Project Details	
Project Code	MRC23NMHBr Drake
Title	Sex Differences in Chronic Pain; A Role for Noradrenaline in Cognitive Flexibility
Research Theme	Neuroscience and Mental Health
Summary	Chronic pain is much commoner in women; this studentship will investigate whether differences in brain noradrenergic signalling underpin the sex differences. Using cutting edge methods for recording and manipulating neurons in rodents, you will investigate the role of noradrenaline in cognitive and behavioural flexibility in chronic pain. The student will benefit from industry interactions to enable translation to the human condition.
Description	Chronic pain is increasingly viewed as a disorder of the brain in which impairment of executive functions like cognition, emotional regulation and adaptive behaviour are central to disease development. Noradrenaline signalling from the Locus Coerelus (LC) to the frontal cortex is important for cortical function in tasks that require flexibility in response to changing rules and conditions. Previous work from our lab implicates LC to frontal cortex noradrenaline signalling (10.7554/eLife.29808) and loss of cortical control (10.7554/eLife.65156) in the development of chronic pain in rats. Additionally, that LC to frontal cortex NA signalling plays a critical role in cognitive flexibility (10.1371/journal.pcbi.1006267). We now wish to bring these concepts together to understand how noradrenaline signalling in the frontal cortex alters cortical output to regulate flexible behaviour, and whether maladaptation of this process underpins the vulnerability to develop chronic pain. Significantly, there are known sex differences in the LC-frontal cortex system. An important aspect of this project will be to identify sex differences in frontal NA signalling, its role in cognitive flexibility and in the maladaptation of the system following injury. The project will utilise experimental techniques that are well developed in our laboratory for the monitoring (electrophysiology, fibre photometry) and manipulation (opto- / chemo-genetics) of specific neuronal populations in behaving animals. The first aim is to investigate how levels of frontal cortex noradrenergic signalling effect behavioural flexibility in uninjured animals during cognitive tasks (e.g. reversal learning, virtual competitor) and/or acutely stressful events. By selectively controlling LC to frontal cortex inputs we can determine its causal contribution to decision making and behaviour. These experiments will reveal the relationship between NA neurotransmission, cortical neuronal activity, and flexibility of behaviour. Additionally, how this differs between male and females and relates to differences in cognitive and behavioural strategies they use. The second aim is to understand how these characteristics in healthy animals can then predict the likelihood of developing chronic pain following injury. We will use a chronic pain model in which female rats show twice as much sensory hypersensitivity than males (mirroring the increased prevalence of pain in women). Using the same experimental approaches used in aim 1, the project will assess how prefrontal NA signalling is altered over the development of chronic pain, whether there are differences in these changes between male and female animals and how this alters sensory,

	affective and cognitive aspects of chronic pain. By relating findings from aims 1 and 2 we will determine how cognitive flexibility in health predicts features of chronic pain in male and females. By relating this to noradrenergic signalling we will identify neuronal pathway, receptors and mechanism that may form therapeutic targets for chronic pain, mental health and neuropsychiatric conditions. An important aspect of this project is bringing together laboratories spanning animal, human and clinical research with specific but complimentary knowledge in pain neurobiology, human psychology and clinical experience. The student will have the opportunity to spend time in both animal and human experimental laboratories as well as specialist pain clinics. This will be important for the refinement of animal behavioural tasks to offer improved translation of findings to the human condition. Additionally, the student will have the opportunity to develop new experimental tools, machine learning for behavioural analysis and the use of implanted miniscopes for recording neuronal populations. This training in translational neurobiology and contemporary experimental methods will allow the student to produce innovative and impactful research outputs.
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