PRESS RELEASE

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NUS Medicine study: Brain connectome phenotype linked to cerebrovascular disease can track cognitive decline

Singapore, *13 January 2025* – Researchers have uncovered novel insights into how brain function disruptions related to cerebrovascular disease (CeVD) interact with Alzheimer's disease (AD) pathology to impact neurodegeneration and cognition in older adults. Led by Associate Professor Juan Helen Zhou, Director of the Centre for Translational Magnetic Resonance Research, Yong Loo Lin School of Medicine, National University of Singapore (NUS Medicine), the research team revealed a brain functional connectome phenotype that is related to multiple CeVD markers and contributes additively to cognitive decline and neurodegeneration alongside AD. The study highlights CeVD as a global disruptor of brain connectivity, reshaping our understanding of its role in dementia.

CeVD, often co-occurring with AD, has long been a significant area of study in ageing and dementia research. It refers to a group of conditions that affect the blood vessels and blood flow in the brain, such as stroke, cerebral atherosclerosis (narrowing or hardening of larger brain arteries due to plaque buildup), and small vessel disease that affects the tiny blood vessels in the brain. These conditions can lead to brain damage by disrupting the delivery of oxygen and nutrients, which are essential for normal brain function.

In the study, published in *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, the team examined the brain's functional organisation in 529 older adult participants across the dementia spectrum, ranging from those with healthy cognition to individuals diagnosed with AD. Analysing how the different markers of CeVD and brain activity patterns correlate to affect the participants, the team identified a global functional connectome phenotype, or a unique pattern in the brain's communication network, that is strongly associated with high levels of burden of four markers of CeVD seen on brain scans. A key finding of the study was the identification of divergent effects of *p-tau181*, a blood-based biomarker for AD, and CeVD-related functional connectome phenotype on cognitive decline and brain atrophy. While the two factors contributed additively to longitudinal cognitive decline and brain atrophy, the study found no evidence of a synergistic relationship between CeVD and *p-tau181*, suggesting that these factors may influence neurodegeneration in distinct pathways.

A/Prof Zhou said, "We discovered that a CeVD-related brain network phenotype, along with a key Alzheimer's disease blood biomarker, can provide powerful insights into the future trajectory of cognitive decline and neurodegeneration. Our findings highlight the potential of brain connectome-based markers to track cognitive decline, particularly for individuals at-risk for dementia, and underscore the importance of integrating neuroimaging and blood biomarkers to better understand the pathophysiology of these co-occurring diseases."

Dr Joanna Su Xian Chong, senior research fellow from A/Prof Zhou's group, who is also first author of the study, added, "This pattern shows how the burden of multiple cerebrovascular disease markers can collectively exert widespread influences on brain function. Importantly, the combination of this pattern linked to CeVD and plasma *p-tau181*, a marker of Alzheimer's disease, had independent and additive effects on long-term outcomes. Together, they contributed to cognitive decline and increased brain atrophy at baseline and over time, but did not interact directly to amplify each other's effects." Both A/Prof Zhou and Dr Chong are also from the Centre for Sleep and Cognition and Healthy Longevity & Human Potential Translational Research Programmes at NUS Medicine.

Moving forward, the team aims to explore how the brain communication pattern linked to CeVD is affected by the severity, cause, and location of CeVD markers throughout the progression of the disease. They also plan to investigate how this pattern interacts with different AD markers to contribute to brain degeneration and decline in multiple cognitive domains. Additionally, they aim to determine if these brain network features can be used as a reliable biomarker to monitor current and future cognitive decline, particularly in individuals at risk for dementia. These features could offer more precise predictions than traditional brain imaging methods and help identify long-term cognitive outcomes earlier. Their goal is to better understand the brain mechanisms behind CeVD and AD to develop advanced imaging tools for early detection and disease monitoring.

This research is supported by the National Research Foundation, Singapore under the NMRC Open Fund – Large Collaborative Grant (MOH-000500) and administered by the Singapore Ministry of Health through the NMRC Office, MOH Holdings Pte Ltd. Participants for the study were recruited from the National University Hospital and St Luke's Hospital.

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Our multidisciplinary and real-world approach to education, research and entrepreneurship enables us to work closely with industry, governments, and academia to address crucial and complex issues relevant to Asia and the world. Researchers in our faculties, research centres of excellence, corporate labs and more than 30 university-level research institutes focus on themes that include energy; environmental and urban sustainability; treatment and prevention of diseases; active ageing; advanced materials; risk management and resilience of financial systems; Asian studies; and Smart Nation capabilities such as artificial intelligence, data science, operations research, and cybersecurity.

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Through a dynamic and future-oriented five-year curriculum that is inter-disciplinary and inter-professional in nature, our students undergo a holistic learning experience that exposes them to multiple facets of healthcare and prepares them to become visionary leaders and compassionate doctors and nurses of tomorrow. Since the School's founding in 1905, more than 12,000 graduates have passed through our doors.

In our pursuit of health for all, our strategic research programmes focus on innovative, cutting-edge biomedical research with collaborators around the world to deliver high impact solutions to benefit human lives.

The School is the oldest institution of higher learning in the National University of Singapore and a founding institutional member of the National University Health System. It is one of the leading medical schools in Asia and ranks among the best in the world (Times Higher Education World University Rankings 2024 by subject and the Quacquarelli Symonds (QS) World University Rankings by subject 2023).

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About the National Medical Research Council (NMRC)

The NMRC was established in 1994 to oversee research funding from the Ministry of Health and support the development and advancement of biomedical research in Singapore, particularly in the public healthcare clusters and medical schools. NMRC engages in research strategy and planning, provides funding to support competitive research grants and core research enablers, and is responsible for the development of clinician scientists through awards and fellowships. The council's work is supported by the NMRC Office which is part of MOH Holdings Pte Ltd. Through its management of the various funding initiatives, NMRC promotes healthcare research in Singapore, for better health and economic outcomes.