Project Details	
Project Code	MRC21NMHBr O'Donnell
Title	Computational modelling of dysfunctional synaptic plasticity in neuropsychiatric disorders
Research Theme	Neuroscience & Mental Health
Summary	Many genes coding for synaptic proteins have been linked to neuropsychiatric disorders like autism and schizophrenia. One puzzle is why these various genetic mutations lead to overlapping cognitive symptoms. This project will tackle the problem using data-driven computational models of biochemical signalling at synapses, focusing on the role of Cacna1c L-type calcium channels. It will be a mix of numerical simulations, mathematical analysis, and data analysis.
Description	This project will develop data-driven computational models of calcium signalling at synapses to understand how genetic mutations may lead to altered synaptic plasticity and learning in neuropsychiatric disorders. It will involve computational modelling, statistical model fitting to physiology data, and mathematical analysis of the model's nonlinear dynamics. Neuropsychiatric disorders such as Autism Spectrum Disorder (ASD) and Schizophrenia are widespread, with around 1.7% of children in the United States diagnosed with ASD and around 0.7% of people being diagnosed with Schizophrenia at some point in life. Current behavioural and pharmaceutical treatments for neuropsychiatric disorders are effective for only a subset of patients, often carry unwanted side-effects, and treatment success is difficult to predict from patient to patient. These shortcomings reflect the fact that almost all existing drug treatments were discovered by chance, rather than being designed based on an understanding of disorder mechanisms. However, a recent wave of discoveries of 70-100 genetic mutations linked to each of ASD and Schizophrenia has given promising clues to the origins of these disorders. Many of the genes code implicated are important for synapses – the connections between neurons that mediate learning and memory in the brain. This implies that many neuropsychiatric disorders may in fact be disorders of synaptic plasticity. This project will focus the effects of mutations in one particular gene: Cacna1c, which encodes the alpha subunit of Cav1.2 (L-type) voltage-gated calcium channels. These ion channels are expressed at synapses and are key mediators for synaptic plasticity induction and neuronal gene expression. Mutations in CACNA1C have been linked with a range of neuropsychiatric disorders such as schizophrenia, bipolar disorder, and ASD. Labs around the world are studying various mouse models of Cacna1c dysfunction. They find a range of behavioural symptoms, with mirrored phenotypes at the cellular and synaptic level. The next challenge for the field is to use these insights to design candidate interventions for patients. This project will help bridge this gap. The project will have three phases: 1. Build a computational model of postsynaptic calcium signalling dynamics at rodent hippocampal Shaffer collateral synapses, with particular emphasis on the L-type calcium channel. This model will be built using Python or Julia programming language, and adapted from a model recently developed in the lab of lead supervisor O'Donnell at Bristol. 2. Use statistical optimisation tools to fit the model's parameters to electrophysiology data from wild type

	mice and Cacna1c -/- mice recorded in the lab of co-supervisor Hall at Cardiff. Use the model to test whether differences in L-type calcium channel properties can explain effects on synaptic plasticity. 3. Use model reduction techniques to derive a compact form of the synapse model, and analyse the reduced model with mathematical tools from nonlinear dynamics, in the group of co-supervisor Tsaneva-Atanasova at Exeter. This analysis will isolate the key functional role of L-type calcium channels in plasticity induction, and offer a theoretically-grounded framework for designing new interventions to rescue synaptic plasticity deficits in Cacna1c mutant animals.
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