genetic loci were associated with hippocampal volume. Three novel loci lie within genes and the fourth novel loci 200 kb upstream of the sonic hedgehog gene. Genetic variants found to be associated with decreased hippocampal volume are also associated with increased risk for Alzheimer's disease.

- Epigenetic changes to DNA have often been associated with biological factors, such as smoking, diet and disease status. Samples from OATS participant contributed to a study determining the effect of educational attainment on the the epigenome of 10,767 individuals. While nine CpG probes were significantly associated with educational attainment, these probes were also associated with smoking. Further, the effect sizes were small and the study concluded that educational attainment is unlikely to have a large effect on the epigenome.
- A total of 44 OATS participants have consented to donate their brain upon death to the OATS brain donor program.

Funding: NHMRC.

The organisation of the elderly connectome

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

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

Aims:

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

Findings: Multivariate analyses elucidated the dependence of latent patterns of resting state functional connectivity on demographic and cognitive measures in cognitively-normal elders. Three modes of co-variation capturing interdependences between phenotypic measures and functional brain networks were identified. The first significant mode captured the opposing influence of age and core cognitive processes, such as attention and processing speed, on functional connectivity patterns. The bilateral functional subnetwork expressed by this mode linked lower-order sensorimotor and visual regions through key areas such as the parietal operculum and posterior insula. The second mode linked a strong and independent association between educational attainment and connectivity patterns, whilst the third captured weak brain-behaviour relations. The opposing pull of age on attention and processing speed within the first mode suggested the parietal operculum and posterior insula were crucial to age-related changes in sensorimotor functioning. The connectivity of this network was influenced predominantly by intrinsic factors such as age. The influence of extrinsic factors such as education split into a second, independent mode which conferred reserve benefits by acting upon network interactions tied to key hub-regions. The findings were published in *Human brain mapping 38*(10), 5094-5114.

Brain structural connectivity was examined using diffusion weighted scans. Whole-brain probabilistic tractography was performed using high-angular diffusion-weighted images acquired from over 100 healthy elderly subjects. The topology of hub-regions was consistent with a young adult population, and previously published adult connectomic data. More importantly, the architectural features of hub connections reflect their ongoing vital role in network communication. Substantial sexual dimorphisms were found, with females exhibiting stronger inter-hemispheric connections between cingulate and prefrontal cortices. Lastly, intriguing left-lateralised subnetworks consistent with the neural circuitry specialised for language and executive functions were identified, whilst rightward subnetworks were dominant in visual and visuospatial streams. These findings provide insights into healthy brain ageing and provide a benchmark for the study of neurodegenerative disorders such as Alzheimer's disease (AD) and frontotemporal dementia (FTD). The findings were reported in *NeuroImage 114*, 414-426.

Funding: NHMRC.

The prevalence of subjective cognitive decline in and across different geographical and ethno-cultural regions

CHeBA staff: Darren Lipnicki, Perminder Sachdev, Nicole Kochan, Henry Brodaty.

Other investigators:

- Workgroup from the University of Leipzig, Germany: Susanne Roehr, Alexander Pabst, Steffi Riedel-Heller.
- Contributing COSMIC study leaders and associates: Representing cohorts from around ten countries.

Aim: Establish the prevalence of subjective cognitive decline in and across different geographical and ethno-cultural regions.

Findings: Data collection currently underway.

Funding: Direct donations to The Dementia Momentum Fund.

The role of polyphenolic compounds in modulating AD pathology

CHeBA staff: Tharusha Jayasena, Anne Poljak (conjoint), Nady Braidy, Perminder Sachdev.

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

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.

Findings: As a component of her PhD research, Dr Jayasena explored the ability of three common polyphenols to prevent the neurotoxicity caused by amyloid and Fenton chemistry on astrocytes using a brain cell model for oxidative stress and amyloid toxicity. She also investigated the effects of polyphenol treatment on amyloid aggregation using electron microscopy and the metal chelating properties of these compounds using mass spectrometry. The polyphenols, EGCG, resveratrol and curcumin, displayed neuroprotective properties against amyloid toxicity in cultured astrocytes by preventing the loss of cell viability caused by amyloid in the presence of transition metals iron and copper and preventing the effects of oxidative stress via Fenton chemistry. Electron microscopy of the amyloid:polyphenol complexes showed that they have the ability to bind directly to amyloid forming non-structured, non-toxic aggregates. Dr Jayasena will finalise this work for publication as a component of her post-doctoral work.

Funding: NHMRC, Rebecca L. Cooper Medical Research Foundation, UPRA PhD Scholarship.

The Sydney Centenarian Study (SCS)

CHeBA staff: Perminder Sachdev, Henry Brodaty, John Crawford, Nicole Kochan, Karen Mather, Adam Theobald, Kristan Kang, Fleur Harrison, Yvonne Leung.

Aims:

- Determine the prevalence of major medical and neuropsychiatric disorders in individuals aged ≥95 years.
- 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'.

Findings:

- We quantified levels of seven different apolipoproteins in 1067 individuals aged 56-105 years. Centenarians had the highest APOE levels and the lowest frequency of the APOE4 allele. The findings suggest that levels of some apolipoproteins, especially APOE, are associated with lifespan and cognitive function in the oldest old (Muenchhoff et al., *Neurobiology of Aging*).
- We examined the relationship between two epigenetic clocks, ageing and exceptional longevity. In the SCS cohort, the Hannum DNAmage underestimated the age of the long-lived participants by up to 11 years. This finding supports the view that centenarians are 'biologically younger' than their chronological age (Armstrong et al., *Future Medicine*).

Funding: NHMRC.

The Sydney Memory and Ageing Study (Sydney MAS)

CHeBA staff: Henry Brodaty, Perminder Sachdev, Julian Trollor (conjoint), Brian Draper (conjoint), Nicole Kochan, Kristan Kang, John Crawford, Karen Mather, Wei Wen, Adam Bentvelzen, Paul Strutt, Kate Maston (Study Coordinator).

Aims:

- Examine the clinical characteristics and prevalence of Mild Cognitive Impairment (MCI) and related syndromes, including Alzheimer's disease, vascular dementia and frontotemporal dementia.
- Determine the rate of change in cognitive function over time.
- Investigate risk factors for and protective factors against cognitive decline and dementia.

- Develop and refine measures for early diagnosis, prognosis and biomarkers.

Findings:

- Mild cognitive impairment (MCI) is considered an intermediate stage between normal aging and dementia. However, our research suggests that objective assessment of cognitive impairment alone is the best predictor of progression to dementia in a community sample. Clinical assessment procedures need to be refined to improve the identification of pre-dementia individuals (Brodaty et al., *The American Journal of Geriatric Psychiatry*).
- Reversion to normal cognition from MCI is common. Up to 46.5% of individuals classified with MCI at baseline reverted to normal cognition at some point during follow-up (Aerts et al., *Neurology*).
- Intraindividual variability of reaction time (IIVT) increases in old age, and has been associated with dementia and mortality. Based on performance on two computerised reaction time tasks, greater IIVRT but not mean reaction time predicted survival time after accounting for age, sex, global cognition score, cardiovascular risk index and apolipoprotein ε4 status. Our findings suggest that greater IIVRT uniquely predicts shorter time to death and that lower global cognition and prodromal dementia in older individuals do not explain this relationship (Kochan et al., *PLOS ONE).*
- Functional connectivity studies examine the neural interactions, or connections, between different regions of the brain. Our research has identified that age and educational attainment confer independent influences on brain patterns supporting cognitive processes. It implies that age-related changes may be resistant to positive lifestyle factors that modify the risk of cognitive impairment such as educational attainment (Perry et al., *Human Brain Mapping*).

Funding: NHMRC.

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 (Black Dog Institute), Dr Donel Martin (Black Dog Institute).

Aim: 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)).

Findings: Our preliminary analyses suggested that combining computerised brain training with mild brain stimulation (tDCS) may produce greater memory improvement than computerised brain training alone. Importantly, these memory improvements were found to be maintained at a 3 month follow-up in both groups.

We plan to conduct the final analyses for the RCT by June 2018 when the last participants have completed their final 3 month follow-up assessments (total expected N = 58). Results at this stage are therefore preliminary.

Funding: Thomas Foundation, DCRC-ABC.

Towards understanding the role of gene expression in ageing-related phenotypes

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

Other key investigators: Professor Bernhard Baune (University of Adelaide), Liliana Ciobanu (University of Adelaide), Dr Nicola Armstrong (Murdoch University) (CHeBA Hon. Research Fellow), Associate Professor John Kwok (NeuRA, UNSW), Professor Peter Schofield (NeuRA, UNSW).

Aim: Identify differentially expressed genes associated with ageing-related phenotypes.

Findings: This work is ongoing with analyses using data from both the Sydney Memory and Ageing Study and the Older Australian Twins Study, examining a variety of phenotypes. Preliminary results suggests there are several differentially expressed genes for blood *MIC-1* (macrophage inhibitory cytokine-1) levels, a marker of inflammation, including the *MMD* gene, which is implicated in macrophage biology. Differentially expressed genes have also been identified for neuroimaging traits, including white matter hyperintensities. Replication cohorts are currently being sought for this work, including cohorts from the CHARGE Consortium.

Funding: Yulgilbar Foundation Alzheimer's Research Program Grant, NHMRC, Thomas Foundation.

