Project Details	
Project Code	MRC23NMHCa Hall
Title	Quantifying the molecular response to memory retrieval and its genetic association with schizophrenia
Research Theme	Neuroscience and Mental Health
Summary	Deficits in the molecular mechanisms of memory are thought to be central to the psychiatric pathology associated with schizophrenia. New methods now allow us to explore deeper into the molecular dynamics of memory and refine our understanding of the impacts from schizophrenia. This interdisciplinary project aims to profile neuronal gene expression required for memory retrieval and extinction, and determine the molecular pathways of relevance to schizophrenia.
Description	Evidence from genomic studies of schizophrenia indicates that genes with synaptic functions involved in learning and memory are central to the pathology of the disorder (1). However, our current understanding of the specific genes and transcripts responsible for these processes is limited by a lack of cell-specific data from high-throughput sequencing methods. By establishing which neuronal genes are particularly important for different phases of learning and memory, we will be able to refine the biology implicated in schizophrenia pathology in view of designing improved treatments. Different profiles of gene expression are evoked by the acquisition, consolidation, retrieval and extinction of memories. Some evidence suggests that genes responsible for memory extinction may be particularly associated with schizophrenia (2). Furthermore, abnormalities in this type of inhibitory learning have been reported in patients (3) and may contribute to the development and persistence of psychotic and cognitive symptoms in the condition. Our proposal provides an opportunity for a PhD student to work on an interdisciplinary project aiming to refine the neuronal gene expression profiles associated with the retrieval and extinction of contextual fear memory. The work will build on a strong foundation of research into memory, transcriptomics and psychiatric disorders by the supervisory team and their experienced lab groups. The first objective will be to model the molecular response to contextual fear conditioning and profile the neuronal-specific transcriptome following memory retrieval and extinction. The student will use mice with neuronal-specific genetically tagged ribosomes to conduct a fear conditioning paradigm and extract ribosome-bound RNA from excitatory neurons during critical phases of memory retrieval and extinction. They will then use next-generation RNA sequencing, bioinformatics and supercomputing to compare these molecular profiles, and study their implications in the context of human co-expression profiles and patient genomics. These steps will afford the student freedom to use the data in pursuit of additional goals of primary interest to them. This may include comparison with published datasets of gene expression associated with specific plasticity processes such as long-term potentiation, or tests for enrichment of genetic association with a range of psychiatric disorders related to schizophrenia. The student may choose to take advantage of existing links with other academic institutions during the optimisation of methods for ribosome profiling and transcriptome analysis, which may include short research visits within the UK or abroad. Together with

	opportunities to attend national and international conferences on psychiatric genomics, this will allow them to begin establishing a network of collaborators and a wider awareness of current work in the field. 1 Trubetskoy V, Pardiñas AF, Qi T, Panagiotaropoulou G, Awasthi S, Bigdeli TB et al. Mapping genomic loci implicates genes and synaptic biology in schizophrenia. Nature 2022; 604: 502–508. 2 Clifton NE, Pocklington AJ, Scholz B, Rees E, Walters JTR, Kirov G et al. Schizophrenia copy number variants and associative learning. Mol Psychiatry 2017; 22: 178–182. 3 Holt DJ, Lebron-Milad K, Milad MR, Rauch SL, Pitman RK, Orr SP et al. Extinction memory is impaired in schizophrenia. Biol Psychiatry 2009; 65: 455–463.
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