Project Details	
Project Code	MRC21NMHBr Mellor
Title	A genetic risk factor underlying impaired cognitive flexibility and neural plasticity in psychiatric disorders.
Research Theme	Neuroscience & Mental Health
Summary	Genetic risk factors for psychiatric disorders are clustered around genes that regulate synaptic function and adaptation indicating common disrupted biological processes. In this project, we will uncover how one of these genes (Dlg2) perturbs a core feature of synaptic signalling to increase susceptibility to early life stress, and leads to abnormal cognitive processing.
Description	The genetic background and early life experiences of children are key determinants in their future mental health. Early life adversity including trauma or disruption of the mother-infant relationship and genetic risk factors are highly significant in determining a child's future susceptibility to a range of psychiatric disorders including anxiety, depression and psychosis. Genetic risk factors cluster around genes involved in synaptic function and plasticity but we know relatively little about the core features of synapses that are disrupted and how these interact with the stress caused by early life adversity. Emerging evidence indicates that many key psychological processes such as perception and cognitive flexibility rely on dendritic signalling events generated by the interaction of multiple synapses on single neurons. These dendritic signals are extremely sensitive to neural network perturbations caused by genetic mutations to synaptic proteins or changes in brain state mediated by neuromodulators such as acetylcholine. Thus, we propose that genetic risk factors and adverse early life events will lead to disrupted dendritic signalling leading to cognitive deficits observed in psychiatric disorders. Furthermore, the combined effects of genetic and environmental factors may prove to be much more pronounced than the individual effects. This demonstrates how genetic mutations that affect dendritic signalling may modulate susceptibility to early life stress, thereby determining psychological outcomes. Ultimately, reversing perturbations to dendritic signalling could ameliorate the behavioural effects of early life adversity in adults. This project will test this hypothesis using transgenic animals bearing mutations in the synaptic protein Dlg2 associated with psychiatric illness and early life stress models developed by the Hall, Wilkinson and Mellor groups. The primary objective will be to determine how these individual and combined factors affect dendritic signalling by making electrophysiological measurements of synaptic transmission coupled with imaging of synaptic and dendritic calcium signals, techniques routinely used in the Mellor and Ashby groups. This work will align closely with ongoing collaborations with early career researcher Cian O'Donnell using computational modelling to decipher the molecular interactions within and between synapses that contribute to perturbed function. We will also measure the effects of these factors on animal behaviours such as cognitive flexibility relevant to psychiatric illness. The ultimate goal will be to find out if manipulating dendritic signalling using pharmacological or optogenetic tools is capable of changing behavioural outcomes in adult animals. The student will be trained in Bristol in dual electrophysiology and 2-photon imaging performed in vitro and in vivo

	and genetic manipulation of neuronal subtypes and related molecular techniques. The student will also receive training in animal behavioural paradigms developed in Cardiff and Bristol. In addition, through collaboration with Cian O'Donnell the project can also be extended to use computational models to predict the likely outcome of dendritic signalling perturbations on behaviour.
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