Upregulation of NAD+ Anabolism to Promote Lifespan

CHeBA staff: Nady Braidy.

Other investigators: Dr Kristine McGrath (UTS), Dr Mojtaba Golzan (UTS).

Aims:

- Determine the effect of SIRT2 transgene on lifespan and underlying age-related degeneration in chow and high fat diet fed aged Wistar rats.
- Examine whether SIRT2 over-expression alters NAD+ levels and improves cognition in chow and high fat diet fed aged Wistar rats.
- Measure the changes in intracellular NAD+ levels and SIRT2 expression in physiologically aged Wistar rats treated with the natural polyphenols: resveratrol (increases NAD+ synthesis) and apigenin (an inhibitor of the NAD+ degrading enzyme CD38).
- Assess whether treatment with the apigenin and resveratrol, can extend lifespan, delay age-related degeneration, and delay/postpone cognitive decline in aged Wistar rats.

Findings: We have developed the first reliable and sensitive LC-MS assay to quantify the levels of the cellular NAD+ metabolome, including NM, methyl-NM, NMN, NA, NR, NAD+, and NADH. This robust assay also allows for the concurrent quantitative determination of adenosine related nucleotides, including adenosine, ATP, ADP, cAMP, and products of PARP-mediated poly(ADP)ribosylation, including ADP-ribose (ADPR), and cADPR. This methodology has been published in *Metabolomics*.

Funding: Better Humans Inc., ARC.

Using the discordant identical twin model to discover epigenetic and environmental factors contributing to ageing-related phenotypes

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

Other key investigators: Dr Nicola Armstrong (Murdoch University) (CHeBA Hon. Research Fellow), Professor David Ames (National Ageing Research Institute, Royal Melbourne Hospital), Associate Professor John Kwok (NeuRA, UNSW), Professor Peter Schofield (NeuRA, UNSW), Associate Professor Margaret J. Wright (QIMR Berghofer Institute, Brisbane, Australia), Professor Naomi Wray (Queensland Brain Institute, University of Queensland), EuroDiscoTWIN Consortium.

Aim: Identify differentially methylated regions of the genome and/or environmental factors associated with various traits, such as arthritis and hypertension.

Findings: Epigenetic clock discordance in identical twins was not associated with lifestyle, health and disease factors in the Older Australian Twins Study. However, this work requires replication in larger samples. The results of this study were presented at the Gene Mappers conference in Geelong in 2017.

Funding: NHMRC, Thomas Foundation, methylation work was supported by NHMRC Grants 613608 and 61302 (held by Professor Naomi Wray, administered by Queensland Brain Institute, University of Queensland).

Validating the VASCOG criteria for Vascular Cognitive Disorders: A comparison with four other sets of criteria for Vascular Dementia

CHeBA staff: Perminder Sachdev, Darren Lipnicki, John Crawford, Henry Brodaty.

Aim: Validate VASCOG criteria by comparing them with other criteria in diagnosing dementia and mild vascular cognitive disorder in a post-stroke cohort, and their ability to predict mortality within 10 years.

Findings: VASCOG criteria compare well with DSM-5 criteria but have lower agreement with other criteria for vascular dementia, largely due to the change in the definition of dementia. VASCOG criteria have an improved predictive validity over the previously used criteria.

Funding: Direct donations to The Dementia Momentum Fund.

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

CHeBA staff: Anne Poljak (conjoint), Nicole Kochan, Fei Song, Wei Wen, John Crawford, Julian Trollor (conjoint), Henry Brodaty, Perminder Sachdev.

Other investigators: 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).

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.
- Assay plasma levels using ELISA quantification. Afamin (vitamin E binding) and VDBP are of specific interest, based on our preliminary discovery proteomics data.

Findings: Dr Fei Song has evaluated an ELISA assay for VDBP, which will facilitate her work on MCI and AD plasma and will progress throughout 2018.

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.

COMPLETED PROJECTS

Abeta (Aβ) peptides in plasma

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

Other investigators: Ms PC Ng (formerly Brain & Ageing Research Program), Associate Professor George Smythe (SOMS, UNSW).

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.

Findings: Plasma Aβ levels and the Aβ1−42/1-40 ratio are related to cognition and hippocampal volumes, with differential associations of Aβ1-40 and Aβ1-42 in ε4 carriers and non-carriers. Our data support the Aβ sink model of AD pathology, and suggest that plasma Aβ measures may serve as biomarkers of AD. The findings were partly the subject of an editorial (Poljak et al., *Expert Review of Neurotherapeutics 17*(1), 3-5).

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

Age-related cognitive decline and associations with sex, education and apolipoprotein E genotype across ethnocultural groups and geographic regions: a collaborative cohort study (Formerly: Age-related cognitive decline and risk associations across ethno-cultural and geographic regions: A collaborative cohort study (COSMIC))

CHeBA staff: Darren Lipnicki, John Crawford, Rajib Dutta, Anbupalam Thalamuthu, Nicole Kochan, Gavin Andrews (conjoint), Henry Brodaty, Perminder Sachdev.

Other investigators: Contributing COSMIC study leaders and associates: M. Fernanda Lima-Cost, Erico Castro-Costa, Carol Brayne, Fiona Matthews, Blossom Stephan, Richard. Lipton, Mindy Katz, Karen Ritchie, Jacqueline Scali, Marie-Laure Ancelin, Nikolaos Scarmeas, Mary Yannakoulia, Efthimios Dardiotis, Linda Lam, Candy Wong, Ada Fung, Antonio Guaita, Roberta Vaccaro, Annalisa Davin, Ki Woong Kim, Ji Won Han, Tae Hui Kim, Kaarin Anstey, Nicolas Cherbuin, Peter Butterworth, Marcia Scazufca, Shuzo Kumagai, Sanmei Chen, Kenji Narazaki, Tze Pin Ng, Qi Gao, Simone Reppermund, Antonio Lobo, Raul Lopez-Anton, Javier Santabarbara.

Aims:

- Compare the rates of age-related decline on various types of cognitive tests across 14 international cohorts, representing 12 countries from North and South America, Europe, Asia, and Australia.
- Investigate the extent to which sex, educational attainment, and apolipoprotein E ε4 (APOE4) allele carrier status were associated with cognitive decline.

Findings: Performance on five different cognitive measures declined with age, with the most rapid rate of change for processing speed. Rates of decline accelerated slightly with age, with executive functioning showing the largest additional rate of decline. There was a considerable degree of heterogeneity in the associations across international cohorts, including a slightly faster decline on the Mini-Mental State Examination (MMSE) for Asians than for whites. Males declined on the MMSE at a slightly slower rate than females, and every additional year of education was associated with a rate of decline slightly slower for the MMSE, but slightly faster for language. Carriers of an APOE4 allele declined slightly more rapidly than non-carriers on most cognitive measures, with processing speed showing the greatest difference. Findings were published in *PLOS Medicine 14(3)*, e1002261.

Funding: Direct donations to The Dementia Momentum Fund.

Are visual-only memory impairments sufficient to diagnose amnestic MCI?

CHeBA staff: Darren Lipnicki, John Crawford, Perminder Sachdev, Nicole Kochan, Henry Brodaty.

Other investigators:

- Workgroup members from the University of Alicante (Spain): Javier Oltra-Cucarella, Rosario Ferrer-Cascales, Miriam Sánchez-San Segundo.
- Contributing COSMIC study leaders and associates: Richard Lipton, Mindy Katz, Nikolaos Scarmeas, Mary Kosmidis, Efthimios Dardiotis, Antonio Guaita, Roberta Vaccaro, Ki Woong Kim, Ji Won Han.

Aim: Compare the risk of conversion to Alzheimer's disease (AD) between three types of amnestic mild cognitive impairment (aMCI): visual, verbal and combined (both visual and verbal).

Findings: Verbal aMCI is more prevalent than visual aMCI, which is more prevalent than combined aMCI. All three types of aMCI have an increased and statistically similar risk of conversion to AD.

Funding: Direct donations to The Dementia Momentum Fund.

Inflammatory markers and brain structure

CHeBA staff: Jiyang Jiang, Wei Wen, Julian Trollor (conjoint), Perminder Sachdev.

Other investigators: Professor Bernhard Baune (University of Adelaide), Associate Professor David Brown (St Vincent's Centre for Applied Medical Research), Dr Haobo Zhang (CHeBA Hon. Research Fellow).

Aims:

- Explore the relationships of brain structural indices with the circulating levels of a spectrum of inflammatory markers available in the Sydney Memory and Ageing Study (MAS), including interleukin (IL)-1β, IL-6, IL-8, IL-10, IL12p70, serum vascular cell adhesion molecule-1 (sVCAM-1), plasminogen activator inhibitor-1 (PAI-1), serum amyloid A (SAA), tumour necrosis factor α (TNFα), C-reactive protein (CRP), and macrophage inhibitory cytokine-1 (MIC-1/GDF15). The aim is to find a robust circulating biomarker of brain structural measures in non-demented older individuals.
- Examine the relationship of MIC-1/GDF15 serum levels with human brain structural measures using multimodal MRI data, in a community-dwelling sample aged 70-90 years over two years.
- Conduct a genome-wide meta-analysis to identify genetic variants of MIC-1/GDF15 serum levels in population-based cohorts, and to test whether these variants influence brain structures and cognitive performance in MAS.

