Project Details	
Project Code	MRC23NMHBr Piggins
Title	Run for Your Life: Leveraging Exercise to Protect Against Dementia
Research Theme	Neuroscience and Mental Health
Summary	Regular physical exercise is beneficial for health and longevity. As we age, many people adopt a sedentary lifestyle which can accelerate decline in brain activity, cognition, and body clock rhythms such as sleep. Incorporating daily regular exercise could promote physical and mental well-being and this project will investigate if and how timed voluntary exercise protects against decline in brain and body clock function in a mouse model of Alzheimer's disease.
Description	Regular physical exercise is fundamental to optimal health and longevity. It promotes cognitive function and can stabilize sleep-wake cycles and regularity in our body's homeostatic state including food and drink intake. In neurodegenerative conditions such as Alzheimer's disease, Parkinson's disease, and Huntington's Disease, cognitive decline is accompanied by impairments in sleep-wake, appetite, thirst, etc. Current evidence indicates that regular physical exercise could be protective in neurodegenerative conditions, but brain regions targeted by exercise remain largely unknown. A likely target is the hypothalamus, the brain's hub of circadian and homeostatic control. Since cognitive decline characterizes neurodegenerative diseases, the focus of much research in this discipline is on learning and memory brain circuits such as the medial prefrontal cortex. By contrast, investigation and understanding of hypothalamic involvement in these diseases is neglected. The lateral septum connects the brain's main learning and memory circuits with energy balance and sleep control centres in the hypothalamus and is affected in mouse models of Alzheimer's disease. Receptors for the hormone, glucagon-like peptide 1 (GLP-1), are expressed in the lateral septum and stimulation of brain GLP-1 receptors enhances cognition and regulate appetite. Physical exercise influences levels of GLP-1 and in this project, the student will assess the hypothesis that regular exercise and GLP-1 signaling are protective cognitive, circadian, and homeostatic decline in a mouse model of Alzheimer's disease. The project will use the J20 mouse line, a validated mouse model of Alzheimer's disease, which overexpresses a mutant form of APP, and will evaluate how timed physical exercise in a running wheel and GLP-1 signaling alter the time-course in decline in learning and memory, brain activity, and daily rhythms in ingestive behavior and sleep. Mice will be housed under different conditions of running-wheel availability and/or administration of GLP-1 receptor stimulants and assessed at different stages of the lifespan for cognitive performance and robustness in circadian rhythms of ingestive behave. Brain activity will be assessed using state of the art multielectrode array recordings as well as electroencephalography. Immunohistochemistry, tract-tracing, and electrophysiology will be used to determine how the lateral septum signaling to the hypothalamus is affected by exercise and GLP-1 agonists at different stages of the lifespan. Specifically, the project will assess: 1) Does scheduled voluntary exercise in a running-wheel delay cognitive decline and disruptions in circadian rhythms and sleep? 2) Does acute treatment with GLP-1 ameliorate cognitive and circadian decline? 3) Is

	communication by the lateral septum to the hypothalamus altered by scheduled voluntary exercise and/or GLP-1? 4) Do scheduled voluntary exercise and GLP-1 signaling exert their effects independently or can they augment each others actions? The Brown and Piggins labs have extensive experience and expertise in neurodegenerative disorders and circadian rhythms and are very well equipped to conduct this research. The student will be supported by experienced post-doctoral researchers as well as other PhD students. This project will build on recent findings (Hughes et al., Commun. Biol. 2021) to explore the effectiveness of regular physical exercise in ameliorating decline in a mouse model of dementia.
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