Project Details	
Project Code	MRC21NMHCa Hall
Title	Epigenetic processes involved in synaptic plasticity and their association with risk for psychiatric disorders.
Research Theme	Neuroscience & Mental Health
Summary	Genetic variants associated with risk for psychiatric disorders are located in the vicinity of genes involved in synaptic plasticity. There is evidence that these variants act through regulatory processes affecting gene expression, including the epigenome. This project will look at whether epigenetic processes involved in regulating plasticity are important in conferring risk to psychiatric disorders such as schizophrenia.
Description	There has been substantial progress in recent years in understanding genetic risk for psychiatric disorders such as schizophrenia. However, a key issue now is to uncover the way these genetic variants act to impact biological systems in the brain. Without such understanding it is difficult to make progress in the development of new treatments and biomarkers. This project examines the role of epigenetic processes involved in plasticity in risk for psychiatric disorders. Many of the genetic variants associated with psychiatric risk do not act directly to change protein coding but instead are likely to impact gene regulation through epigenetic processes. There is increasing evidence that risk variants for schizophrenia and related conditions do indeed act to alter the regulation of nearby genes through changes in epigenetic factors such as DNA methylation (see eg Hannon et al Nature Neuroscience 19, 48–54 (2016)). It is notable that many risk variants for schizophrenia and related conditions are located close to genes involved in synaptic plasticity. This suggests that risk for these conditions may particularly arise from altered regulation of biological processes involved in associative learning and plasticity. Indeed, previous studies have suggested alterations in associative plasticity and learning in schizophrenia and related disorders, which may contribute to the development of symptoms such as psychosis. In the present proposal we will seek to investigate whether epigenetic changes that occur during synaptic plasticity and learning are indeed associated with risk for schizophrenia and related disorders. In particular, we will examine genome-wide epigenetic changes that occur after learning in animal models (using conditioning or electrophysiological models of learning) and test their convergence on pathways of risk for psychiatric disorders using bioinformatic approaches. Based on our previous findings in relation to gene expression we will particularly focus on epigenetic changes following fear extinction learning (see eg Clifton et al Molecular Psychiatry, 22, 178–182(2017)). The project will utilise a range of state-of-the-art methods and will combine in vivo work in animals (behavioural and electrophysiological techniques) with molecular approaches (epigenetic assays) and bioinformatic techniques (pathway and genetic association analysis) to test whether pathways impacted by learning are involved in psychiatric risk. As well as illuminating mechanisms of risk for psychiatric disorder, the current project will have the potential to inform the development of novel treatments for disorders like schizophrenia. In this context the supervisory team have extensive collaboration with industrial partners including the

	international pharmaceutical company Takeda which would provide further opportunities for external interactions. Specific aims: 1. Examine whole genome epigenetic changes induced by different phases of associative learning in the hippocampus, initially focussing on extinction learning. 2. Use bioinformatic approaches to investigate whether genetic risk loci for schizophrenia and related disorders are enriched for genes and pathways showing epigenetic changes in specific phases of associative learning and plasticity.
Supervisory Team	
Lead Supervisor	
Name	Professor Jeremy Hall
Affiliation	Cardiff
College/Faculty	College of Biomedical and Life Sciences
Department/School	Neuroscience and Mental Health Research Institute
Email Address	hallj10@cardiff.ac.uk
Co-Supervisor 1	
Name	Professor Jonathan Mill
Affiliation	Exeter
College/Faculty	College of Medicine and Health
Department/School	School of Medicine
Co-Supervisor 2	
Name	Dr Kerrie Thomas
Affiliation	Cardiff
College/Faculty	College of Biomedical and Life Sciences
Department/School	School of Biosciences
Co-Supervisor 3	
Name	Dr Nicholas Clifton
Affiliation	Cardiff
College/Faculty	College of Biomedical and Life Sciences
Department/School	School of Medicine
Co-Supervisor 4	
Name	
Affiliation	
College/Faculty	
Department/School	