Findings:

Genetic variants located in a locus on chromosome 19, containing the *GDF-15* gene, were significantly associated with GDF-15 blood concentration in Sydney MAS and three other international cohorts. A manuscript describing this work is currently under review.

- Among the eleven circulating inflammatory biomarkers, the serum level of MIC-1/GDF15 shows high correlation over time, making it a robust biomarker.
- Previous studies from our group have shown the significantly negative associations between serum levels of MIC-1/GDF15 and cognitive performance both cross-sectionally and longitudinally.
- Following previous findings, the effect of this inflammatory marker on brain structures was investigated. MIC-1/GDF15 serum levels were inversely associated with cerebral integrity, including grey matter (GM) volumes and white matter (WM) microstructural integrity in both cross-sectional and longitudinal studies.
- In collaboration with CHeBA's Genetics & Genomics Group, genetic variants affecting MIC-1/GDF15 blood concentration were identified in the largest meta-analysis of genome-wide association studies (GWAS) examining this trait. The findings identified a significant locus on chromosome 19 and a putative locus on chromosome 1. A manuscript describing this work is currently under review.
- Three journal papers were published on this theme and one is currently under review.

Funding: NHMRC, John Holden Family Foundation.

The differential impacts of completed and incomplete pregnancies on the risk of Alzheimer's disease in women

CHeBA staff: Perminder Sachdev, Darren Lipnicki.

Other investigators: Workgroup members and members of contributing COSMIC studies: Hyesue Jang, Jong Bin Bae, Efthimios Dardiotis, Nikolaos Scarmeas, Ji Won Han, Tae Hui Kim, Kyung Phil Kwak, Bong Jo Kim, Shin Gyeom Kim, Jeong Lan Kim, Seok Woo Moon, Joon Hyuk Park, Seung-Ho Ryu, Jong Chul Youn, Dong Young Lee, Dong Woo Lee, Seok Bum Lee, Jung Jae Lee, Jin Hyeong Jhoo, Mary Yannakoulia, Mary Kosmidis, Giorgos Hadjigeorgiou, Paraskevi Sakka, Ki Woong Kim.

Aim: Determine if completed pregnancy with childbirth (CPREG) and incomplete pregnancy without childbirth (IPREG) have different effects on women's late life risk of Alzheimer's disease (AD).

Findings: CPREGs increase while IPREGs decrease the risk of AD in later life. In non-demented women, those with five or more CPREGs had worse Mini-Mental State Examination (MMSE) scores than those with between 0 and 4 CPREGs, while those who never experienced an IPREG had worse MMSE scores than those who experienced IPREG once or more.

Funding: Direct donations to The Dementia Momentum Fund.

MicroRNAs as biomarkers for Alzheimer's disease (AD): Comparison between Australian & Chinese populations

CHeBA staff: Helen Wu (PhD student), Karen Mather, Henry Brodaty, Perminder Sachdev.

Other investigators: Professor Shifu Xiao (Shanghai Mental Health Centre, School of Medicine), Dr Tao Wang (Shanghai Mental Health Centre, School of Medicine).

Aim: Examine the differences in microRNA (miRNA) expression among Chinese and Australian persons with mild cognitive impairment (MCI) and Alzheimer's disease (AD) compared to cognitively normal controls.

Findings: Cross-sectional miRNA expression was investigated using blood RNA collected from 48 Australian Caucasian participants with established clinical diagnoses (16 AD, 16 mild cognitive impairment, and 16 normal cognition). MiRNA data were normalised and expression compared across the diagnostic groups. Similarly, miRNA expression analyses were performed for an age and gender-matched Chinese cohort. Significant miRNAs in both the Chinese and Australian cohorts were selected for validation. 126 miRNAs were significantly differentially expressed between patients with AD and normal cognition in the Australian cohort, and 45 miRNAs were differentially expressed in the Chinese cohort. MiR-550a-3p was significantly upregulated in AD compared to controls in both the Australian ($p<0.05$) and Chinese groups ($p<0.05$), and similarly upregulated in AD compared to MCI. There were no significant differences between MCI and control groups. MiR-550a-3p has not been investigated by previous AD biomarker studies. Potential targets of miR-550a-3p include AD-relevant genes *AP3B2, SORL1, NEUROD6, MEF2C, APP, BACE2, and CASP3.* The biological pathway of miR-550a-3p and its potential as a biomsarker candidate for AD will be investigated in future studies.

Funding: Shanghai Jiao Tong University SJTU-UNSW Collaborative Research Fund.

White matter hyperintensity extraction pipeline development

CHeBA staff: Wei Wen, Jiyang Jiang, Perminder Sachdev.

Other investigators: Dr Wanlin Zhu (Beijing Normal University) (CHeBA Hon. Research Fellow), Associate Professor Tao Liu (Beihang University, China) (CHeBA Hon. Research Fellow).

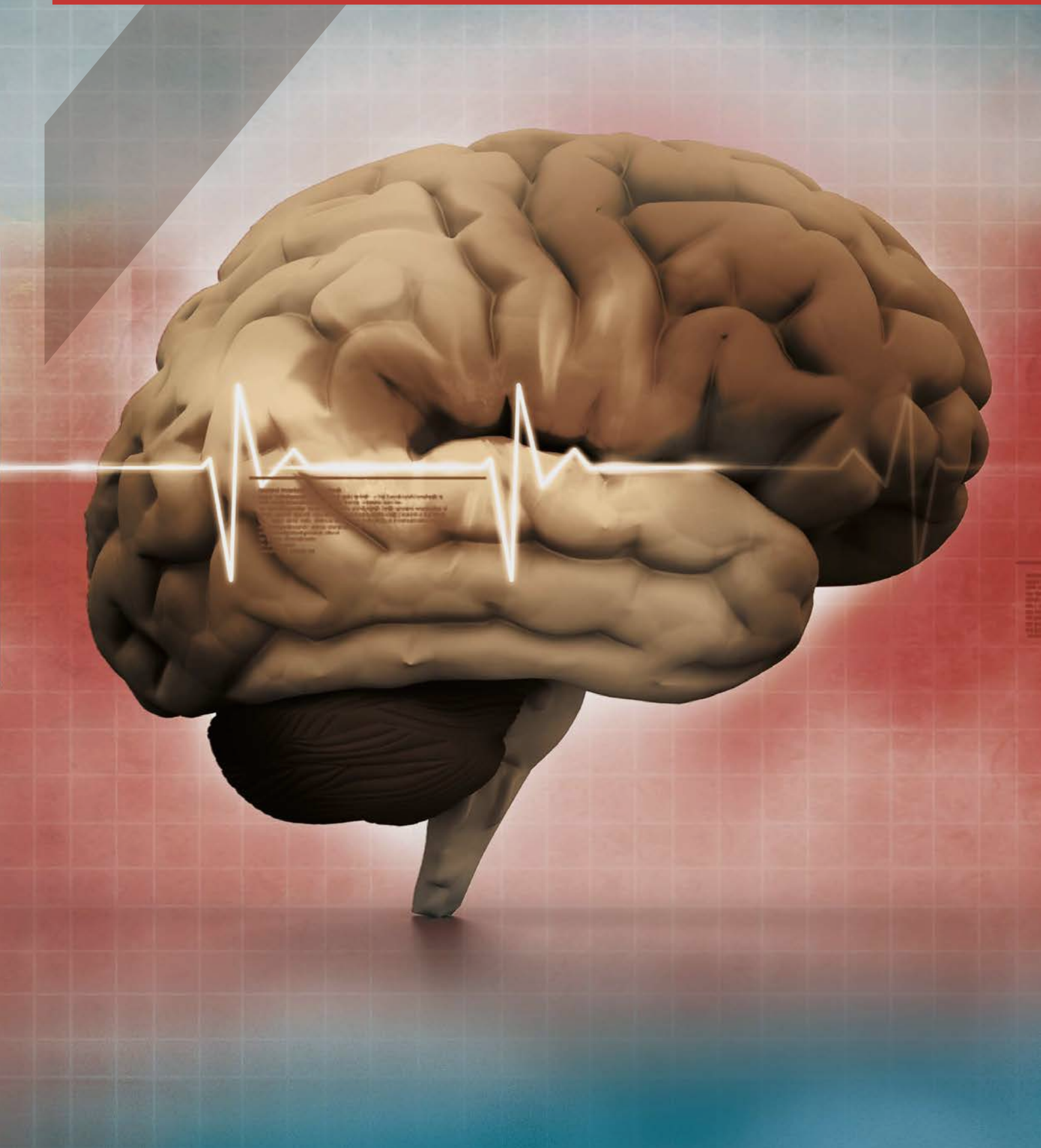
Aim: Build an automated white matter hyperintensity (WMH or UBO - unidentified bright objects) extraction pipeline for the cerebral small vessel disease consortium, and other WMH processing tasks with large sample sizes.

Findings: A fully automated WMH segmentation pipeline, UBO Detector, was developed. The correspondence between UBO Detector-derived WMH segmentation and manually traced results is high, indicating that UBO Detector is a reliable alternative to manual tracing with its advantage being amplified in large-scale datasets. The associations of WMH volumes calculated by UBO Detector with a commonly used visual rating scale (Fazekas scale results) and neuropsychological performances were investigated in a multi-centre cohort. In addition, the performance of UBO Detector in longitudinal datasets was also examined with data from three-time points. WMH volumes extracted by UBO Detector were

significantly associated with Fazekas scores and cognitive performance, and highly correlated between acquisition time points with a clear increase over time. The processing of UBO Detector is relatively fast at approximately 15 minutes/brain on average. The findings suggest that UBO Detector is a reliable and efficient tool for WMH segmentation. CHeBA's UBO detector is now available for download free-of-charge at https://cheba.unsw.edu.au/group/neuroimaging-pipeline. A journal paper describing the methodology is under review.

