Project Details	
Project Code	MRCNMH24Br Ashby
Title	The interplay between genetics and brain development in schizophrenia
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	Brief Background: 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. SETD1A encodes a histone methyltransferase that epigenetically regulates many downstream targets, including genes involved in neuronal maturation and synaptic signalling. Adult SETD1A knockout mice have behavioural endophenotypes disease-relevant (Isles), but schizophrenia is rooted in abnormal brain development. Therefore, we will 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 key research question is how and when neural circuitry and associated activity goes awry during postnatal development of SETD1A deficient mice. To address this question, the student will have 3 specific objectives: -Pinpoint how and when maturation of neocortical activity diverges from normality in SETD1A knockout mice (Ashby). -Establish behavioural developmental milestones to determine when social deficits emerge in SETD1A knockout mice (Cahill/Ashby/Isles/Mary Lyon Centre - MLC). -Define the epigenetic and transcriptomic links between SETD1A knockout mice and schizophrenia patients (Mill) Experimental details: 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. Between Bristol and the Mary Lyon Centre, we will measure behavioural developmental milestones via customised homecage video monitoring and ultrasonic vocalisation recording to determine when social deficits emerge (Cahill/Ashby/Isles/MLC). This element benefits directly from the newly-funded National Mouse Genetics Network that links Ashby/Isles to the Mary Lyon Centre in a project designed to establish home-cage monitoring across the early life period in mouse models of schizophrenia. The students will therefore benefit from their project being embedded in this UK-wide network, facilitating training and development at Bristol and in visits to the MLC. 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. All these approaches and training needed are in place across the supervisors' labs. Student ownership: During the setup period, the student will have the chance to visit each host lab and the MLC to understand the experiments. While focus will remain on understanding of SETD1A in brain development, the balance of future directions can be shaped by the preferences and skills of the student. The student will receive training in each experimental approach, but can then emphasise particular directions. For example, should the student take to brain slice electrophysiology, then we can pursue a more synaptic development angle, whereas the cortex-wide in vivo imaging would allow us to develop a more circuit-based analysis, dependent on the student preference. They will therefore also have the chance to shape how much time they spend at each Institution.
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