Project Details	
Project Code	MRCNMH24Br Hodge
Title	Modelling the role of L-type voltage-gated calcium channels (CACNA1C) signalling in epilepsy and mental health
Research Theme	Neuroscience & Mental Health
Summary	Variations in the CACNA1C gene are strongly associated with risk of neuropsychiatric conditions such as epilepsy and psychoses, and specific CACNA1C gain-of-function mutations cause Timothy syndrome. To better understand the role of CACNA1C in disease mechanisms the project will combine functional and behavioural analyses of genetic CACNA1C mutant fly models with computational modelling based on functional and molecular data from human tissue, rodent and fly models.
Description	The student will receive high quality multi-disciplinary cross-GW4 training in modelling CACNA1C signalling in epilepsy, Timothy Syndrome (TS), bipolar disorder and schizophrenia. These conditions share symptoms, are poorly understood and treated. Epilepsy is the most common primary neurological disorder worldwide with CACNA1C mutations causing treatment resistant epilepsy. TS is a characterised by neurological, developmental and cardiac (long-QT) defects resulting from CACNA1C mutations (e.g. G406R) delaying channel closing causing hyperexcitability. Bipolar disorder and schizophrenia are common affecting ~5% of people with sequencing revealing an association with CACNA1C L-type voltage-gated calcium channels. Overlapping symptoms of these diseases include social impairment, depression, disrupted activity, circadian rhythms, sleep, learning, and sensory processing. CACNA1C controls Ca2+ signalling, excitability and synaptic plasticity with blockers used to treat hypertension, epilepsy and pain. Therefore, there is a great unmet need for research to understand better these overlapping diseases to aid diagnosis and development of better treatments including a huge potential for drug repurposing for CACNA1C diseases. The aim of this PhD is to determine the mechanisms by which CACNA1C signalling is disrupted in these diseases and how they can be corrected to develop novel treatments. The student will benefit from training, established techniques, reagents and resources of the collaborating host labs to address the following outstanding research questions: 1) Does bioinformatic analysis of methylomic and transcriptomic data from brain tissue we have obtained from epileptic patients (with/out CACNA1C mutations), ALSPAC and UK biobank, etc datasets identify shared (epi)genetic changes and signalling pathways underlying the different CACNA1C diseases. Training by Dr Doretta Caramaschi (DC, University of Exeter, UoE). 2) Do CACNA1C and signalling molecule mutants (from 1) cause interacting disease relevant phenotypes in flies? The student will learn to use Drosophila to characterise CACNA1C and gene interactor mutants. The fly orthologue of CACNA1C is Ca-alpha(a)1D gene, for which we have RNAi mutants. They will use a Ca-a1D promoter insert which is a null, and will be crossed with: A) GFP to check Ca-a1D expression B) fly Ca-a1D or human CACNA1C to check genetic rescue of the fly Ca-A1D null and functional conservation between the genes. C) human CACNA1C and fly Ca-a1D G406R mutant TS transgenes (the residue is conserved between

	species). They will phenotypically characterise these using activity, circadian rhythms, sleep, learning, sensory processing, social interaction and mood assays. They will perform mechanistic studies to understand underlying pathway changes in e.g. Ca++ signalling, molecular interactions, synaptic plasticity, neuronal excitability, morphology and development. Training by Dr James Hodge (JH, University of Bristol (UoB)) 3) Are the CACNA1C and signalling molecule mutant phenotypes conserved between flies, rats and humans? The student will compare electrophysiological recordings from: A) fly neurons (with/out CACNA1C mutations above) B) rats with/without a hemizygous CACNA1C mutation C) human epileptic brain tissue (with/out CACNA1C mutations) Data will be acquired with parallel recording protocols and used to generate computational models that will describe the neuronal behaviour mediated by CACNA1C and interacting signalling molecules in the different diseases and animals. Revealing how each mutation may lead to pathology. The mechanistic and modelling experiments will help suggest genetic and pharmacological approaches to reverse CACNA1C mutant phenotypes which they will test in an iterative process suggesting novel approaches to treatment of CACNA1C diseases. Training by JH, Dr Cezar Tigaret (CT, Cardiff University (CU)) and Prof Alain Nogaret (AN, Bath University (BA)).
Supervisory Team	
Lead Supervisor	
Name	Professor James Hodge
Affiliation	Bristol
College/Faculty	Life Sciences
Department/School	Physiology, Pharmacology and Neuroscience
Email Address	james.hodge@bristol.ac.uk
Co-Supervisor 1	
Name	Dr Doretta Caramaschi
Affiliation	Exeter
College/Faculty	Faculty of Health and Life Sciences
Department/School	Psychology
Co-Supervisor 2	
Name	Dr Cezar Tigaret
Affiliation	Cardiff
College/Faculty	Neuroscience and Mental Health Innovation Institute
Department/School	School of Medicine
Co-Supervisor 3	
Name	Professor Alain Nogaret
Affiliation	Bath
College/Faculty	Centre for Networks and Collective Behaviour
Department/School	Physics