Funding: NHMRC, John Holden Family Foundation.

APPENDICES



APPENDIX A: STAFF LIST

Leadership

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

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

Angela (Angie) Russell
Centre Manager

Academic Staff

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

Anne-Nicole Casey
Postdoctoral Fellow

Vibeke Catts
Postdoctoral Fellow, *Older Australian Twins Study (OATS) Study Co-ordinator*

Lynn Chenoweth
Professor of Nursing

Debjani Das
Postdoctoral Fellow

Megan Heffernan
Postdoctoral Fellow, *Maintain Your Brain Project Coordinator*

Tharusha Jayasena
Postdoctoral Fellow

Jiyang Jiang
Postdoctoral Fellow

Nicole Kochan
Research Fellow, *Co-Leader Neuropsychology Group*

Mari Kondo
Postdoctoral Fellow

Yvonne Leung
Postdoctoral Fellow, *ICC-Dementia Consortium Co-ordinator*

Jessica Lo
Postdoctoral Fellow, *STROKOG Consortium Co-ordinator*

Steve Makkar
Postdoctoral Fellow

Karen Mather
Senior Research Fellow, *Leader Genetics & Genomics Group*

Adith Mohan
Research Fellow

Matt Paradise
Research Fellow

Anbupalam Thalamuthu
Research Fellow

Wei Wen
Associate Professor, *Leader Neuroimaging Group, Director Neuroimaging Laboratory*

Professional & Technical Staff – Research

Eashwar Anbupalam
Student Assistant, *Neuroimaging (Casual) (until December 2017)*

Suzanne Artiss
Research Assistant, ***OATS*** (Casual) *(until November 2017)*

Amelia Assareh
Research Study Coordinator, *OATS (until April 2017)*

Adam Bentvelzen
Research Assistant, *MAS*

Tiffany Chau
Research Assistant, *Maintain Your Brain*

John Crawford
Senior Statistician

Catriona (Keenie) Daly
Research Assistant, *ICC-Dementia Consortium Co-ordinator (until March 2017)*

Nicole Dargue
Research Assistant, *OATS (Casual) (until August 2017)*

Tanya Duckworth
Research Assistant, *OATS (until September 2017)*

Rajib Dutta
Research Officer / Statistician *(until March 2017)*

Sumangali (Sumi) Gobhidharan
Research Officer, *Genetics & Genomics*

Fleur Harrison
Research Assistant, *OATS*

Mahboobeh (Mabi) Hosseini
Research Assistant, *Biobank Officer*

Sri Chandana Kanchibotla
Research Assistant, *Genetics & Genomics* (Casual)

Kristan Kang
Data Manager

Forrest Koch
Student Assistant, *Neuroimaging* (Casual)

Manish Kumar
Research Data Management Officer, *Maintain Your Brain (until April 2017)*

Darren Lipnicki
Research Officer, *COSMIC Consortium Co-ordinator*

Kate Maston
Research Officer, *Sydney Memory & Ageing Study (MAS) Co-ordinator (until December 2017)*

Tamara Paulin
Research Assistant, *Sydney Memory & Ageing Study (MAS) (until February 2017)*

Juan Carlo San Jose
Research Officer, *Maintain Your Brain*

Dr Fei Song
Research Assistant (Casual) *(until July 2017)*

Paul Strutt
Research Assistant, *Sydney Memory & Ageing Study (MAS)*

Adam Theobald
Research Officer, *OATS Coordinator*

Professional & Technical Staff – Support

Melissa Chungue
Administrative Assistant

Kate Crosbie
Administrative Assistant (Casual)

Sophia Dean
Administrative Officer

Craig Douglass
Administrative Assistant (Casual)

Heidi Douglass
Marketing & Communications Officer

Suzanne (Suzy) Forrester
Administrative Assistant, *OATS*

Michelle Savignano
Web Coordinator

Hsu Hnin (Brenda) Wai
Administrative Assistant (Casual) ***(until June 2017)***

Conjoint Staff

Gavin Andrews
Professor of Psychiatry, Chief Investigator, *NHMRC Program Grant ID1093083*

Brian Draper
Professor, Associate Investigator, *Sydney Memory & Ageing Study (ongoing)*

Nicola Gates
Senior Lecturer *(2014-2018)*

Rebecca Koncz
Associate Lecturer *(2015-2018)*

Teresa Lee
Senior Lecturer, *Co-Leader Neuropsychology Group (ongoing)*

Charlene Levitan
Adjunct Associate Lecturer *(2015-2019)*

Anne Poljak
Lecturer, Protein Chemist, *Leader Proteomics Group*

Melissa Slavin
Senior Lecturer *(2014-2018)*

Julian Trollor
Professor, *Leader Neuroinflammation Group*

Visiting Academics

Bernhard Baune
Visiting Professorial Fellow *(January 2013 - present)*

David Bunce
Visiting Professorial Fellow, *Epidemiological Studies of Cognition and Dementia (February 2014-December 2017)*

Zheng Chen
Visiting Senior Lecturer *(January-December 2017)*

Lee-Fay Low
Senior Visiting Fellow *(May 2014-May 2017)*

Kuldip Sidhu
Visiting Honorary Associate Professor, *Co-Leader Molecular Biology & Stem Cells Group (December 2015-December 2018)*

Dr Wanlin Zhu
Visiting Fellow *(1 September 2016-31 December 2018)*

Dr Tamar Ziehm
Visiting Senior Researcher *(22 May-31 July 2017)*

CHeBA Honorary Research Fellows

Dr Nicola Armstrong

Dr Tao Liu

Dr Julia Muenchhoff

Dr Simone Reppermund

Dr Haobo Zhang

APPENDIX B: EXTERNAL APPOINTMENTS

Dr Nady Braidy

- Honorary Fellow, Australian School of Advanced Medicine, Macquarie University
- Adjunct Lecturer, School of Biotechnology and Biomolecular Sciences, UNSW
- Health Services Advisor, Department of Aged Care and Rehabilitation, Bankstown-Lidcombe Hospital, Sydney, Australia
- Scientific Advisor, Better Humans Inc.
- Editor: *Current Alzheimer Research; CNS and Neurological Disorders; Analytical Cellular Pathology*
- Reviewer for ARC, NHMRC

Professor Henry Brodaty

- Scientia Professor, Ageing and Mental Health, (previously Professor of Psychogeriatrics, 1990-2010), School of Psychiatry, UNSW (2011-present)
- Co-Director, Centre for Healthy Brain Ageing (CHeBA)
- Montefiore Chair of Healthy Brain Ageing (2012-present)
- Director, Dementia Centre for Research Collaboration, UNSW (2006-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); Immediate Past-President (2015-2017)
- Member, International Advisory Committee of the National Institute of Dementia, South Korea (2013-present)
- Honorary Professor, Kiang Wu Nursing College, Macau (2014-present)
- Honorary Lifetime Vice-President, Alzheimer's Disease International (ADI) (2005-present)
- Honorary Medical Advisor, Alzheimer's Australia NSW (1992-present)
- Chairman, Dementia Research Foundation Ltd, Alzheimer's Australia (2002-2016)
- 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)
- WHO Advisory Group of Global Dementia Observatory (2015-2017)
- Ambassador, Montefiore Homes (2006-present)
- Chair, Clinical Advisory Committee, Montefiore Homes (2012-present)
- Expert Advisory Panel, NHMRC National Institute for Dementia Research (2016-present)
- Member, Commonwealth Department of Health, Consultative Group for Special Care Dementia Units (2017-)
- Member, International Research Network for Dementia Prevention Advisory Group (2017-)
- Editorial board member 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), *International Psychogeriatrics* (1996-2017), *Neurodegenerative Disease Management* (2010-present), ***The*** *Australian Journal of Dementia Care* (2012-present)
- Deputy Editor, *International Psychogeriatrics* (2017-)

Professor Lynn Chenoweth

- Member, Research Advisory Group, Parkinson's Australia
- Member, Conference Advisory Committee, Alzheimer's Disease International
- Honorary Research Associate, Macau College of Nursing
- Member, UTS Centre for Mechatronic and Intelligent Systems, University of Technology Sydney
- Member, UTS Centre for the Study of Choice (CenSoc), University of Technology Sydney

- Approved Supervisor, Faculty of Health, University of Technology Sydney
- Adjunct Professor, School of Nursing, Notre Dame University
- Member, Nursing Curriculum Advisory Committee, Notre Dame University
- Member, Primary Health Care Curriculum Advisory Committee, Notre Dame University
- Member, Executive Board Advisory Committee, Australian Multicultural Aged care Nursing (AMAN), Lebanese Muslim Association
- Member, Expert Advisory Research Group, University of Bradford
- Editorial board for *International Journal of Older People Nursing, Nursing Older Person Journal, Austin Journal of Nursing and Health Care.*

