Project Details	
Project Code	NMH27Ca Murphy
Title	Unravelling the Physiological Drivers of Sleep-Dependent Glymphatic Flow in Alzheimer's Disease using Advanced MRI
Research Theme	Neuroscience & Mental Health
Project Type	Other
Summary	Poor sleep is linked to increased future dementia risk. The SleepBoost study is a £4.3m multi-centre investigation into this link and aims to demonstrate interventions that improve slow-wave sleep can increase waste clearance in the brain, which may slow or even reverse Alzheimer's disease (AD) pathology. In this PhD project, advanced magnetic resonance imaging (MRI) measures of brain blood vessel function and cerebral spinal fluid flow will be implemented to demonstrate the mechanisms by which improved waste clearance can occur. The work will augment the truly revolutionary SleepBoost study that hopes to change the future of AD treatment.
Description	Background Over 55 million people worldwide live with dementia, costing over US$1.3trillion annually. Alzheimer's disease (AD), the most common form, is slowly progressive, with changes occurring in the brain long before noticeable clinical symptoms. Early treatment is optimal for retaining independence and quality of life. Current disease-modifying therapies are not very effective, with cost and side-effects often a barrier to treatment. Good sleep is key for general health and well-being, with poor sleep linked to increased future dementia risk. Modifying sleep quality is an untapped opportunity to delay neurodegenerative diseases such as AD, promoting physiological processes that improve cognition, mental health and wellbeing. Disturbances in non-REM, slow-wave sleep cause short-term reductions in cerebral spinal fluid dynamics, a key component of the brain's glymphatic system. Brain glymphatic function and cerebral spinal fluid (CSF) flow pathways are emerging as clinically significant markers of neurological and neuropsychiatric health. Glymphatic function supports the clearance of metabolic waste by driving CSF through perivascular spaces and facilitating exchange with interstitial fluid. Glymphatic dysfunction can lead to impaired waste clearance and accumulation of potentially toxic Alzheimer's-related proteins, impairing synaptic plasticity and memory consolidation. An intervention that improves slow-wave sleep, thus improving glymphatic function and associated waste clearance, may slow or even reverse Alzheimer's-associated pathologies. The SleepBoost study The £4.3m SleepBoost study was recently funded by the MRC and is led by Prof. Coulthard. The aim is to determine the mechanisms by which slow-wave sleep is linked to Alzheimer's pathology. A randomized, multi-site, placebo-controlled design will study three year-long interventions that have defined effects on slow-wave sleep. The focus will be on individuals in the early clinical stages of AD, a critical window for intervention where mild cognitive problems are present but daily independence is still maintained.

	The SleepBoost study consists of many work packages and sub-studies in a number of research centres and hospitals across the UK; using Magnetic Resonance Imaging (MRI), fluid biomarkers and genetic technologies. The MRI arm is led by Cardiff University Brain Research Imaging Centre (CUBRIC). The core MRI study, which all participants across the country will undergo, consists of structural measures to assess cortical thickness, brain region volumes, white matter hyperintensities (WMH) linked to small vessel disease, quantification of perivascular spaces, iron deposition, microbleeds and white matter microstructural properties. CUBRIC will also be running the extended MRI sub-study (60 participants). This leverages our world-leading expertise in imaging cerebrovascular physiology and function with MRI. More advanced structural measures (sensitive to myelination, neuromelanin and the locus coeruleus) will be coupled with our cutting-edge MR sequences that measure vessel structure, cerebral blood flow, arterial arrival times, arterial pulsatility, venous oxygenation and blood flow dynamics. Cerebrovascular function is inherently linked to glymphatic function, since arterial pulsatility is thought to be the driver of CSF flow around the brain. The extended MRI sub-study of the SleepBoost study offers a PhD student the unique opportunity to demonstrate that this phenomenon is measurable with MRI and that the measurements are sensitive enough to track improvements in glymphatic flow after AD-targeting interventions. Key Research Questions Can advanced MR measures of cerebrovascular function demonstrate the link between arterial pulsatility and glymphatic function? Can they help unveil the mechanisms behind improvements in glymphatic dysfunction in early AD patients after a slow-wave sleep intervention? Specific PhD Objectives Over the course of the PhD, the student will: 1) Using measures from both the core and extended MRI study, demonstrate the link between cerebrovascular function, arterial pulsatility and clinically relevant measures of brain structure (e.g. choroid plexus volume), in participants who are known to have reduced glymphatic function. 2) Optimise the analysis of the advanced cerebrovascular measures to directly demonstrate the link between arterial pulsatility and CSF flow, thus unveiling the physical mechanisms behind glymphatic function and waste clearance. 3) Validate the sensitivity of these methods in tracking improvements in glymphatic function in early AD after a year-long intervention to improve slow-wave sleep. Student Ownership and Opportunities: By being embedded in SleepBoost, a large, prestigious, multi-centre study, this project presents an excellent opportunity for a PhD student to interact with world-renowned researchers in a wide range of scientific areas across the UK. Research outputs from this project will feed into and augment a truly revolutionary study that hopes to change the face of AD treatment. Due to the sheer scale of the data collection, the student will have the freedom to follow their interests and ideas in this

	area throughout the project. Taking advantage of the 50 free hours of scanning that CUBRIC offers PhD students, they will be able to add extra measurements as their interest and expertise develops. Throughout the PhD, the student will gain cutting-edge skills in neuroimaging, neurodegeneration, cerebrovascular physiology, advanced data analyses and multi-modal data synthesis, leaving them ideally placed to excel in their future academic research career.
Can be completed part time?	Yes
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