

HEALTHY LONGEVITY GLOBAL COMPETITION

2025 Catalyst Awardees

Sponsor: Ministry of Health of Singapore

A single-arm, open-label study to examine the effectiveness of an accelerated theta burst stimulation to enhance cognitive function among patients with amnesia mild cognitive impairment

Principal Investigator	Xiaowei Tan
PI Primary Affiliation	Institute of Mental Health
Co-Investigator(s)	Dr Yao Fengyuan, MD. Dr Tor Phern Chern, MD. Dr Goh Shih Ee, MD. Dr Jonathan Lee, MD

PROJECT DESCRIPTION

Emerging evidence suggests that repetitive transcranial magnetic stimulation (rTMS) enhances cognition in patients with mild cognitive impairment (MCI). Accelerated intermittent theta burst stimulation (iTBS), the subtype of rTMS protocols, is promising to treat MCI as it substantially reduces disease burden by shortening the treatment course, but the effectiveness, safety, feasibility, and acceptability of iTBS have not been established.

A total of 30 adults with amnesic MCI will be enrolled in a phase I trial of a single-arm, open-label study of an accelerated iTBS targeting the left dorsolateral prefrontal cortex (five stimulation sessions of 1800 pulses of iTBS/day for five working days). Enrolled participants will complete a neuropsychiatric evaluation toolbox, which includes several memories, mood conditions, daily functional activities, subjective quality of life and other cognitive function tests before and after treatment and being followed up for three months. The primary outcome is the change in the Montreal Cognitive Assessment score immediately after treatment. Participants will also rate possible common side effects during and after treatment.

The findings of this trial will help to examine the treatment effectiveness, feasibility, and safety profile of a novel accelerated iTBS treatment regime among the local aged population to improve cognitive function as well as mood conditions. This intervention might also delay the conversion rate of MCI to dementia and provide preliminary data for a larger scale study with longer-term follow-up to assess the clinical utility of precision and personalized iTBS as a preventive tool for dementia disease.

Harnessing Metaplasticity Through Transcranial Direct Current Stimulation: A Novel Approach to Combat Age-Related Cognitive Decline

Principal Investigator	Saji Kumar Sreedharan
PI Primary Affiliation	National University of Singapore
Co-Investigator(s)	Tor Phern Chern, MBBS (Singapore), MMed (Psychiatry), FAMS, Department of Psychological Medicine, National University Hospital, Singapore Xiaowei Tan MBBS, Ph.D,

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PROJECT DESCRIPTION

Age-related cognitive decline compromises health and independence, largely due to impairments in neural plasticity and memory mechanisms. This project investigates whether transcranial direct current stimulation (tDCS) can fine-tune metaplasticity—an adaptive process that regulates synaptic plasticity thresholds—to preserve memory and enhance cognition in aging brains. We hypothesize that tDCS restores aberrant metaplasticity in aged neural networks, thereby improving synaptic plasticity and associative memory.

Using an optimized Animal Transcranial Electrical Stimulation (tES) system, we will apply precisely controlled tDCS protocols in aged (22–24 months) and young control (2–3 months) rodents. Cognitive outcomes will be evaluated through behavioral tasks, while electrophysiological recordings will assess synaptic plasticity, including mechanisms such as synaptic tagging and capture (STC). Efficacy will be measured at one day, one week, and one month post-stimulation to establish both immediate and sustained effects.

This study leverages existing laboratory infrastructure and collaboration with clinician-scientists specializing in transcranial magnetic stimulation (TMS). Their expertise will help standardize metaplasticity time windows, enhancing translational relevance. Expected outcomes include identifying effective tDCS protocols for restoring metaplasticity and generating mechanistic insights into how neural plasticity can be maintained during aging.

The findings will lay the groundwork for non-invasive interventions against cognitive decline and provide essential preclinical data to support larger collaborative grants and future clinical trials. Ultimately, this project seeks to bridge preclinical discoveries with real-world healthcare solutions, advancing scalable therapies to improve cognitive resilience in aging populations.

High-throughput screening to identify drugs that reverse aging clocks in vitro and could mitigate progeroid phenotypes

Principal Investigator	Prof. Brian Kennedy
PI Primary Affiliation	National University of Singapore
Co-Investigator(s)	Vincenzo Sorrentino Prof. Jan Gruber Kamil Pabis, Oliver Dreesen, Tay Jian Hua

PROJECT DESCRIPTION

Our long-term goal is to find drugs that can slow the process of aging, thereby improve neurocognitive outcomes in the elderly, and substantially boosting healthy lifespans. Towards this goal, we aim to develop a new in vitro epigenetic clock (“CellPopAgeV2”) and use it screen for drugs that reverse epigenetic aging clocks. The CellPopAgeV2 clock will be a dual-purpose clock optimized for high-throughput screening which captures aspects of in vitro cell aging, while maintaining the ability of predicting mortality from blood.

Furthermore, we will combine the screening hits with data from internal screens and published databases to identify candidates most likely to improve aging, progeroid and neurodegenerative phenotypes. The internal screens include a large screen for lifespan extending drugs in yeast and another screen for activators of the TFEB/autophagy pathway. Published databases include DrugAge to identify hits that extend lifespan, earlier published data from studies that used the LOPAC library and Cmap to identify candidates most likely involved in neurodegeneration pathways.