Dr Rebecca Koncz

- Neuropsychiatric Institute, Prince of Wales Hospital
- Fellow, Royal Australian and New Zealand College of Psychiatrists (RANZCP)
- Member, Section of Neuropsychiatry, RANZCP
- Member, Section of Psychiatry of Intellectual and Developmental Disabilities, RANZCP
- Fellow in Psychiatric Research, Health Education and Training Institute
- Research Affiliate, Discipline of Psychiatry, Sydney Medical School, University of Sydney

Dr Teresa Lee

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

Dr Karen Mather

- Research Fellow and Group Leader, Neuroscience Research Australia (NeuRA)

Dr Adith Mohan

- Consultant Neuropsychiatrist, Neuropsychiatric Institute, Prince of Wales Hospital
- Senior Lecturer, School of Psychiatry, UNSW
- Fellow, Royal Australian and New Zealand College of Psychiatrists (RANZCP)
- NSW jurisdictional representative, Section of Neuropsychiatry, RANZCP

Dr Anne Poljak

- Senior Research Scientist, Bioanalytical Mass Spectrometry Facility, Mark Wainwright Analytical Centre, UNSW
- Conjoint Lecturer, School of Medical Sciences, UNSW
- Member, Scientific Review Committee, NSW Brain Bank Network (NSWBBN)
- Member, Scientific Advisory Committee, Rebecca L. Cooper Medical Research Foundation
- Member, NHMRC National Institute for Dementia Research, Working Group: Standardisation Protocol for Blood Collection and Storage
- Member, Cochrane Community
- Reviewer, Alzheimer's Association International Conference (biomarkers, non-neuroimaging).

Professor Perminder Sachdev

- Scientia Professor, Neuropsychiatry (previously Professor of Neuropsychiatry, 1999-2009), School of Psychiatry, UNSW (2009-)
- Clinical Director, Neuropsychiatric Institute, Prince of Wales Hospital, Sydney (1987-present)
- Co-Director, Centre for Healthy Brain Ageing (CHeBA)
- Visiting Fellow, Australian National University (2009-present)
- Visiting Professor, National University of Korea, Seoul (2014-2018)
- Visiting Professor, Jiao Tong University, Shanghai (2018-)
- Committee Member of the WHO's Expert Advisory Committee for the Global Dementia Observatory (GDO)
- Executive Member of the International Society of Vascular Behavioural and Cognitive Disorders (VASCOG) (2012-present)
- Member, Scientific Program Committee, Alzheimer's Association International Conference
- Member, Expert Advisory Panel, NHMRC National Institute of Dementia Research
- 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)
- Chair, Medical Advisory Committee of the Tourette Syndrome Association of Australia (1996-present)
- Fellow of the Australian Academy of Health & Medical Sciences (2015-present)
- Fellow of the NHMRC Academy 2011 (2011-present)
- Member of the NHMRC Assigner's Academy (2012-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, Middle Eastern Journal of Psychiatry & Alzheimer's, Brain and Mind Matters*, *The Open Neuroimaging Journal, American Journal of Geriatric Psychiatry, International Psychogeriatrics.*

Hon. Associate Professor Kuldip Sidhu

- Guest Visiting Professor, Department of Neurology, Tianjin Huanhu Hospital, Huanhu, China (2016-2018)
- Research Grant Assessor, National Science Centre, Poland
- Executive Board Member, Society for Brain Mapping & Therapeutics, USA
- Editorial board member for *Journal of Stem Cells & Clinical Practice, Journal of Neurological Disorders, World Journal of Stem Cells, OMICS Biomedical Journal, Recent Patents on Regenerative Medicine, International Journal of Stem Cells Research & Therapy, International Neuropsychiatric Disease Journal, Austin Alzheimer's and Parkinson's Disease, Journal of Neurology and Neuroscience*

APPENDIX C: POSTGRADUATE STUDENTS

CURRENT

Andrew Affleck

- Effects of anti-hypertensive medications on Alzheimer and cerebrovascular disease brain pathology
- PhD student
- School of Psychiatry, Faculty of Medicine, UNSW
- Supervisors: Professor Perminder Sachdev, Professor Glenda Halliday

Xi (Sophie) Chen

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

Lucia Premilla Chinnappa-Quinn

- A study of the effect of acute physical illness requiring hospitalisation on the long-term cognitive and functional trajectory of two elderly cohorts: the Sydney Memory and Aging Study (MAS) and the Older Australian Twins Study (OATS)
- PhD student
- School of Psychiatry, Faculty of Medicine, UNSW
- Supervisors: Professor Michael Bennett, Professor Perminder Sachdev, Dr Nicole Kochan, Dr John Crawford

Fleur Harrison

- Apathy in older community-dwelling persons: improving assessment, investigating its association with immune markers, differentiating from depression and fatigue and modelling its longitudinal course
- PhD student
- School of Psychiatry, Faculty of Medicine, UNSW
- Supervisors: Professor Henry Brodaty, Dr Liesbeth Aerts, Dr Katrin Seeher, Professor Adam Guastella, Professor Julian Trollor, Professor Andrew Lloyd

Fatemeh Khorshidi

- Pharmacological Promotion of NAD+ Anabolism to reduce AD pathology and Delay Cognitive Decline
- PhD student
- School of Psychiatry, Faculty of Medicine, UNSW
- Supervisors: Dr Nady Braidy, Professor Perminder Sachdev

Rebecca Koncz

- The relative genetic and environmental contributions to amyloid deposition in the brains of older adults: amyloid imaging using the twin design
- PhD student
- School of Psychiatry, Faculty of Medicine, UNSW
- Supervisors: 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

Janet Mitchell

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

Adith Mohan

- Influence of ageing on the human brain transcriptome
- PhD student
- School of Psychiatry, Faculty of Medicine, UNSW
- Supervisors: Dr Karen Mather, Professor Perminder Sachdev, Dr Anbu Thalamuthu

Matthew Paradise

- Neuroimaging of cerebrovascular disease
- PhD student
- School of Psychiatry, Faculty of Medicine, UNSW
- Supervisors: Professor Perminder Sachdev

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
- Proposed end date: 2020

Upul Senanayake

- Computer aided early identification system for Individuals at risk of dementia
- PhD student
- School of Computer Science and Engineering, Faculty of Engineering, UNSW
- Supervisors: Professor Arcot Sowmya, Dr Laughlin Dawes, Professor Perminder Sachdev and A/ Professor Wei Wen

Annette Spooner

- Machine learning techniques for identifying individuals at risk of developing Alzheimer's disease
- PhD student
- School of Computer Science and Engineering, Faculty of Engineering, UNSW
- Supervisors: Professor Arcot Sowmya, Professor Perminder Sachdev

Ruby Tsang

- Nature and nurture: Insights from genetic, environmental and epigenomic studies 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

Gurjeet Kaur Virk

- Blood biomarkers for Alzheimer's disease using omics technology
- Scientia PhD student
- School of Psychiatry, Faculty of Medicine, UNSW
- Supervisors: Dr Anne Poljak, Dr Nady Braidy, Professor Perminder Sachdev

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

Matthew Wong

- Biomarkers of oxidative stress in healthy human brain ageing and Alzheimer's disease
- PhD student
- School of Psychiatry, Faculty of Medicine, UNSW
- Supervisors: Dr Nady Braidy, Professor Perminder Sachdev, Dr Anne Poljak

Helen Wu

- The role of peripheral blood microRNAs as biomarkers of early Alzheimer's disease
- PhD student
- School of Psychiatry, Faculty of Medicine, UNSW
- Supervisors: Dr Karen Mather, Professor Perminder Sachdev, Professor Henry Brodaty

Liu Yue

- Using fluid biomarkers to examine the relationship between CVD and AD pathologies
- Masters by Research
- School of Psychiatry, Faculty of Medicine, UNSW
- Supervisors: Professor Perminder Sachdev, Dr Nady Braidy, Dr Anne Poljak, Associate Professor Wei Wen

COMPLETED

Anne-Nicole Casey

- The Friendship and Relationship Interactions in the Elderly Networks Description (FRIEND) Study
- PhD student
- School of Psychiatry, Faculty of Medicine, UNSW
- Supervisors: Prof Henry Brodaty, A/Prof Lee-Fay Low (Faculty of Health Sciences, University of Sydney), Prof Yun-Hee Jeon (Sydney Nursing School, University of Sydney)
- PhD conferred: December 2016 (graduated 14 June 2017)

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
- PhD conferred June 2017

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
- PhD conferred 2017

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
- PhD conferred November 2017

APPENDIX D: AWARDS & PROMOTIONS

Dr Karen Mather

- Promoted to Senior Lecturer in the School of Psychiatry.

