Project Details	
Project Code	MRCNMH25Br Mellor
Title	Linking neuronal function to mental health: How genetic risk factors impair cognitive flexibility and neural plasticity in schizophrenia.
Research Theme	Neuroscience & Mental Health
Summary	Genetic risk factors for schizophrenia are clustered around genes that regulate synaptic function and adaptation, indicating common disrupted biological processes that underpin the cognitive impairments in memory and flexible learning. We have revealed how loss of function in one of these genes (Dlg2) perturbs core features of synaptic signalling and adaptation and are investigating others including Grin2A and Gria3. In this project, we will uncover how these mechanisms lead to abnormal cognition by directly measuring neuronal adaptations during tasks demanding cognitive flexibility. We will then test mechanisms to rescue cognition including drugs that target neuromodulator systems.
Description	Genetic risk factors are highly significant in determining susceptibility to a range of psychiatric disorders including anxiety, depression and schizophrenia. Many of these psychiatric risk factors cluster around genes involved in synaptic function and plasticity but we know relatively little about the core features of synapses that are disrupted and how these lead to cognitive impairments common to many of these conditions. Emerging evidence indicates that many key psychological processes such as perception, memory and adaptability rely on dendritic signalling events generated by the interaction of multiple synapses on single neurons. These dendritic signals are extremely sensitive to neural network perturbations caused by genetic mutations to synaptic proteins or changes in brain state mediated by neuromodulators such as acetylcholine or serotonin. We have discovered that the genetic risk factor Dlg2, which is associated with schizophrenia, autism and intellectual disability, disrupts dendritic signalling and synaptic plasticity (PMID: 35115661) and are currently investigating other risk factors including Grin2A and Gria3. In this project we aim to determine how these disrupted neuronal processes lead to impairments in flexible neuronal representations of behaviour and whether they may be rescued by targeting these specific processes. In this way we will directly link biological processes to cognitive impairments observed in psychiatric disorders and develop practical strategies for treatment. The project will test these hypotheses using transgenic animals bearing mutations in the synaptic protein Dlg2 (Hall, Wilkinson). The project will first determine how dendritic calcium signalling is impaired in these animals using electrophysiology coupled with imaging of synaptic and dendritic calcium signals, techniques routinely used in the Mellor and Ashby groups (PMID: 26758963, 30242046). The project will then determine how hippocampal representations of spatial features adapt during changing environmental conditions by measuring hippocampal place cell activity using 2-photon imaging during animal exploration of a virtual reality environment, using early career researcher Witton's expertise. We will test whether reduction in Dlg2 expression impairs the flexible representation of changing environments at neuronal and

	behavioural levels. Finally, the project will test whether impairments in neuronal representations and behaviour may be rescued by application of clinically relevant drugs such as muscarinic receptor agonists or psychedelics that target serotonin receptors. The ultimate goal will be to find out if manipulating dendritic signalling using pharmacological tools is capable of changing behavioural outcomes in adult animals. This will form the basis of future therapeutic strategies for the treatment of psychiatric disorders The student will be trained in Bristol in dual electrophysiology and 2-photon imaging performed in ex vivo brain slices. Subsequently, training will transition to 2-photon imaging in vivo and animal behaviour paradigms developed in Cardiff, Exeter and Bristol. Aligned with this the student will be trained in complex data analysis and manipulation of virtual reality environments. Our collaboration with Dan Dombeck's group (www.dombecklab.org) offers the opportunity to learn from world leaders in virtual reality behaviour in rodents. In addition, the project can also be extended to use computational models to predict the likely outcome of dendritic signalling perturbations on behaviour through our collaborations with Cian O'Donnell (Ulster and Bristol). The student will be encouraged to choose which approaches best suit their interests and skills and shape the project accordingly. Through our collaborations with pharmaceutical companies including Compass pathways, SoseiHeptares, Lilly and Takeda we have access to novel drug pipelines that we can test. For example, Compass have shown psilocybin is effective in depression and SoseiHeptares have a suite of muscarinic receptor ligands in development for clinical trials in schizophrenia (PMID: 34822784).
Supervisory Team	
Lead Supervisor	
Name	Professor Jack Mellor
Affiliation	Bristol
College/Faculty	Faculty of Health and Life Sciences
Department/School	Physiology, Pharmacology and Neuroscience
Email Address	jack.mellor@bristol.ac.uk
Co-Supervisor 1	
Name	Dr Jon Witton
Affiliation	Exeter
College/Faculty	Institute of Biomedical and Clinical Science
Department/School	Medical School
Co-Supervisor 2	
Name	Professor Jeremy Hall
Affiliation	Cardiff
College/Faculty	Division of Psychological Medicine and Clinical Neurosciences
Department/School	Neuroscience and Mental Health Innovation Institute
Co-Supervisor 3	
Name	Dr Michael Ashby
Affiliation	Bristol
College/Faculty	Faculty of Health and Life Sciences
Department/School	Physiology, Pharmacology and Neuroscience