Centre for Healthy Brain Ageing (CHeBA)

PhD Research Topics

PhD Research Topics with Prof Perminder Sachdev

Scientia Professor of Neuropsychiatry, CHeBA Co-Director and Clinical Director of the Neuropsychiatric Institute

1. Epidemiology

This work will be based on the three longitudinal studies of cognitive ageing and dementia being conducted at CHeBA – Sydney Memory and Ageing Study (MAS), Older Australian Twins Study (OATS) and Sydney Centenarian Study (SCS), and three international consortia of studies – COSMIC, STROKOG and ICC-Dementia. Some examples of the potential topics:

a) Ageing and cognitive decline in diverse ethnic and geographical groups.

b) Differential risk and protective factors for MCI and dementia in diverse international cohorts.

c) The differential effects of vascular risk factors on cognitive impairment and decline in Eastern and Western countries.

d) The interaction of genetic and environmental factors in dementia risk.

e) Examining risk factor models for dementia across international cohorts.

f) Longitudinal trajectories of cognitive function and their trajectories.

2. Specific risk factors

a) Homocysteine, brain abnormalities and cognitive impairment.

b) Diabetes, brain changes and cognitive impairment in diverse settings.

c) Nutrition and cognition in diverse populations.

d) The application of new analytical techniques such as machine learning.

3. Neuropsychology

a) Computerised neuropsychological testing – reliability and validity.

b) The cognitive profile of exceptionally old individuals.

4. Neuroimaging

a) The relative effects of vascular and Alzheimer's pathology on cognitive impairment in older individuals.

b) Cerebral microbleeds and their relationship to AD and SVD pathology and cognition.

c) Imaging microinfarcts and examining their significance.

d) The blood-brain barrier (BBB) in vascular dementia and Alzheimer's disease.

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5. Genetics

a) The genetics of exceptional longevity.

b) CNV, ageing and cognition.

c) DNA methylation and its relationship to cognitive function.

d) Rare genetic variants associated with healthy ageing and dementia, using whole genome sequencing.

e) Gene expression and changes with ageing and dementia.

6. Omics and Neurobiology of Ageing Group

a) Plasma biomarkers of ageing, MCI and AD using normal population cohorts (Sydney Memory and Ageing Study [MAS], Sydney Centenarians Study [SCS]) and specialised cohorts such as the Older Australian Twins Study (OATS), Dominantly Inherited Alzheimer Network (DIAN) and Australian Imaging, Biomarker & Lifestyle Study of Ageing (AIBL).

b) Proteomic changes in plasma that associate with ageing and health status (frailty, MCI, APOE allele, etc) and disorders such as MCI and dementia.

c) Explore the functional roles that specific, disease associated proteomic markers play in neurodegenerative diseases of ageing. Specific protein families of interest include: apolipoprotein family (APOE, APOJ, APOH, APOA1, etc), albumin/vitamin binding family (afamin, vitamin D binding protein), sirtuin family, amyloid precursor protein family (Abeta1-40, Abeta1-42 and other variants).

d) Plasma lipidome changes associated with ageing and neurodegenerative disease of ageing. In particular, plasma phospholipids and fatty acid associations with ageing, health status (frailty, MCI, APOE allele, etc) and disorders such as MCI and dementia.

e) Peripheral blood markers of vascular risk and/or CVD which alone, or in combination with markers of AD, can predict the onset of clinical symptoms and vascular dementia progression.

f) Influence of vascular and AD pathology on disruption of neuronal networks as the final common pathway to cognitive impairment using cellular and animal models for both AD (transgenic) and CVD (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 (BBB), and stress response in the genesis of either pathology.

g) Develop and test a series of novel superparamagnetic iron oxide nanoparticles that can penetrate the blood-brain barrier (BBB) and provide a superparamagnetic signal for amyloid imaging using MRI with limited toxicity.

h) Promotion of cellular nicotinamide adenine dinucleotide (NAD+) anabolism as a strategy to improve cellular senescence and cognitive function.

i) In vitro and in vivo studies on polyphenols as an integral strategy in preventing and treating diseases associated with neurodegeneration.

Further information can be found at:

https://cheba.unsw.edu.au/our-people/scientia-professor-perminder-sachdev
https://cheba.unsw.edu.au/research-groups/epidemiology
https://cheba.unsw.edu.au/research-groups/neuropsychiatry

PhD Research Projects with Dr Nady Braidy & Dr Anne Poljak

Omics and Neurobiology of Ageing Group

1. Biomarker discovery in autosomal dominant Alzheimer's disease using proteomics and metabolomics techniques

The most common cause of dementia is Alzheimer's disease (AD), which currently has no cure. Early diagnosis of AD is still challenging but would allow for therapeutic intervention before extensive damage to the brain has occurred, resulting in the clinical symptoms of AD. Biomarkers could prove invaluable for assisting with diagnosis and monitoring the effects of new drugs and therapeutic strategies. Studying the early pathological changes that take place in AD before clinical symptoms are evident is difficult as it cannot be predicted who will develop sporadic late onset AD in the future. By contrast, the rare autosomal dominant form of AD has near absolute certainty of onset in mutation carriers and the age at onset is also predictable based on family history. This enables well-informed prospective studies to identify early changes associated with AD pathology. Furthermore, the relatively young age of these patients minimises age-related changes and co-morbidities, which can interfere with biomarker discovery in older adults.