APPENDIX E: RESEARCH GRANTS & FUNDING

GRANTS

COSMIC: An international consortium to identify risk and protective factors and biomarkers of cognitive ageing and dementia in diverse entho-racial groups and geographical settings

Funding Source: National Institute on Aging (NIA) | National Institutes of Health (NIH)
Project ID: RG172507
Investigator/s: Prof Perminder Sachdev, Prof M Ganguli, Prof Karen Ritchie, Prof Ki Woong Kim, Prof Richard Lipton, Prof Ron Petersen
Duration: 5 years: September 2017-June 2020
Total Funds: USD2,573,572

Cross-comparison, validation and performance of computerised neuropsychological assessment devices in the evaluation of mild cognitive impairment and dementia

Funding Source: National Healthy & Medical Research Council (NHMRC)
Project ID: RG163145
Investigator/s: Dr Nicole Kochan
Duration: 3 years: 2017-2020
Total Funds: $700,482

Social cognitive change in late adulthood

Funding Source: Australian Research Council (ARC)
Project ID: RG170732
Investigator/s: Prof Julie Henry, Prof Perminder Sachdev, Dr Karen Mather
Duration: 4 years: 2017-2020
Total Funds: $323,250

Modulation of SIRT2 through upregulation of NAD+ anabolism to promote lifespan

Funding Source: Australian Research Council (ARC) DECRA
Project ID: RG161166A | RG161166
Investigator/s: Dr Nady Braidy
Duration: 3 years: 2017-2019
Total Funds: $372,000

Involvement of SIRT3 and related energy metabolite changes in the Alzheimer brain

Funding Source: Alzheimer's Australia Dementia Research Foundation Dementia (AADRF)/Dementia Grants Program
Project ID: RG170876
Investigator/s: Dr Tharusha Jayasena, Prof Perminder Sachdev, Dr Anne Poljak, Dr Naidy Braidy
Duration: 2 years: 2017-2019
Total funds: $50,000

Centre of Research Excellence in Cognitive Health: Evidence, intervention and population modelling

Funding Source: National Health & Medical Research Council (NHMRC)
Project ID: RG161515
Investigator/s: Prof Perminder Sachdev
Duration: 2 years: 2017-2018
Total Funds: $147,322

Infrastructure Support for the Centre for Healthy Brain Ageing (CHeBA)

Funding Source: Black Dog Institute/NSW Health Medical Research Support Program
Project ID: RG170787
Investigator/s: Prof Perminder Sachdev, Prof Henry Brodaty
Duration: 2 years: 2017-2018 (+optional 2019-2020)
Total Funds: $377,086

Slowing progression of Alzheimer's disease by modulating the kynurenine pathway

Funding Source: National Health & Medical Research Council (NHMRC)
Project ID: RG171146-A
Investigator/s: Dr Nady Braidy
Duration: 2 years: 2017-2018
Total Funds: $10,000

The role of peripheral blood microRNAs as biomarkers of Alzheimber's disease

Funding Source: National Health & Medical Research Council (NHMRC)
Project ID: RG161785
Investigator's: Dr Karen Mather (Supervisor), NHMRC Postgraduate Scholarship for Dr Helen Wu
Duration: 2 years: 2017-2018
Total Funds: $83,867

Development and pilot testing the dignity in care survey for acute and subacute care settings

Funding Sources: Alzheimer's Australia Dementia Research Foundation Dementia (AADRF)/Dementia Grants Program
Project ID: RG162710
Investigator/s: Prof Lynn Chenoweth (Supervisor), Scholarship for Louise Heuzenroeder
Duration: 1 year: 2017*
Total Funds: $15,000

*Project closed & acquitted 29 November 2017 – Candidate changed institutions

Safety-Net Support Fellowship – Dr Nicole Kochan

Funding Source: Office of the Deputy Vice-Chancellor (Research), UNSW Sydney
Project ID: PS42929
Investigator/s: Dr Nicole Kochan
Duration: 1 year: 2017*
Total Funds: $38,460

*Project closed & acquitted 31 Dec 2017

Risk factors, early diagnosis and effective interventions for neurocognitive disorders

Funding Source: National Health & Medical Research Council (NHMRC)
Project ID: RG141685
Investigator/s: Prof Perminder Sachdev, Prof Henry Brodaty, Prof Gavin Andrews
Duration: 5 years: 2016-2020
Total Funds: $6,782,730

BRIDGET: Brain imaging, cognition, Dementia and next generation GEnomics: a Transdisciplinary approach to search for risk and protective factors of neurodegenerative disease

Funding Source: NHMRC NIDR-EU JPND Co-funded Project Grant
Project ID: RG152067
Investigators: Prof Perminder Sachdev, Dr Karen Mather, Dr Anbupalam Thalamuthu, A/Prof Wei Wen, Dr Nicola Armstrong
Duration: 3 years: 2016-2018
Total Funds: $1,081,489

A European DNA bank for deciphering the missing heritability of Alzheimer's disease (EADB)

Funding Source: NHMRC NIDR-EU JPND Co-funded Project Grant
Project ID: RG152100
Investigators: Prof Perminder Sachdev, Dr Karen Mather, Dr Anbupalam Thalamuthu, Dr Nicola Armstrong, Prof Henry Brodaty
Duration: 3 years: 2016-2018
Total Funds: $1,556,995

Apathy in older community-dwelling persons: assessment, investigation, differentiation

Funding Source: Alzheimer's Australia Dementia Research Fund (AADRF)/DCRC Early Diagnosis and Prevention Shared Grant – PhD Scholarship for Ms Fleur Harrison
Project ID: RG161424
Investigator/s: Prof Henry Brodaty (Supervisor), Ms Fleur Harrison
Duration: 4 years: 2016-2019
Total Funds: $60,000

A novel MRI-based cerebrovascular pathology index: development and validation

Funding Source: ANU NNIDR DCRC Early Diagnosis and Prevention Shared Grant
Project ID: RG161864
Investigator/s: Dr Matthew (Matt) Paradise
Duration: 1 year: July 2016- July 2017*
Total Funds: $56,717

*Project closed & acquitted 19 September 2017

MicroRNAs as biomarkers for Alzheimer's disease – comparison between Australian and Chinese populations

Funding Source: SJTU-UNSW Collaborative Research Fund – Seed Grant
Project ID: RG152795
Investigator/s: Prof Henry Brodaty, Dr Helen Wu
Duration: 1 year: 2016, extended to June 2017*
Total Funds: $10,000

*Project closed & acquitted 24 November 2017

Maintain Your Brain

Funding Source: NHMRC
Project ID: RG142234
Investigator/s: Prof Henry Brodaty, A/Prof Michael Valenzuela, Prof Perminder Sachdev, Prof John McNeil, Prof Anthony Maeder, Prof Nicola Lautenschlarger, Prof Louisa Jorm, Prof Maria Fiatarone Singh, Prof Kaarin Anstey, Prof Gavin Andrews
Duration: 5 years: 2015-2019
Total Funds: $6,467,015

The genetic and environmental determinants of amyloid deposition in older individuals: an amyloid imaging study using the twin design

Funding Source: NHMRC
Project ID: RG140593
Investigators: Prof Perminder Sachdev, Prof Christopher Rowe, A/Prof Wei Wen, Dr Melissa Slavin
Duration: 3 years: 2015-2017
Total Funds: $625,404

Improved accessibility and long-term storage of biospecimens from the Centre for Healthy Brain Ageing's (CHeBA) longitudinal studies

Funding Source: UNSW Australia MREII Grant
Project ID: RG142871
Investigator/s: Prof Perminder Sachdev, Prof Henry Brodaty, Dr Julia Muenchhoff, Dr Anne Poljak, Dr Nady Braidy, et. al
Duration: 1 year: 2015*
Total Funds: $173,871

*Project closed & acquitted 15 November 2017

Isoform-dependent apoE processing by human induced pluripotent stem cells: A novel pathway linking APOE genotype and Alzheimer's disease risk

Funding Source: University of Wollongong / NHMRC Project Grant Shared Grant
Project ID: RG143042
Investigator/s: A/Prof Kuldip Sidhu
Duration: 1 year: 2015* (Full duration 2015-2017)
Total Funds: $28,944

*Project closed & acquitted 23 March 2017

Biomarkers of late-life depression and associated cognitive impairment

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

*Project acquitted & closed 31 August 2017

Cognition following non-cardiac surgery and anaesthesia (PhD Project)

Funding Source: NHMRC / DCRC-ABC
Project ID: RG161541-B (ex-RG102939-O)
Investigator/s: Prof Perminder Sachdev, Premilla Chinnappa-Quinn
Duration: 3 years: 2013-2015*
Total funds: 30,000

*Project acquitted & closed 10 August 2017

Cognition following non-cardiac surgery and anaesthesia: a study of neuropsychological and functional changes in the first year post-procedure

Funding Source: Australian Society of Anaesthetists / PhD Grant Support
Project ID: RG123624
Investigator/s: Premilla Chinnappa-Quinn
Duration: 3 years: 2013-2015*
Total Funds: $9091

*Extended to March 2017

PHILANTHROPIC

The Montefiore Chair of Health Brain Ageing at UNSW

Funding Source: The Sir Moses Montefiore Jewish Home
Project ID: PS34587_PS34590
Awardees: Prof Henry Brodaty
Prof Perminder Sachdev
Duration: 5 years: November 2017-November 2021
Total Funds: $529,183

The CHeBA Cerebral Small Vessel Disease (SVD) Fund

Funding Source: John Holden Family Foundation
Project ID: PS41604_PS41625
Awardees: Prof Perminder Sachdev
Duration: 6 years: 2016-2020
Total Funds: $600,000

The Dementia Momentum Initiative, incorporating the Wipeout Dementia Campaign

Funding Source: Roth Charitable Foundation
Project ID: PS38235_PS38252
Awardees: Prof Perminder Sachdev
Prof Henry Brodaty
Duration: 5 years: 2016-2020
Total Funds: $90,000

Funding Source: Sachdev Foundation
Project ID: PS38235_PS38252
Awardees: Prof Perminder Sachdev
Prof Henry Brodaty
Duration: 2 year: 2016-2017
Total Funds: $80,000

