Project Details	
Project Code	MRCNMH25Br 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. This project aims to investigate the neurobiology of apathy and explore the mechanisms of potential therapeutics using a combination of behavioural studies, pharmacology and targeted manipulations of underlying circuits implicated in motivated behaviours. The project will also be supported by clinical colleagues currently involved in clinical trials in Parkinson's disease.
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. The student will first learn about different behavioural models, benefiting from expertise in both Bristol and Cardiff, and including the use of rodent disease models of PD to characterise behavioural changes relating to apathy. The supervisory team bring together unique expertise in translational behavioural approaches to study motivated behaviours (Jackson), reward (Dwyer) and emotional behaviour (Robinson). By triangulating data across these different domains, the project will be able to specifically explore mechanisms relevant to apathy. Building from these behavioural studies, the project will then focus on experiments to explore the mechanisms which underlie these apathy related behaviours. 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. The 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, hedonic processes and emotional behaviour to better understand the behaviours associated with apathy, identify novel treatment targets and inform future therapeutic strategies. Finally, the student will investigate the effects of potential therapeutics from novel compounds and those in phase 3 clinical trials. In addition to the main supervisory team, the

	student will additionally benefit from clinical insight from Dr Henderson, lead of a large UK Clinical Trial investigating the benefits of the anticholinesterase inhibitor, rivastigmine as an adjunct treatment for PD patients. This study includes specific measures of apathy and the relative efficacy of current treatments for Parkinson's disease on this important clinical symptom. As these data are analysed, we will have access to the findings prior to publication and will be able to integrate these into the design of our preclinical experiments. The PhD will also be informed by the earlier neurobiological studies and steered by independent student research developed within the 3 month preparation period, when 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 multi-dimensional 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.
Supervisory Team	
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