Project Details	
Project Code	MRCNMH25Br Warburton
Title	Finding the missing link in memory networks: Deciphering cortical-thalamic communication pathways critical for successful memory.
Research Theme	Neuroscience & Mental Health
Summary	Our memories are stored in networks across the brain. Two regions, the lateral entorhinal cortex (LEC) and nucleus reuniens (NRe) are key parts of such a network, and pathology in these regions causes memory loss in old age and in brain disorders, such as dementia and schizophrenia. LEC and NRe are strongly interconnected, but we don't know how they communicate during memory processing. To answer this question the project will use a range of cutting-edge behavioural, optical and electrophysiological techniques to explore when and how information is relayed between the cortex and thalamus to enable us to learn and remember.
Description	A major important challenge in neuroscience is to understand how information from our environment is learned, stored and recalled. One important type of memory, associative recognition memory enables us to remember and recognise relevant stimuli, such as objects, within a complex environment. For example, we use associative recognition memory to recognise our car in a car park, or that the furniture in our living room has been rearranged. Research from our laboratory has shown that two brain regions, the lateral entorhinal cortex (LEC) and nucleus reuniens of thalamus (NRe) are both essential for associative recognition memory. In addition pathology in both these regions has been implicated in neurodegenerative and psychiatric conditions, including dementia and schizophrenia. Decades of research has shown that our memories are stored, not within isolated regions, but within brain-wide networks. As there is evidence of a large anatomical projection from NRe to LEC, it suggests that communication between these areas may be essential for associative recognition memory, yet this hypothesis has yet to be tested. Understanding the function of the NRe to LEC projection in cognition is likely to be important because 1) it will provide a key understanding of how memory information is organised within brain networks and 2) study of NRe-LEC functional connectivity may provide avenues for novel therapeutic interventions for memory loss and other cognitive impairments. To examine the role of the projection from the NRe to LEC in associative recognition memory, this project has three specific aims. We will investigate: i) the physiological properties of the specific subsets of neurons in the NRe that connect to the LEC; (ii) how the activity of these projection neurons changes during associative recognition memory function; (iii) whether the NRe to LEC connection is specifically necessary for different components of memory i.e. learning information, storing that information or retrieving the memory after learning. To address Aim 1, the project will begin by examining the electrophysiological properties, of neurons in NRe that project to the LEC. We will identify the neurons that form this projection using

	retrogradely transported viruses which express a green fluorescent protein and then use whole-cell patch clamp techniques to record activity in these cells at a single cell level. The intrinsic electrical properties of these cells will be compared to other cells which are not part of the NRe-LEC circuit. To tackle Aim 2, we will record cell activity patterns during behaviour, at a population level, using fibre photometry. Neurons projecting from NRe to LEC will be labelled with a retrograde viral vector expressing the fluorescent biosensor GCaMP, which enables the measurement of intracellular calcium levels through changes in fluorescence. Such changes in fluorescence, which indicate changes in activity, will be detected using fibre photometry in freely moving animals performing a range of memory tasks. The student can take ownership of the project to determine the next steps. For example, further experiments could use the fibre photometry techniques to investigate neuronal activity in different neuronal populations, anatomical projections or during different behavioural tasks depending on the results and student's interests. Aim 3 will be addressed by a series of experiments to test the necessity of cells projecting from NRe to LEC for memory performance. Optogenetics will be used to inactivate the projection at different phases of the memory task (i.e. learning, consolidation or retrieval). The optogenetic technique depends on the expression of inhibitory light sensitive opsins (e.g. GTACR2) in NRe neurons, and the implantation of fibre optic cannula over the LEC to allow the delivery of light to activate the opsins and inactivate the projection. As optogenetics allows inactivation of specific neuronal populations with tight temporal control, the NRe to LEC projection can be 'switched off' at different stages of the memory task to investigate effects on learning, information storage or retrieval. Here the student will take ownership of the project to determine next steps, depending on the results obtained, and the student's interests, for example different behavioural tasks, or inactivation of other defined pathways or neuronal populations within the memory circuitry. Together these experiments will provide novel insights into the functioning of this under-investigated pathway in key cognitive processes. All the techniques (molecular, cellular and behavioural) are well established in the lab. However, given the highly interdisciplinary nature of the supervision team there will be opportunities throughout the project, i.e. within Aims 1-3, for the student to drive the project in different directions depending on results obtained, including in developing new computational approaches to analyse the neuronal activity and behavioural data.
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