Funding Source: Vincent Fairfax Family Foundation
Project ID: PS42069_PS42704
Awardees: Prof Perminder Sachdev
Prof Henry Brodaty
Duration: 5 years: 2015-2019 (Final 2 years contingent on meeting outcomes)
Total Funds: $500,000

Funding Source: The Yulgilbar Foundation
Project ID: PS38235_PS38252
Awardees: Prof Perminder Sachdev
Prof Henry Brodaty
Duration: 5 years: 2015-2019 (Final 2 years contingent on meeting outcomes)
Total Funds: $250,000

The Montefiore Chair of Health Brain Ageing at UNSW

Funding Source: The Sir Moses Montefiore Jewish Home
Project ID: PS34587_PS34590
Awardees: Prof Henry Brodaty
Prof Perminder Sachdev
Duration: 5 years: 2011-2015*
Total Funds: $665,000

*Funds utilised by 30 October 2017

Thomas Foundation Faculty Matching Funds

Funding Source: UNSW Medicine
Project ID: PS39895*
Awardees: Prof Perminder Sachdev
Prof Henry Brodaty
Duration: 3 years: 2015-2017
Total Funds: $335,000

*Amalgamated with PS34586_PS34589 November 2016

The Thomas Foundation Grant

Funding Source: The Thomas Foundation
Project ID: PS34586_PS34589
Awardees: Prof Henry Brodaty
Prof Perminder Sachdev
Duration: 5 years: 2011-2015*
Total Funds: $1,000,000

*Extended to December 2017

OTHER

The Health Brain Ageing Fund

Funding Source: Miscellaneous Donor Contributions
Project ID: PS22384_PS4163
Awardees: Prof Henry Brodaty
Prof Perminder Sachdev
Duration: Ongoing
Total Funds: $245,505*

*As at 31 December 2017

Centre for Healthy Brain Ageing Event & Sponsorship Fund

Funding Source: Miscellaneous
Project ID: PS33379_PS33397
Awardees: Prof Henry Brodaty
Prof Perminder Sachdev
Duration: Ongoing
Total Funds: $28,965*

*As at 31 December 2017

APPENDIX F: STATEMENT OF IN-KIND CONTRIBUTIONS

- ARIA Restaurant Sydney
- Breathe Fire Specialised Training
- Charter Hall
- Colliers International Residential
- Dripping Wet
- Hurley
- HWL Ebsworth Lawyers
- KPMG Sydney
- Queenscliff Surf Life Saving Club
- The Bucket List

APPENDIX G: STATEMENT OF FINANCIAL PERFORMANCE

STATEMENT OF FINANCIAL PERFORMANCE FOR THE YEAR ENDED 31 DECEMBER 2017

	Notes	2017	2016
		$	$
Funds			
Research Revenue		3,011,949	5,154,650
Donations		866,627	819,627
Fees		-	-
Faculty Funds	3	-	-
UNSW Contribution - Competitive	1	29,636	67,161
UNSW Contribution - Strategic	2	39,507	40,000
Sundry Other Revenue		50,160	1,309
Total Funds		**3,997,879**	**6,082,747**
Costs			
People Costs		3,104,235	2,520,381
Scholarship Stipends		110,372	92,190
Contract & Consulting Services		378,725	377,587
Repairs and Maintenance		163	779
Consumables		132,717	56,770
Travel		81,039	57,305
Equipment		54,820	60,376
Other Expenses		139,007	69,623
Internal Expense		(41,322)	(39,515)
Total Costs		**3,959,755**	**3,195,494**
Operating result		38,125	2,887,254
Opening Balance		3,347,592	460,338
Closing Balance		**3,385,716**	**3,347,592**

Notes to the Statement of Financial Performance

1. UNSW Contribution - Competitive relates to funding awarded to CHEBA from UNSW through various competitive schemes supporting research activities and infrastructure.
2. UNSW Contribution - Strategic relates to funding provided to CHEBA from UNSW as a strategic investment in the centre's research activities.
3. Faculty Funds - Operating funds provided by the faculty are budget allocations, with no revenue transferred to CHEBA.

APPENDIX H: PUBLICATIONS

Book Chapters

Braidy N, Poljak A, Jayasena T, Sachdev P. Natural Plant-Derived Acetylcholinesterase Inhibitors: Relevance for Alzheimer's Disease. In: Andrade PB, Valentão P, Pereira DM (eds) Natural Products Targeting Clinically Relevant Enzymes. Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany. 2017: p. 297-318. ISBN: 9783527805921 / Online ISBN: 9783527805921. DOI: 10.1002/9783527805921.ch12.

Mohan A, Lee T, Sachdev P. Chapter 4: An Atypical Variant of a Common Neurodegenerative Disorder. In: Priller J, Rickards H (Eds) Neuropsychiatry Case Studies. Springer International Publishing, Switzerland. 2017; p. 17-23. ISBN: 978-3-319-42188-9 / 978-3-319-42190-2 (eBook) DOI: 10.1007/978-3-319-42190-2_4.

Sachdev PS, Mohan A, Taylor L. Neuropsychiatric disorders. In: Bloch S, Green S, Janca A, Mitchell P, Robertson M (Eds) Foundations of Clinical Psychiatry, 4th edition. Melbourne University Press: Carlton, VIC, Australia. 2017 Jan 3. ISBN: 0522870961 / 9780522870954 / 9780522870954 (ebook).

Sachdev P, Mohan A. Chapter 12: Neuropsychiatry and key clinical competencies. In: Faruqui RA, Agrawal N, Bodani M (Eds) Oxford Textbook of Neuropsychiatry. Oxford University Press: Oxford, UK. 2017; in press.

Theobald A, Daly C, Yang Z, Mather KA, Muenchhoff J, Crawford J, Sachdev P. Sydney Centenarian Study. In: Pachna NA (Ed) Encyclopedia of Geropsychology. Springer: Singapore. 2017; p. 2365-2372. ISBN: 9789812870810. DOI: 10.1007/978-981-287-080-3_140-1 / 10.1007/978-981-287-082-7_140 [Epub 2016 Mar 29].

Journal articles

Aerts L, Heffernan M, Kochan NA, Crawford JD, Draper B, Trollor JN, Sachdev PS, Brodaty H. Effects of MCI subtype and reversion on progression to dementia in a community sample. Neurology. 2017 May 10; 88(23):2225-2232. DOI: 10.1212/wnl.0000000000004015. PMID: 28490651 [Epub 2017 May 12].

Armstrong NJ, Mather KA, Thalamuthu A, Wright MJ, Trollor JN, Ames D, Brodaty H, Schofield PR, Sachdev PS, Kwok JB. Aging, exceptional longevity and comparisons of the Hannum and Horvath epigenetic clocks. Epigenomics. 2017 May 4. DOI: 10.2217/epi-2016-0179. PMID: 28470125.

Barber RM, Fullman N, Sorensen RJD, Bollyky T, McKee M, …, Sachdev PS et al. Healthcare Access and Quality Index based on mortality from causes amenable to personal health care in 195 countries and territories, 1990–2015: a novel analysis from the Global Burden of Disease Study 2015. Lancet. 2017 Jul 15; 390(10091):231-266. DOI: 10.1016/S0140-6736(17)30818-8. PMID: 28528753 [Epub 2017 May 18].

Braidy N, Poljak A, Marjo C, Rutlidge H, Rich A, Jugder B-E, Jayasena T, Inestrosa NC, Sachdev PS. Identification of cerebral metal ion imbalance in the brain of ageing Octodon degus. Front Aging Neurosci. 2017 Mar 29; 9:66. DOI: 10.3389/fnagi.2017.00066. PMID: 28405187 / PMCID: PMC5370394 [Epub 2017 Mar 29]. Corrigendum in Front Aging Neurosci. 2017 May 15; 9:134. DOI: 10.3389/fnagi.2017.00134. PMID: 28515691 / PMCID: PMC5430069.

Benyamin B, He J, Zhao Q, Gratten J, Garton F, Leo PJ, Liu Z, …, Sachdev PS et al. Cross-ethnic meta-analysis identifies association of the GPX3-TNIP1 locus with amyotrophic lateral sclerosis. Nat Comm. 2017 Sep 20; 8(1): 611. DOI: 10.1038/s41467-017-00471-1. PMID: 28931804 / PMCID: PMC5606989.

Brodaty H, Aerts L, Crawford JD, Heffernan M, Kochan NA, Reppermund S, Kang K, Maston K, Draper B, Trollor JN, Sachdev PS. Operationalizing the Diagnostic Criteria for Mild Cognitive Impairment: The Salience of Objective Measures in Predicting Incident Dementia. Am J Geriatr Psychiatry. 2017 May; 25(5):485-497. DOI: 10.1016/j.jagp.2016.12.012. PMID: 27960092 [Epub 2016 Dec 23].

Brouwer RM, Panizzon MS, Glahn DC, Hibar DP, Hua X, Jahanshad N, Abramovic L, de Zubicaray GI, Franz CE, Hansell NK, Hickie IB, Koenis MMG, Martin NG, Mather KA, McMahon KL, Schnack HG, Strike LT, Swagerman SC, Thalamuthu A, Wen W, Gilmore JH, Gogtay N, Kahn RS, Sachdev PS, Wright MJ, Boomsma DI, Kremen WS, Thompson PM, Hulshoff Pol HE.Genetic influences on individual differences in longitudinal changes in global and subcortical brain volumes: results of the ENIGMA Plasticity Working Group. Hum Brain Mapp. 2017 Sep; 38(9):4444-4458. DOI: 10.1002/hbm.23672. PMID: 28580697 [Epub 2017 June 5].

