Project Details	
Project Code	MRCNMH24Br Robinson
Title	Investigating the neurobiological mechanisms underlying apathy in Parkinson's disease
Research Theme	Neuroscience & Mental Health
Summary	Apathy is a debilitating and highly prevalent symptom in people with Parkinson's disease. It is often refractory to conventional dopaminergic therapy and is associated with poorer health-related quality of life. No specific treatment for apathy exists, partly as little is known about its neurobiology. Using clinical data and preclinical in vivo methods, this project aims to investigate the neurobiology of apathy and explore the mechanisms of promising therapeutics.
Description	Apathy is a prominent and severe non-motor psychiatric symptom of Parkinson's Disease (PD). It is multi-dimensional, consisting of behavioural, emotional and cognitive symptoms which ultimately lead to a loss of motivation to engage with and react appropriately to the environment. It is associated with poor response to motor-related treatments, increased risk of dementia and overall poorer health-related quality of life for both the patient and the caregiver. Despite this, no specific treatment regime for apathy currently exists, and little is known about its underlying neurobiology. This project seeks to advance our understanding of the biological mechanisms and behavioural changes associated with apathy in PD. During the first year of the PhD, the student will work with Dr Henderson, lead of a large UK Clinical Trial investigating the benefits of the anticholinesterase inhibitor, rivastigmine as an adjunct treatment for PD patients. The student will have access to a large data set obtained from these patients which includes a number of behavioural, emotional and cognitive measures. They will investigate both baseline measures of apathy in the patient population and how these relate to healthy controls as well as how these respond to treatment in the trial. This will provide an excellent opportunity to gain hands on experience of working with clinical data and patient insights into apathy which will inform the design of the preclinical studies. The preclinical work forms the main focus of the PhD. The student will first learn about different behavioural models, benefiting from expertise in both Bristol and Cardiff, and including the use of rodent models of PD to characterise behavioural changes relating to apathy. To gain mechanistic insight into these behavioural changes, the main focus of the PhD will be on neurobiological studies. The student will utilize genetic techniques such as Targeted Recombination in Active Populations (TRAP) mice to image the neural circuits which underlie apathy, and Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) to modulate the identified neural pathways to generate a better understand the biological mechanisms underpinning apathy. Choice of neurobiological targets for these techniques will be steered by the student based on a review of available literature relating to human imaging data, the findings from the analysis of the clinical literature and relevant preclinical data. As part of this objective, the student will utilize behavioural measures to distinguish between motivation and hedonic processes to better understand the behaviours associated with apathy and inform treatment approaches. Finally, the student will investigate

	the effects of potential therapeutics from novel compounds and those in phase 3 clinical trials. Informed by the earlier neurobiological studies and steered by independent student research developed within the 3 month preparation period, the student will select compounds of particular interest for further investigation. Together, output from this project will advance our understanding of apathy and potential new treatments which could dramatically improve the outcomes for patients with PD. By utilizing an integrated clinical and preclinical approach, this project will provide the student with a unique training experience in translational, in vivo neuroscience techniques informed by clinical data and PPI (patient and public involvement). Using an evidence-based approach developed during the three month preparation period, and drawing on personal interest, the student will have the opportunity to steer the project at key milestones and therefore take ownership of it.
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