The PhD student working on this project will apply proteomic and metabolomic techniques to plasma samples from people carrying mutations causing the autosomal dominant form of AD to identify proteins and metabolites that could serve as biomarkers for early AD pathology.

2. Metabolomics for biomarker discovery in neurodegenerative disease

Blood in the form of plasma or serum contains a multitude of low molecular weight metabolites that bear a wealth of information about the physiological state of the individual. The composition of the metabolome is influenced by disease, drugs, genetics, diet and lifestyle. Hence it is not surprising that metabolite signatures can be used to diagnose diseases or predict progression of a disease. Using NMR-based as well as GC- and LC-MS methods, this project will identify metabolite signatures specific for neurodegenerative diseases such as Alzheimer's disease or Vascular dementia.

3. Validation of protein biomarker candidates for Alzheimer's disease and their potential role in AD pathology

Using proteomics methods, we have previously identified a number of proteins that are differentially abundant in plasma from patients with Alzheimer's disease (AD) or mild cognitive impairment, a prodrome of AD, and healthy elderly individuals. These proteins are promising biomarker candidates and we are looking for a PhD student to validate these findings in larger numbers of samples and investigate the potential involvement of these proteins in AD pathology.

4. The role of apolipoproteins in ageing and Alzheimer's disease

Apolipoproteins are constituents of lipoprotein particles, such as chylomicrons, VLDL, LDL and HDL, which transport lipids between tissues for fuel and cholesterol metabolism.

As such, they are crucial components in lipid metabolism with implications for cardiovascular disease, obesity and diabetes mellitus. Recently, apolipoproteins have emerged as a protein family of particular interest in Alzheimer's disease (AD), since alterations in lipid metabolism has been associated with AD pathology and the APOE ε4 allele is the most significant genetic risk factor for AD. Furthermore, plasma levels of clusterin (also known as apolipoprotein J) are emerging as a meaningful biomarker for AD, and carriers of CLU risk alleles show faster rates of cognitive decline. This PhD project will examine the mechanisms by which certain apolipoproteins influence healthy ageing and AD.

Further information can be found at:

https://cheba.unsw.edu.au/our-people/dr-nady-braidy
https://cheba.unsw.edu.au/our-people/dr-anne-poljak

PhD Research Projects with A/Prof Wei Wen

Leader, Neuroimaging Group

1. Connectome of older brains – both structural and functional descriptions.
2. Longitudinal studies of the brain in older brains – atrophy, connectivity and functionality.
3. Predicting the brain ageing trajectory using imaging, genetics and clinical data.
4. Mapping genetic influences on brain structures and functions using the twins design.
5. Functional and structural connectivity and its cognitive relevance.
6. Development of computational algorithms to segment brain lesions.
7. Development of a pipeline for automatic lesion detection and computation.
8. Construction of a MRI index for measuring cerebrovascular disease (CVD) burden: a computational approach (together with Dr. Anbu Thalamuthu).

Further information can be found at:

https://cheba.unsw.edu.au/our-people/associate-professor-wei-wen
https://cheba.unsw.edu.au/research-groups/neuroimaging

PhD Research Projects with Dr Karen Mather

Leader of the Genetics and Epigenomics Group

My research focuses on gaining a better understanding of the genetic and epigenetic factors involved in healthy ageing and age-related decline and disease. These genetic factors include variation at the nucleotide level, epigenetic variation such as DNA methylation, and the transcriptome including non-coding RNA such as miRNAs, epistasis and gene- environmental interactions. Current research is being undertaken using large population cohorts of older Australians. Potential students are more than welcome to come and discuss possible projects with me. Data available will include whole genome sequencing, gene expression data including RNA sequencing, DNA methylation and genome-wide genotyping. There may be opportunities to work in the laboratory.

Potential projects include:

1. The genetics and epigenetics of exceptional longevity.
2. The relationship of the epigenome, particularly DNA methylation, and non-coding RNAs to cognitive function and dementia, the environment and other age-related phenotypes.
3. The transcriptome and ageing.

Further information can be found at:

https://cheba.unsw.edu.au/our-people/dr-karen-mather
https://cheba.unsw.edu.au/research-groups/genetics-and-epigenomics

PhD Research Projects with Dr Anbu Thalamuthu

Statistician, Genetics & Epigenomics Group

Identifying genes and environmental factors responsible for complex traits or disease phenotypes is the focus in human genetics research. The genetic contribution to phenotype variability can be studied based on the data from several types of biological experiments such as DNA, RNA, microRNA and methylation. Environmental factors may include nutrition and behavioural traits. Greater insight and statistical power can be gained though integrated analysis of data from multiple biological experiments together with environmental factors.

Several statistical methodological projects can be developed based on various types of data sets from the genetics and neuroimaging groups in CHeBA.

Some of the potential statistical genetics projects include:

1. Integrated analysis of data sets from multiple genomic experiments.
2. Joint association analysis of multiple phenotypes and multivariate genomic data.
3. Comparative analysis of Centenarian genomes.
4. Genetic basis of structural, functional imaging and brain networks: These include heritability, genetic correlations and cluster analysis of structural and functional brain metrics and networks. Association of analysis of network works modules to multiple age related phenotypes such as memory and cognitive functions.
5. Statistical methods for copy number variant (CNV) calling using sequence data and tests for CNV associations with multiple age related phenotypes.

Further information can be found at:

https://cheba.unsw.edu.au/research-groups/genetics-and-epigenomics
https://cheba.unsw.edu.au/our-people/dr-anbu-thalamuthu