Bunce D, Haynes BI, Lord SR, Gschwind YJ, Kochan NA, Reppermund S, Brodaty H, Sachdev P, Delbaere K. Intraindividual stepping reaction time variability predicts falls in older adults with mild cognitive impairment. J Gerontol A Biol Sci Med Sci. 2017 Jun 1; 72(6):832-837. DOI: 10.1093/gerona/glw164. PMID: 27591431 [Epub 2016 Sep 3].

Cations M, Withall A, Horsfall R, Denham N, White F, Trollor J, Loy C, Brodaty H, Sachdev P, Gonski P, Demirkol A, Cumming RG, Draper B. Why aren't people with young onset dementia and their supporters using formal services? Results from the INSPIRED study. PLoS One. 2017; 12(7):e0180935. DOI: 10.1371/journal.pone.0180935. PMID: 28723931 [Epub 2017 July 21].

Cherbuin N, Shaw ME, Walsh E, Sachdev P, Anstey KJ. Validated Alzheimer's Disease Risk Index (ANU-ADRI) is associated with smaller volumes in the default mode network in the early 60s. Brain Imaging Behav. 2017 Dec 14. DOI: 10.1007/s11682-017-9789-5. PMID: 29243120 [Epub 2017 Dec 16].

Chopra S, Shaw M, Shaw T, Sachdev PS, Anstey KJ, Cherbuin N. More highly myelinated white matter tracts are associated with faster processing speed in healthy adults. NeuroImage. 2017; pii: S1053-8119(17)31093-5. DOI: 10.1016/j.neuroimage.2017.12.069. PMID: 29274747 [Epub 2017 Dec 25].

Connors MH, Ames D, Woodward M, Brodaty H. Predictors of Driving Cessation in Dementia: Baseline Characteristics and Trajectories of Disease Progression. Alzheimer Dis Assoc Disord. 2017 Oct 3. DOI: 10.1097/wad.0000000000000212. PMID: 28984640 [Epub 2017 Oct 7].

Cross AJ, George J, Woodward MC, Ames D, Brodaty H, Elliott RA. Dietary Supplement Use in Older People Attending Memory Clinics in Australia. J Nutr Health Aging. 2017; 21(1):46-50. DOI: 10.1007/s12603-016-0742-x. PMID: 27999849 [Epub 2016 Dec 22].

Cross AJ, George J, Woodward MC, Ames D, Brodaty H, Wolfe R, Connors MH, Elliott RA. Potentially Inappropriate Medication, Anticholinergic Burden, and Mortality in People Attending Memory Clinics. J Alzheimers Dis. 2017 Sep 1. DOI: 10.3233/jad-170265. PMID: 28869467 [Epub 2017 Sep 5].

Deutsch A, Siegel E, Cations M, Wright C, Naganathan V, Brodaty H. A pilot study on the feasibility of training nurses to formulate multicomponent oral health interventions in a residential aged care facility. Gerodontology. 2017 Aug 23. DOI: 10.1111/ger.12295. PMID: 28836301 [Epub 2017 Aug 23].

Duncan T, Lowe A, Sidhu K, Sachdev P, Lewis T, Lin RCY, Sytnyk V, Valenzuela M. Replicable expansion and differentiation of neural precursors from adult canine skin. Stem Cell Rep. 2017 Aug 8; 9(2): 557-570. DOI: 10.1016/j.

stemcr.2017.07.008. PMID: 28793248 [Epub 2017 Aug 10].

Eramudugolla R, Mortby ME, Sachdev P, Meslin C, Kumar R, Anstey KJ. Evaluation of a research diagnostic algorithm for DSM-5 neurocognitive in presdisorders in a population-based cohort of older adults. Alzheimers Res Ther. 2017 Mar 4; 9(1):15. DOI: 10.1186/s13195-017-0246-x PMID: 28259179 / PMCID: PMC5336665 [Epub 2017 Mar 4].

a) Evered L, …, Sachdev PS et al. Recommendations for the nomenclature of cognitive change associated with anaesthesia and surgery. Br J Anaestheia. 2017; in press. Accepted 2 Oct 2017. Manuscript BJA-2017-00200-HH076.R4.

b) Anesth & Analg. 2017; in press.

c) Anesthesiology. 2017; in press.

d) Can J Anaesth. 2017; in press.

e) J Alzheimers Dis. 2017; in press.

f) Acta Anaesthesiol Scand. 2017; in press.

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APPENDIX I: CONFERENCE/PUBLISHED ABSTRACTS

Braidy N, Sachdev P et al. Sirtuin Protein and Related Energy Metabolite Changes in the Alzheimer Brain [Abstract Poster P2-182]. *Alzheimer's Imaging Consortium (AIC) Preconference*. 15 July 2017; London, UK.

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APPENDIX J: WORKSHOPS, CONFERENCES & SPEAKING ENGAGEMENTS

Braidy N. Promotion of cellular NAD+ anabolism as a strategy to improve cellular senescence. 18th *ISANH Middle East World Congress* 3-4 May 2017; Beirut, Lebanon.

Brodaty H. A successful approach to reducing antipsychotic medications in long-term care: The HALT Project. *32nd International Conference of Alzheimer's Disease International (ADI)*. 27 April 2017; Kyoto, Japan.

Brodaty H. Dementia – Where are we up in Science of Care? Presentation at the *32nd International Conference of Alzheimer's Disease International (ADI)*. 28 April 2017; Kyoto, Japan.

Brodaty H. Invited Presentation. Centenarians living mentally well to 100. *The Commonwealth Fund's 20th International Symposium on Health Care Policy, "The Health Care System of the Future – What Does it look Like and How Do We Get There?"* 15-17 Nov 2017; Washington DC, USA.

Brodaty H, Sachdev P, Maintain Your Brain Research Team. Maximising technology and methodology for internet prevention of cognitive decline: the Maintain Your Brain trial. *Alzheimer's Association International Conference (AAIC) 2017*. 6-20 July 2017; London, UK.

Lipnicki D, Crawford J, Dutta R, Thalamuthu A, Kochan N, Sachdev N. Rates and determinants of cognitive decline in diverse ethno-racial and geographical settings: The COSMIC collaboration. Paper presented at the *16th Congress of the International Federation of Psychiatric Epidemiology Congress. Melbourne, Australia;* 17-20 Oct 2017.

Mather KA. Tick Tock: Epigenetic Clock Differences in an Older Monozygotic Twin Cohort. *GeneMappers 2017 Conference.* 26-28 Apr 2017; Geelong, VIC, Australia.

Mather KA. Invited speaker. Genetic and epigenetic studies of human ageing from the Centre of Healthy Brain Ageing, Australia. Leibniz Aging Institute. Sep 2017; Jena, Germany.

Mohan, A. (2017). "Gene expression in the ageing human brain", Behaviour Genetics Association Annual Conference"

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Sachdev P. Invited speaker. The Cognitive profile and role of hypertension, diabetes and other vascular risk factors in post-stroke cognitive function: The STROKOG (Stroke and Cognition) Consortium. *Vascular Neurodegeneration Symposium*. 2 Mar 2017; Melbourne, VIC.

Sachdev P. Invited Speaker. Can science help psychiatry? *6th World Congress of Asian Psychiatry (6th WCAP 2017)*. 24 Mar 2017; Abu Dhabi, UAE.

Sachdev P. Invited Speaker. Maintain Your Brain: A Randomised Controlled Trial of an Internet-Based Multi-Component Lifestyle Intervention to Prevent Cognitive Decline and Dementia [F4-05-01]. *AAIC 2017*; 19 July 2017; London, UK.

Sachdev P. Invited symposium chair for the session, COSMIC: An international consortium of longitudinal studies of cognitive decline and dementia. *16th Congress of the International Federation of Psychiatric Epidemiology;* 17-20 Oct 2017; Melbourne, Australia.

Sachdev P. Invited Speaker. *Community Care & Well Being (CCNB) "Let's talk about dementia: a symposium for families and carers".* 30 June 2017; Sydney, NSW.

Thalamuthu, A. (2017). Workshop on statistical computing using SPSS and R, conducted at the Department of Statistics, Manonmaniam Sundaranar University, Tirunelveli, India. June 1-2, 2017.

Thalamuthu, A. (2017). R-programming and data analysis and meta-analysis. Conducted three day workshop, Organized by the institute for statistics and analytical research (ISAR), Chennai, India, June 5-7, 2017.

Thalamuthu, A. (2017). "Heritability Analysis of Cortical and Subcortical Brain Structures". Invited talk at the International Conference on Statistics for Good Governance, organized by The Institute of Applied Statistics, Sri Lanka, (IASSL), , Taj Samudra hotel in Colombo, Sri Lanka, 28-29th December, 2017

Wu, H. (2017). "MicroRNAs as biomarkers of Alzheimer's disease – validation in Australian and Chinese poulations". Human Genetics Society of Australasia

Wu, H. (2017). "Emerging periperhal blood microRNAs as biomarkers of Alzheimer's disease". International Conference of Alzheimer's Disease International, Kyoto, Japan.