As a proof of principle, we will test whether the identified candidates improve progeroid phenotypes in vitro at the end of the grant period. Finally, these candidates will be tested in mouse models, invertebrates and human studies using internal funding or future Catalyst funding.

In silico discovery of natural NNMT inhibitors as Alzheimer's disease therapeutics

Principal Investigator	Vincenzo Sorrentino
PI Primary Affiliation	National University of Singapore
Co-Investigator(s)	Prof Sajikumar Sreedharan, Ph.D, NUS Cui Liang

PROJECT DESCRIPTION

Alzheimer's disease (AD) is the most common dementia type, affecting around 8.8% of Singaporeans aged 60 and above. No effective therapies exist, and drug development has yet to achieve consistent clinical improvement.

Recent findings highlight the role of nicotinamide adenine dinucleotide (NAD⁺) metabolism in AD and brain health. NAD⁺ is essential for energy metabolism and DNA repair; its depletion is implicated in AD pathology. Another critical alteration observed in AD is epigenetic changes of the brain. These have been linked to risk and progression of AD, likely contributing to the dysregulation of AD-related gene expression.

In mammals, the primary methyl donor involved in DNA methylation events is S-adenosylmethionine (SAM), whose modulation has also been linked to AD.

Importantly, the cross-talk between NAD⁺ metabolism and SAM-mediated methylation processes is controlled by the enzyme nicotinamide N-methyltransferase (NNMT). NNMT uses SAM to methylate nicotinamide (NAM), a vital NAD⁺ precursor, impacting NAD⁺ synthesis. Increased NNMT expression in AD disrupts both NAD⁺ and epigenetic regulation, making NNMT inhibition a promising therapeutic approach to optimize NAD⁺ and SAM in the brain, potentially slowing AD progression.

This project aims to discover and validate the first natural NNMT inhibitors to ameliorate AD pathology. The approach includes in silico compound library screenings and NNMT structure prediction, validation of inhibitors in neuronal cells, and mechanistic exploration in AD rodent models. Identifying first-in-class natural NNMT inhibitors for brain health applications holds potential for rapid clinical development of supplements or novel pharmaceuticals, offering an alternative approach to managing AD and related conditions.

Reversing Brain Aging Through Individualized fMRI-Based Thought Manipulations

Principal Investigator	Junhong Yu, PhD
PI Primary Affiliation	Nanyang Technological University
Co-Investigator(s)	Goh Wen Bin Wilson, PhD; Andrea Maier, MD PhD FRACP

PROJECT DESCRIPTION

Our brains can 'age' more rapidly in relation to disease and ill health, making them appear older than those of healthy individuals of the same age. Such 'older' brains are often associated with impairments in memory and other mental abilities. We propose a personalized method to "rewire" the brain, making it appear younger and thereby reversing brain aging. Unlike typical treatment approaches, designed in a one-size-fits-all manner to improve brain health, that shows limited success, we calibrate our approach according to our participant's neural characteristics. In the proposed study, 62 seniors, who have a normal level of cognitive functioning, will be recruited to take part in our research. We will study their brain activity as they watch a movie while being scanned in the magnetic resonance imaging scanner. This information will be used to guide participants to recreate 'youthful' thoughts with the aid of personalized sets of AI-generated images. We believe that these youthful thoughts will rewire the brain and ultimately reverse brain aging. This study represents the first attempt to reverse brain aging on a personalized level, potentially leading to new strategies for enhancing brain health tailored to each individual's unique neural responses.

Vocal Biomarkers for Early Detection and Subtype Differentiation of Mild Cognitive Impairment in Singapore

Principal Investigator	Feng Lei
PI Primary Affiliation	National University of Singapore
Co-Investigator(s)	Bao Zhiming Cao Luwen Christopher Chen Li Hsian

PROJECT DESCRIPTION

Singapore's rapidly aging population faces a growing burden of dementia, making early detection of Mild Cognitive Impairment (MCI) and its subtypes a critical public health priority. Current MCI diagnostic methods, such as neuropsychological assessments and neuroimaging, are often resource-intensive and not readily scalable for population-level screening. This research investigates acoustic voice analysis as a novel, cost-effective, and non-invasive approach for MCI detection and subtype differentiation (amnesic and non-amnesic) in older Singaporeans. We hypothesize that subtle, quantifiable changes in specific voice quality parameters reflect underlying neurological and cognitive decline, differentiating individuals with MCI from healthy controls. This differentiation is crucial early identification, and for enabling more personalized intervention tailored to specific cognitive deficits. We did a preliminary acoustic analysis of 100 voice recordings from older Singaporeans with and without MCI, and the results are promising. In collaboration with the Mind Science Centre and the Memory Aging and Cognition Centre (MACC) at NUS, the proposed study employs a combined cross-sectional and longitudinal design. We will use existing voice recordings from MACC's cohort studies (30% with MCI) and contribute to collect new data, which will enable us to investigate the predictive validity of vocal biomarkers for conversion to dementia and for subtype-specific trajectories. This research aims to identify and validate vocal biomarkers for MCI subtypes and establish the feasibility of voice analysis as a scalable screening tool readily integrated into Singapore's healthcare system, ultimately enabling earlier intervention, improved disease management, and a reduction in societal and economic impact of dementia in Singapore.