Project Details	
Project Code	MRCNMH24Br Anastasiades
Title	Understanding the role of disease-causing NMDA receptor mutations in synaptic development and function
Research Theme	Neuroscience & Mental Health
Summary	Neurodevelopmental disorders are a major global health burden. One main challenge is understanding how, despite influencing the same genes, individual mutations can cause distinct symptoms, that emerge at distinct stages of development. This project combines mouse genetics, high-throughput imaging, and sophisticated circuit and behavioural analyses to understand how mutations in the NMDA receptor gene NR2A cause changes to brain development and function.
Description	Neurodevelopmental disorders, such as schizophrenia, are highly debilitating diseases that impact 1-2% of the global population. There is significant evidence for a genetic basis to these disorders, yet the underlying causal relationships between genes and symptoms are currently poorly understood. An example of this is mutations in the NR2A subunit of the glutamatergic NMDA receptor, which have been strongly linked to risk of developing schizophrenia, but where individual mutations in the GRIN2A gene cause distinct symptom presentation amongst patient groups. It is possible that this may occur because the mutations have dissociable effects on brain development, for example preferentially impacting distinct brain areas or causing unique changes to NMDA receptor function. To better understand the mechanisms through which this occurs, we propose to map the maturation of excitatory (i.e glutamatergic) synapses across the developing mouse brain and compare changes between WT mice and two distinct GRIN2A mutants. The main aims of the project are: 1. Perform high-throughput brain imaging of transgenic PSD95 mice across the whole brain to establish brain structures and developmental time points that are strongly impacted by GRIN2A mutations (Ashby / Anastasiades) 2. Record electrophysiological properties from identified brain regions to understand the cellular and circuit level changes that occur (Anastasiades) 3. Perform behavioural analyses related to identified brain regions to link cellular changes to behaviour (Isles) Recent work from the Anastasiades & Ashby labs has performed a developmental characterisation of transgenic mice where the glutamatergic synaptic organiser PSD95 is tagged with GFP, allowing us to visualise synaptic development. Using support from an MRC equipment grant, we have developed a pipeline that allows us to explore changes in GFP fluorescence across the entire mouse brain, spanning postnatal brain development. This project will explore how the developmental trajectories we have mapped in healthy mice are impacted in transgenic mice provided by the Mary Lyon Centre (MLC) that express known disease-causing mutations in the NR2A subunit of the NMDA receptor. The first aim of the project will involve crossing the two transgenic lines to the PSD95 reporter. The student will then perform whole brain tissue preparation and image GFP fluorescence to uncover changes in PSD95 expression caused by the mutations. Based on our current findings, we will focus on two main developmental periods. Early postnatal, postnatal day (P)5-15, and adolescence, P35-55. This will

	highlight novel brain structures and circuits associated with neurodevelopmental disorders. To target these structures, we will then go in and perform slice electrophysiological recordings. This will involve measurements of cell morphology, intrinsic physiology and synaptic composition (for example AMPA/NMDA ratios). This will be facilitated by Anastastasiades expertise in optogenetic circuit interrogation and will provide key training in rodent stereotaxic surgery to allow opsin delivery to the intact brain. Finally, the student will perform behavioural analysis with Prof Isles focusing on behaviours linked to the brain structures and developmental time points identified in aims 1 and 2. In summary, these experiments benefit from the newly funded National Mouse Genetics Network in a project designed to link synaptic development to behaviour across the early life period in mouse models of schizophrenia. The students will benefit from being embedded in this network, facilitating training and development at Bristol, Cardiff and in visits to the MLC. The student will develop a powerful array of interdisciplinary skills that can be tailored to the interests of the student based on the experimental emphasis of the project, yielding impactful science and high-quality doctoral training.
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