

HEALTHY LONGEVITY GLOBAL COMPETITION

2023 Catalyst Awardees

Sponsor: Ministry of Health of Singapore

Brain structure and function underlying sarcopenia and cognitive decline in ageing – the SG70 study

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PROJECT DESCRIPTION

Sarcopenia and cognitive impairment are two of the most prevalent causes of disability in the aging population of Singapore and around the world. Sarcopenia is a condition of physical frailty marked by loss of muscle mass, strength, and function. Importantly, sarcopenia is associated with an increased risk of cognitive impairment and often co-occurs with neurologic diseases including cerebrovascular disease and dementia. It has been suggested that convergent age-related changes in brain structure and function may underlie this relationship between physical frailty and cognitive function in older adults. However, such possible overlapping neural mechanisms remain poorly elucidated, especially in community-dwelling older adults and Asian populations. Therefore, here we aim to examine brain structural and functional underpinnings of sarcopenia and cognition in 250 Singaporean community-dwelling older adults from the SG70 cohort, nested in the prospective Singapore Chinese Health Study cohort. We hypothesize that the key measures of sarcopenia would be related to specific brain microstructure and functional network measures, which would in turn link to domain-specific cognition and midlife lifestyle factors. This study is the first step to understand the shared neural mechanisms underlying physical-cognition relationship in ageing. Outcomes of this study would allow future longitudinal characterization of brain-physical-cognition trajectories and facilitate the development of new interventions to mitigate age-related cognitive and physical decline.

Brain-Computer Interface based Neuroenhancement System for Sustaining Short-term Memory, Focused Attention, Visuospatial Attention and Error-related Potentials in Mild Cognitive Impairment Patients

Principal Investigator	Vinod Achutavarrier Prasad
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PROJECT DESCRIPTION

Mild Cognitive Impairment (MCI) has been identified as an early sign of more severe neurological disease and is considered a prodromal state to clinical Alzheimer's disease. The main symptoms of MCI are loss of short-term memory, attentional processing and visual/spatial perception. There is presently no proven pharmacological treatment for MCI. Hence, there is increasing interest in the use of Brain Computer Interface (BCI)-based Neurofeedback Training (NFT) that could potentially regulate brain activity underlying the symptoms of MCI, targeting slowing down the deterioration of cognitive functions. BCI-based NFT utilizes operative conditioning principles by selectively enhancing or suppressing the frequency, location, amplitude, or duration of a specific brain activity which allows subjects to maintain their brain state in a desirable condition and to improve their cognitive function through training. This project will develop computer games controlled by a non-invasive wireless Electroencephalograph-based BCI for MCI patients that will help to slow down the deterioration of their cognitive capabilities of sustained attention, short-term memory and visuospatial attention, by fine-tuning their respective neural correlates. We will investigate Error-related Potentials (ErrP) evoked in short-term memory and visuospatial attention (VSA)-based target selection task, and quantify the modulations in ErrP caused by the severity of the error, which in turn help to develop subject-specific NFT interventions. The project will develop a computer-based virtual system mimicking daily life scenarios that can be controlled by focussed attention, short-term memory and VSA using BCI, assess the impact of the training sessions on MCI patients, and recommend optimized subject-specific NFT interventions.

DNA methylation status in human pancreatic islets as a function of biological metabolic health

Principal Investigator	Adrian Teo
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Co-Investigator(s)	Co-Is: Brian Kennedy, NUS

PROJECT DESCRIPTION

Ageing is a major risk factor for diabetes, with one in three elderly Singaporeans having diabetes. However, the link between ageing and beta cell failure in diabetes remains unclear. Increasingly, there is substantial evidence pointing to epigenetic alterations that are associated with ageing, giving rise to age-related diseases. A small number of studies have started to evaluate the link between DNA methylation in islets and diabetes in ageing. However, the studies suffered from low sample size or lack of tissue-specificity. Here, we hypothesise that as pancreatic islets age, key functional genes are differentially methylated, altering gene expression and metabolic function/health. We aim to 1) determine the DNA methylation status of human pancreatic islets and their correlation with chronological age, and 2) correlate the transcriptome of human pancreatic islets with DNA methylation status and identify key beta cell genes that are dysfunctional with ageing, leading to beta cell functional decline. Using machine learning, we will derive an islet-specific algorithm (epigenetic clock) to predict beta cell biological age and metabolic health of an ageing individual. We will also identify beta cell genes that can potentially be altered to improve beta cell functional decline in ageing. Overall, the improvement of metabolic health of ageing individuals will delay the onset of metabolic disorders such as diabetes.

Drug discovery and mechanism investigation in novel 3D systemic in vitro model for Alzheimer's disease

Principal Investigator	ZHANG YIZHONG
PI Primary Affiliation	BII - Bioinformatics Institute
Co-Investigator(s)	Co-Is: Frank Eisenhaber, BII Mohammad Alfatah. BII

PROJECT DESCRIPTION

Human life expectancy has been rising drastically over the past two centuries, healthspan does not increase to the same degree as lifespan due to chronic diseases accompanying aging. For example, Alzheimer's disease is a neurodegenerative disorder characterized by the profound loss of cognitive functions and behavioral abilities. The number of affected individuals is growing rapidly due to the aging of human populations, and the severe effects of such diseases on the quality of life have increased the burden on healthcare systems and societal support systems. Currently, there is neither effective treatment nor a clear understanding of the disease's pathophysiology. It is crucial to build a new model for Alzheimer's disease that is both human origin and systemically representative. In this proposal, we aim to develop a medium-throughput assay to validate chemicals we previously identified to extend the cellular lifespan in an Alzheimer's disease model. We also aim to combine previously available iPSC cells, 3D organoids, and fluidic systems to construct an integrated system that provides a highly accurate model for Alzheimer's disease in vitro. This novel model will be used to analyze the mechanism of action of chemical compounds, providing new insights into the disease's pathophysiology.

Investigating Associations Between Biological Age measured by Blood-Based DNA Methylation, with Cognitive Performance, Neuroimaging Markers and Conversion to Dementia – A Nested Case Control Longitudinal Study

Principal Investigator	Ming Ann Sim
PI Primary Affiliation	National University Hospital (NUH)
Co-Investigator(s)	Co-Is: A/Prof Christopher Chen, NUS Prof Andrea Britta Maier, NUS Collaborators: Prof Roger Foo Sik Yin, IMCB Dr Rajkumar s/o Dorajoo, GIS

PROJECT DESCRIPTION

This proof-of-concept study will leverage upon an existing memory clinic cohort, with longitudinal data collected. 360 patients stratified into 3 groups for inclusion: 60 dementia converters, 150 cognitively normal controls, 150 with baseline dementia.

The primary outcomes are 1) Cross-sectional cognitive performance, 2) Neuroimaging markers, and 3) Longitudinal conversion to dementia with 4) Stratification for dementia causative subtype.

High-throughput measurement of DNA methylation on a genome wide scale will be performed. Four machine-learning derived blood-DNA methylation aging clocks will be calculated. Differences in DNA methylation clocks will be evaluated on cross-sectional and longitudinal analysis of cognitive outcomes. The incremental predictive value of DNA methylation clocks will be compared with existing circulating biomarkers for dementia.

Differentially methylation region analysis and gene pathway analysis will be employed to identify significant differences in methylation profile with regards to neurocognitive outcomes of interest.

Taken together, this study will 1) Investigate biomarkers of biological age which may add predictive value to current markers for dementia, 2) Uncover mechanistic insights between the epigenome and dementia pathophysiology; and 3) Identify potential therapeutic targets for dementia.