Project Details	
Project Code	MRC22NMHBr Hodge
Title	Modelling the role of L-type voltage-gated calcium channels (CACNA1C) in behaviour and mental health
Research Theme	Neuroscience & Mental Health
Summary	CACNA1C regulates neuronal excitability underlying memory, sleep and circadian rhythms and has been associated with schizophrenia, autism, bipolar disorder and ADHD. CACNA1C blockers are prescribed for hypertension, pain, epilepsy and neurodegenerative disease. We propose to characterise CACNA1C disease variants in Drosophila using behaviour, electrophysiology, imaging, pharmacology and computational modelling to understand plasticity and pathology mechanisms.
Description	Schizophrenia, autism spectrum disorder (ASD), bipolar disorder (BD) and attention deficit hyperactivity disorder (ADHD) are very common (affecting 1-10% of the population), poorly understood, poorly treated and severely debilitating mental disorders. Patients suffer from a range of symptoms that often overlap between the disorders including social impairments, depression as well as disrupted activity, circadian rhythms, sleep, learning, attention and sensory processing. The causes of these psychiatric disorders are mostly genetic, with human sequencing revealing a number of genes and mutations associated with the disease. Both rare and common variants in the gene encoding the CACNA1C L-type voltage-gated calcium (VGCCs) have been associated with these disorders and more generally with developmental delay with genome-wide significance. CACNA1C controls calcium signalling, neuronal excitability and synaptic plasticity. Furthermore, drugs which target VGCCs including CACNA1C are used to treat hypertension, epilepsy and pain. Therefore, there is a large potential for CACNA1C drug repurposing for psychiatric disease. Currently there are only limited treatments for schizophrenia, ASD, BD and ADHD which have many adverse effects. None currently target CACNA1C. Therefore, there is a great unmet need for research to understand better these overlapping diseases to aid diagnosis and development of better drugs. The overall aim of this PhD is to understand how and why so many CACNA1C mutations lead to such a range of psychiatric diseases. The student will learn to harness the powerful genetics, speed and experimental tractability of Drosophila to compare the effect of CACNA1C mutations associated with the different diseases. The fly orthologue of CACNA1C is Ca-alpha1D gene, for which we have targetable and inducible RNAi loss-of-function (LOF) mutants. They will also use a promoter insert in the Ca-alpha(a)D gene which is a null/strong LOF mutant which can be crossed with a pre-existing GFP lines to check when and where Ca-aD is expressed. They will then order or generate (using CRISPR) a promoter responsive human CACNA1C and fly Ca-aD wildtype transgene to check genetic rescue of the fly Ca-aD promoter mutant. They will also make promoter responsive transgenes for human CACNA1C nonsense truncation (1175Q>*), missense (1452A>S and 2077A>T) mutations associated with the different psychiatric disease. They will use these existing and novel models to study the resulting changes in disease-relevant behaviours e.g. activity, circadian rhythms, sleep, learning, attention, sensory processing, social interaction and mood. They will then be trained in mechanistic studies to

	understand underlying pathway changes in e.g. calcium signalling, interacting genes, synaptic plasticity, neuronal excitability, mitochondria and organelle/neuronal morphology. They will be trained in computational modelling of VGCC function in neuronal signalling and how each mutation may lead to pathology in flies and mammals. Their mechanistic and modelling experiments will help suggest genetic and pharmacological approaches to reverse CACNA1C mutant phenotypes which they will test in an iterative process in flies. Our objectives will address important unmet needs and bottlenecks in current psychiatric disease research including the lack of new animal models based on the ever-increasing number of new gene variants associated with the disorders and the need for high-throughput in vivo drug and genetic screening platforms for better psychiatric disease treatments. The PhD will develop L-type VGCC as a target to reverse deficits caused by CACNA1C schizophrenia, ASD, BD and ADHD associated mutations. The student will have the opportunity to translate their findings to mammals, as the host-lab has a MRC project grant on rodent models of CACNA1C in synaptic plasticity and behaviour and have clinical grants to study CACNA1C in disease cohorts thereby maximising impact of the PhD.
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