Project Details	
Project Code	MRCNMH26Ex Clifton
Title	Capturing the Molecular Basis of Altered Learning in Schizophrenia
Research Theme	NMH
Project Type	Wet lab
Summary	In this interdisciplinary PhD project, you will explore how memory is altered in schizophrenia by investigating the neurons activated during learning. Using cutting-edge techniques, including activity-dependent cell tagging, long-read RNA sequencing, and electrophysiology, you will profile gene expression and excitability in memory-encoding cells from mouse models carrying rare schizophrenia risk mutations. This project bridges behavioural neuroscience, molecular biology, and functional genomics, offering you the opportunity to drive your own analyses and shape experimental directions. Your work will advance understanding of how psychiatric risk genes impact memory circuits and contribute to developing targeted strategies for intervention.
Description	Schizophrenia is a highly heritable psychiatric disorder marked by profound disturbances in cognition, perception and learning. Among the cognitive features consistently observed in patients are abnormalities in associative learning and memory, underpinned by the plasticity of neuronal circuits in regions such as the hippocampus and prefrontal cortex. Recent large-scale genomic studies have identified a number of rare, high-penetrance mutations in genes encoding synaptic regulators that confer substantial risk for the disorder. However, the biological processes by which these variants disrupt learning at the molecular and circuit level remain incompletely understood. This project aims to uncover the molecular and physiological properties of neurons activated during associative learning in mouse models carrying penetrant rare mutations associated with schizophrenia. Mice carrying heterozygous mutations in genes TRIO and GRIN2A will be crossed with the Fos-TRAP2 x EYFP system, allowing permanent fluorescent tagging of neurons activated during defined behavioural experiences. Using associative learning paradigms, we will induce distinct learning episodes and capture the associated engram cells in the hippocampus and medial prefrontal cortex. Following associative learning, tissues will be taken following a post-training interval to allow optimal tagging of active cells and downstream transcriptional changes. Brain tissue will be dissociated and fluorescently tagged neurons isolated via fluorescence-activated cell sorting. These labelled engram populations will be pooled and subjected to full-length transcriptome sequencing using Oxford Nanopore Technologies (ONT) long-read RNA sequencing. This approach enables accurate mapping of transcript isoforms, identification of alternative splicing events, and assessment of transcript-specific regulation associated with learning and genotype. In parallel, electrophysiological patch-clamp recordings will be conducted in acute brain slices prepared from a separate cohort of animals. Targeted recordings from eYFP+ve engram cells in hippocampal CA1 and medial prefrontal cortex layer 5 will quantify intrinsic excitability and firing properties associated with learning conditions. Parameters such as resting membrane potential, input resistance,

	rheobase, spike frequency adaptation and afterhyperpolarisation will be measured to assess how recent learning alters the physiological properties of activated neurons. By characterising the molecular identity and physiological behaviour of learning-activated neurons in health and disease-relevant genetic contexts, this project will yield new insight into the synaptic and cellular foundations of associative memory. The combination of behavioural tagging, transcript-specific profiling, and targeted electrophysiology offers a powerful and coherent framework for understanding how rare genetic variants associated with schizophrenia disrupt brain function at the level of the engram. The results of this work will deepen our mechanistic understanding of psychiatric risk and help to prioritise molecular targets for therapeutic intervention. The student will be encouraged to take ownership of specific aspects of the project according to their emerging interests and expertise. In the early stages, they will be supported to shape the experimental design, including behavioural paradigms, timepoints for tissue collection, and electrophysiological protocols. As data are generated, the student will have the opportunity to lead transcriptomic analyses and pursue additional hypotheses derived from their findings. Depending on their interests, the student may also choose to validate their findings using molecular biology assays, and to contribute to developing novel visualisation or analysis tools. The supervisory team will provide structured guidance and training, while actively fostering independent thinking, critical analysis, and the development of a scientific niche that the student can carry forward in future work.
Supervisory Team	
Lead Supervisor	
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