Project Details	
Project Code	NMH27Br Anastasiades
Title	Uncovering interneuron dysfunction in a mouse model of schizophrenia
Research Theme	Neuroscience & Mental Health
Project Type	Wet lab
Summary	This project seeks to understand how disease-causing mutations linked to neurodevelopmental disorders, such as schizophrenia, alter cell types in the brain. The brain contains many neuronal subtypes, each with distinct functional roles. However, we don't currently understand if certain cells are preferentially impacted in schizophrenia, or the consequences of such changes on brain function. Using sophisticated optical and electrical recording methods combined with genetic analysis, we will study different neuronal subtypes across transgenic mice that harbour mutations in genes that increases the risk of developing schizophrenia. Having determined cellular alterations, we will establish how these changes impact learning and memory.
Description	Schizophrenia is a highly debilitating neurodevelopmental disorder impacting about 1% of the global population. While it is well established that schizophrenia is associated with altered function in key brain areas, such as the hippocampus, the precise cellular mechanisms are unknown. Recent studies highlight glutamatergic NMDA receptors (NMDA-Rs) as a key genetic risk factor for schizophrenia, consistent with convergent evidence for altered glutamate signalling in the brain of people with schizophrenia. Although NMDA-R dysfunction has been studied extensively at excitatory neurons, the impact of altered GABAergic interneuron function is poorly understood. This is important because emerging evidence implicates interneurons in schizophrenia. There are many subtypes of GABAergic cells. However, little research has looked at the diversity of interneuron subtypes. Our hypothesis is that Somatostatin interneurons will play a key role in the disorder, given NMDA-Rs are key to their normal function and they are known regulators of learning and neural plasticity in the developing and adult brain. The goal of this proposal is to explore how altered NMDA-R function impacts the properties of Somatostatin interneuron subtypes in the hippocampus, and in so doing better link the Glutamate and GABAergic hypotheses of Schizophrenia. The project comprises three aims: Aim 1: How do NMDA-R mutations impact the cellular properties of Somatostatin interneuron subtypes? The student will use electrophysiology, 2-photon uncaging and calcium imaging to explore how loss of NMDA-Rs impacts the intrinsic, synaptic and dendritic integration properties of Somatostatin interneurons. These findings will inform how mutations impact their respond to high-frequency inputs known to elicit plasticity in the brain. Aim 2: To understand the molecular mechanisms underlying observed changes, we will perform bulk transcriptome analysis of fluorescently labelled Somatostatin interneuron subtypes in the hippocampus. Our hypothesis is that NMDA-R mutations will alter the expression of key synaptic proteins and dendritic ion channels. The student will use pharmacology to study the functional impact of gene expression changes, yielding possible targets to restore normal function.

	Aim 3: How does altered interneuron function impact plasticity in the brain? The student will study how NMDA-R mutations impact hippocampal plasticity and the role of altered Somatostatin interneuron function in this process. Using targeted pharmacological and chemogenetic manipulations building on results from aims 1 and 2, they will determine if it is possible to restore normal plasticity by modulating the activity of different Somatostatin populations. This interdisciplinary project will combine expertise in cellular physiology and neural circuits at the University of Bristol and genomic research into neurodevelopmental disorders at the University of Exeter. The proposal builds on shared interest in the neurobiology of schizophrenia across all labs and recent work exploring the diversity, neuromodulation, and role in plasticity of different interneuron subtypes. Anastasiades PG*, Collins DP*, Carter AG (2021). Mediodorsal and ventromedial thalamus engage distinct L1 circuits in the prefrontal cortex. Neuron. Jan 20;109(2):314-330 Anastasiades PG, et al., (2019). Cell-type-specific D1 dopamine receptor modulation of projection neurons and interneurons in the prefrontal cortex. Cerebral Cortex. Jul 5;29(7):3224-3242 Udakis, M., et al. (2025) Hippocampal OLM interneurons regulate CA1 place cell plasticity and remapping. Nat Commun 16, 9912. Udakis, M., et al. (2020) Interneuron-specific plasticity at parvalbumin and somatostatin inhibitory synapses onto CA1 pyramidal neurons shapes hippocampal output. Nat Commun 11, 4395. Griesius, S., et al. (2022) Reduced expression of the psychiatric risk gene DLG2 (PSD93) impairs hippocampal synaptic integration and plasticity. Neuropsychopharmacol. 47, 1367–1378. The proposal will provide training in a cutting-edge array of experimental methods, including transgenic models of mental health disorders, electrophysiology, 2-photon imaging, pharmacology, genetic analysis of neural cell types and viral tools to label and manipulate neurons. The student will be led by the supervisory team but encouraged to take ownership of the project over the course of the PhD. The student will be able to increase, or decrease the relative focus of different sub-aims based on their specific interests or experimental outcomes. For example, expanding more on the specific circuit-level deficits that emerge downstream of synaptic changes using optogenetic circuit mapping, focusing on the molecular mechanisms or ion channels pulled out from the genetic screen, or exploring different plasticity paradigms and the molecular/cellular influences on learning and memory. The supervisory team have extensive experience across these different domains and all the necessary equipment to expand the project in different directions are in place. In summary, the project will develop novel understanding into the altered function of key cell types in models of neurodevelopmental disorders. This project will integrate more widely into research being undertaken across the GW4 as part of a wider MRC funded MURIDAE project to understand how NMDA-R mutations alter the formation and function of key brain circuits and associated behaviours. The pharmacological studies will provide insight to ground future therapeutic

	approaches to develop new drugs for the treatment of schizophrenia and the underlying mechanisms through which they work.
Can be completed part time?	Yes
Supervisory Team	
Lead Supervisor	
Name	Dr Paul George Anastasiades
Affiliation	Bristol
College/Faculty	Health and Life Sciences
Department/School	Psychology and Neuroscience
Email Address	paul.anastasiades@bristol.ac.uk
Co-Supervisor 1	
Name	Professor Jack Mellor
Affiliation	Bristol
College/Faculty	Health and Life Sciences
Department/School	Psychology and Neuroscience
Co-Supervisor 2	
Name	Professor Albert Basson
Affiliation	Exeter
College/Faculty	University of Exeter Medical School
Department/School	Clinical and Biomedical Sciences
Co-Supervisor 3	
Name	
Affiliation	
College/Faculty	
Department/School	