Project Details	
Project Code	MRCNMH26Ex Zhang
Title	Unveiling the Journey from Action Potential to Behaviour: Exploring Dopamine and Acetylcholine in Health and Disease
Research Theme	NMH
Project Type	Wet lab
Summary	How does the brain's dopamine system drive learning, memory, and motivation? And what goes wrong in diseases like Parkinson's? This project will explore how dopamine and acetylcholine signals interact to control learning and behaviour, using cutting-edge techniques such as fast-scan cyclic voltammetry, next-generation neurotransmitter imaging, electrophysiology, and computational modelling. You will work at the interface of neuroscience, physiology, and data science to help uncover fundamental brain mechanisms and identify potential therapeutic targets. The project offers excellent training and the chance to contribute to research with real translational impact.
Description	**Background** Dopamine plays a central role in learning, motivation, and motor control. Disruption of dopamine signalling underlies conditions such as Parkinson's disease (PD), where patients experience not only motor deficits but also impairments in learning and decision-making. While the importance of dopamine in brain function is well established, emerging evidence suggests that dopamine's effects are strongly shaped by its interactions with other neuromodulators, particularly acetylcholine. My recent work (Zhang et al., 2025, Nature Neuroscience) has shown that striatal cholinergic interneurons can dynamically regulate dopamine release at the axonal level, effectively decoupling dopamine neuron firing from dopamine output in target regions. However, the precise mechanisms by which this cholinergic-dopaminergic interplay shapes learning and memory, and how these processes go awry in disease, remain poorly understood. Understanding these mechanisms is critical for advancing basic neuroscience and for developing novel treatments for PD and related disorders. This project will use advanced experimental and computational approaches to dissect how cholinergic modulation of dopamine release influences striatal function during learning and decision-making. **Key research question** How does cholinergic control of dopamine axonal release influence learning, memory formation, and striatal network activity in health and Parkinsonian conditions? Objective 1: Characterise cholinergic control of dopamine release during learning • The student will use in vivo fibre photometry or 2 photon imaging to record dopamine and acetylcholine signals in the striatum during behaviour in mice. • They will assess how cholinergic modulation shapes dopamine dynamics during different stages of Pavlovian and operant conditioning. Objective 2: Determine how cholinergic-dopaminergic interactions contribute to striatal microcircuit function

	• The student will perform in vivo recordings (e.g. multiunit recording) to investigate how acetylcholine and dopamine release shape excitability of spiny projection neurons. • They will explore how these interactions differ across striatal regions in D1 and D2 spiny projection neurons. Object 3: Model how cholinergic modulation shapes dopamine-dependent learning • The student will use computational modelling, building on reinforcement learning frameworks, to link their experimental data to predictions about behaviour and plasticity. • The student will be encouraged to integrate their experimental findings into models that can guide further hypotheses and data collection. Objective 4: Assess alterations in cholinergic-dopaminergic interactions in Parkinson's disease models • The student will apply these approaches in established mouse models of Parkinson's disease (e.g. 6-OHDA lesion or transgenic models). • They will assess whether cholinergic control of dopamine is altered, and whether these changes contribute to behavioural deficits. Opportunities for student ownership and steering This project offers multiple areas where the student can take intellectual ownership and shape the direction of their work. For example: • The student will have the opportunity to design and refine behavioural tasks to probe specific aspects of learning or motivation relevant to their findings. • The student will be able to tailor the balance of experimental and computational work based on their interests and strengths. For instance, a student with strong computational skills may wish to develop more sophisticated models of dopamine-acetylcholine interactions, whereas a student more focused on experimental work could prioritise developing novel in vivo recording or manipulation techniques. • The choice of disease model(s) to study (e.g. acute lesion vs. genetic model) can be adapted based on initial findings and the student's developing hypotheses. • The student will be encouraged to present their data at conferences, write manuscripts, and propose follow-up experiments as they gain confidence and expertise. **Training environment** The student will be embedded within a vibrant neuroscience research environment at the University of Exeter, with access to cutting-edge facilities for in vivo recording, ex vivo physiology, imaging, and computational support. The supervisory team includes Prof Jack Mellor at the University of Bristol, a leading expert in two-photon imaging of acetylcholine signals in the brain, providing the student with exceptional training in advanced optical approaches. The student will benefit from a multidisciplinary supervisory team and will have the opportunity to work closely with both my national and international collaborators, including Prof Peter Magill at the University of Oxford, Prof Micheal Lin at Stanford University, Prof Alexandre Mourot at Sorbonne University, Dr Mark Howe at Boston University, further broadening their technical expertise and scientific network. This environment will support the development

	of technical, analytical, and professional skills that will prepare the student for an independent research career.
Supervisory Team	
Lead Supervisor	
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