Alzheimer's disease risk factor: Circadian regulation of synaptic function and neurodegeneration in the brain

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Brain ageing is associated with the development of cognitive impairments (dementia). These effects are particularly pronounced in age-associated neurodegenerative diseases, such as Alzheimer's disease (AD). AD patients typically suffer from abnormal behavioural and physiological symptoms, including aberrant sleep-wake cycles. The implication of this is that the circadian day-night cycle has a critical role in brain function. Our endogenous circadian rhythm and sleep-wake cycle is driven by 'clock' genes. How clock gene dysregulation might have pathological consequences is an important as yet unanswered question, especially given that dysfunction of the body's circadian clock system can exacerbate neurodegeneration.

Here we suggest a pivotal link between sleep-pattern and bran function: we and others have reported a relationship between circadian rhythm related stress and brain atrophy. Whilst glucocorticoid levels oscillate as a function of the circadian rhythm, their levels actually impact on the activity of clock genes. This project therefore seeks to define the causal interactions between (1) circadian clock genes and AD pathology in postmortem human brain tissue, and (2) the sleep patterns and cognitive function in early and progressed stages of AD. Our approach will utilise two complementary strands driven by an established working group within Bristol (Kei Cho, Stafford Lightman, Elizabeth Coultard, Daniel Whitcomb):

Strand 1: Map the relationships between clock gene regulation (including proteome) and progression of Alzheimer's disease from postmortem human brain (Supervised by Cho, Whitcomb and Lightman).

Strand 2: Characterise the impact of sleep-awake pattern in glucocorticoid production and determine the consequences on cognition in different stages of AD patients (Supervised by Coultard, Lightman, Cho).

Reference:
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