Project Details	
Project Code	MRC22NMHEx Belle
Title	Understanding how altered GABA signalling in the brain's master clock contributes to circadian rhythm disruption in Alzheimer's disease.
Research Theme	Neuroscience & Mental Health
Summary	Circadian rhythm times our sleep and its disruption exacerbates Alzheimer's disease (AD) pathology. The brain's master clock uses GABA for circadian timekeeping. GABA signals are affected in AD, but the effect on clock function is unknown. We will study how GABA drives excitability in healthy and AD mouse clock neurons, to restore clock function and improve health.
Description	Our daily or circadian body clock is one of the most important timing systems in our body, ensuring that the neuronal activity throughout our CNS is appropriately aligned with our homeostatic, physiological, and behavioural needs across the day. These needs include the timing in our sleep-wake cycle, peak cognition ability, and optimum brain toxin clearance, such amyloid-Beta (AB). Disruption of this daily rhythm can lead to severe health consequences, which include premature ageing and mental health disorders. Indeed, circadian rhythm disruption is a common symptom of Alzheimer's disease (AD) and recent knowledge has identified that circadian disruptions often occur early in the course of the disease and may precede the development of cognitive symptoms. The sleep–wake cycle regulates the levels of pathogenic AB peptide and tau in the brain, and manipulating the sleep-wake cycle can influence AD-related pathology in mouse models. Indeed, the circadian system has long been identified as having a key role in the neurodegenerative process of AD. In mammals, the master circadian clock is found in a region of the hypothalamus called the suprachiasmatic nucleus (SCN). In the SCN, the activity of clock genes produces daily excitability rhythms in SCN neurons, making them fire at higher rates during the day with high intracellular calcium and less active at night with low intracellular calcium. This daily rhythm in clock and electrical activity is well-conserved between Drosophila and mammals, and is vital for clock function, promoting well-being, cognition, and health, but blunts in ageing and AD in both models. GABA is the main neurotransmitter in the SCN and is critical for the generation of circadian rhythms. Remarkably, although GABAergic signalling in the SCN is critical for our sense of daily rhythm, and is affected during AD, the mechanisms governing how GABA signals regulate SCN electrical and intracellular calcium activity remain poorly understood. Here, we will investigate when and how GABA signalling regulates SCN neurophysiology, clock gene rhythms, and behaviour in healthy and AD-mice. To achieve this, we are combining some state-of-the-art electrophysiology, imaging, and optogenetic methods, with circadian clock activity-reporting transgenic mouse models (Period1-Venus mouse without or containing human AB or Tau), and sophisticated behavioural measurements and computational analysis. To understand the impact of AD on brain-wide clock function, which is possible in the fly but difficult in mice, we will perform appropriate clock and calcium imaging studies in healthy Drosophila and AD-fly models throughout their lifespan. The hope is to appropriately combine our knowledge from both organisms to

	understand how a deficient and weakened master circadian clock contributes to AD pathology, and identify key GABAergic mechanisms and therapeutic targets. These targets will then be screened in Drosophila to restore clock function in aged and AD flies, and see if it rescues sleep and memory loss, neurodegeneration, and shortened lifespan. This will then be translated to mammals.
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