Project Details	
Project Code	MRC22NMHBr Ashby
Title	How does the schizophrenia risk gene, SETD1A, alter the early life development of brain circuits?
Research Theme	Neuroscience & Mental Health
Summary	Schizophrenia is a severe neurodevelopmental psychiatric disorder with high heritability, but we don't know how genetic variation leads to abnormal maturation of brain function. Disruption of the SETD1A gene is linked to elevated schizophrenia risk. In this project, we will investigate the cortical development of a mouse model of SETD1A deficiency using molecular, electrophysiological, imaging and behavioural techniques to link aberrant neurobiology to pathology.
Description	Significance: Schizophrenia is a severe psychiatric illness that cause psychosis, depression and cognitive impairment. Genetic variation plays a key role in determining susceptibility to schizophrenia, but we do not understand how genetic differences lead to symptom-related abnormalities in brain function. This lack of understanding limits development of new therapies. SETD1A is one of few genes identified in both GWAS and exome sequencing of patients as underlying a substantially increased risk of schizophrenia. In this project, we will study a mouse model of disease-mimicking SETD1A haploinsufficiency to establish how this genetic alteration leads to schizophrenia-related phenotypes. Originality: SETD1A encodes a histone methyltransferase that epigenetically regulates many downstream targets, including genes involved in neuronal maturation and synaptic signalling. One example is the transcription factor MEF2, which we showed is involved in expression of long-term synaptic plasticity. We have shown that adult SETD1A knockout mice have behavioural endophenotypes disease-relevant (Isles), but schizophrenia is rooted in abnormal brain development. Therefore, we will take an original approach to assess the impact of SETD1A on the developmental process itself by measuring cellular, circuit and behavioural phenotypes as they emerge early in life. As such, the overall broad aim is to identify how and when neural circuitry and associated activity goes awry during postnatal development. Degree of challenge: Development is understudied because of technical challenges of assessing the working neonatal mouse brain. However, our existing technical expertise means that the project will generate data from early stages, but the student will be able to extend their skills by further refining the recording and analysis of neonatal data. Research Training: In the Ashby lab, the student will learn in vivo imaging of head-fixed, behaving neonatal mice that express a fluorescent reporter of neuronal activity to assess development of cortical neural dynamics. These experiments benefit from bespoke adjacent rodent housing and surgical/experimental labs. To assess synaptic development, the student will learn whole cell patch clamp electrophysiology in acutely-prepared brain slices. Also in Bristol, we will measure behavioural developmental milestones via customised homecage video monitoring and ultrasonic vocalisation recording to determine when social deficits emerge (Cahill/Ashby/Isles). In the Mill lab, the student will use bioinformatics to analyse epigenetic data from human brain tissue to compare disease-associated differences with

	those in the SETD1A mouse. Furthermore, the student will investigate the epigenetic and transcriptomic regulation of selected target genes in SETD1A mouse tissue, linking to aberrant neurophysiological findings. Feasibility: This project is feasible because the mouse model is available and we know that important phenotypes must emerge during development (Isles). The core experimental approaches are already established in the host labs (Ashby, Cahill, Mill). Epigenomic and transcriptomic data from developing human brain and post-mortem schizophrenia patients are already generated (Mill). Added value/Impact/Knowledge Transfer: Image analysis will involve student training in advanced statistical and mathematical approaches supported by existing collaboration with Dr Nick Whiteley (School of Mathematics, University of Bristol). A planned collaboration between Isles, Ashby and the Mary Lyon Centre (MLC) would allow the student to take attend MLC training courses in mouse development and to be part of knowledge transfer in establishing a nationwide developmental phenotyping platform. Impact will be promoted by influencing decision making of industrial collaborators (Cahill - Boehringer Ingelheim; Mill, Ashby – Eli Lilly, Astex) with the student having the chance to engage with these partners.
Supervisory Team	
Lead Supervisor	
Name	Dr Michael Ashby
Affiliation	Bristol
College/Faculty	Faculty of Life Sciences
Department/School	School of Physiology, Pharmacology & Neuroscience
Email Address	m.c.ashby@bristol.ac.uk
Co-Supervisor 1	
Name	Professor Anthony Isles
Affiliation	Cardiff
College/Faculty	Division of Psychological Medicine and Clinical Neurosciences
Department/School	School of Medicine
Co-Supervisor 2	
Name	Dr Emma Cahill
Affiliation	Bristol
College/Faculty	Faculty of Life Sciences
Department/School	School of Physiology, Pharmacology & Neuroscience
Co-Supervisor 3	
Name	Professor Jonathan Mill
Affiliation	Exeter
College/Faculty	College of Medicine and Health
Department/School	Medical School
Co-Supervisor 4	
Name	
Affiliation	
College/Faculty	
Department/School	