

Project Details	
Project Code	NMH27Ex Lawrenson
Title	Translational models to predict emotional susceptibility to chronic pain
Research Theme	Neuroscience & Mental Health
Project Type	Wet lab
Summary	This project aims to investigate how our emotions make individuals susceptible to the experience of pain. By identifying and applying a translational model of emotional flexibility, the neural networks that underly comorbidities of fear and anxiety disorders will be correlated with pain phenotypes to determine underlying mechanisms that predict susceptibility to pain.
Description	Chronic pain presents a major biological and societal challenge in the UK and worldwide affecting a substantial proportion of the population and imposing significant healthcare and socioeconomic costs. It remains difficult to treat effectively, reflecting an incomplete mechanistic understanding of how pain is generated, regulated and maintained in the brain. The experience of pain is dynamic beyond nociceptive signaling, affected by emotional, motivational and cognitive factors. There is a strong comorbidity between emotional disorders and the experience of pain where individuals with fear, anxiety and depression are more likely to develop chronic pain. Likewise, chronic pain can trigger long term negative emotional states. The neural substrates that represent fear and anxiety overlap with pain control demonstrating key mechanisms that could be targeted therapeutically. The brain is constantly updating information from a range of sensory inputs to modify our internal view of the world called internal models. Measuring the ability to update emotionally relevant internal models, could provide predictive insights to the pain experience. For example, a reduction in emotional flexibility might predict individuals who can become 'stuck' in an enhanced pain state, while an individual in a more emotionally flexible state might better adapt to pain leading to an overall reduction in the pain experience. The student will be based within the Exeter pain group, with the advantage of conducting research techniques that span rodent and human models. If this project is successful, measures of emotional flexibility could be used to better understand the neural mechanisms of high impact pain and have the potential to be used for more targeted therapeutics. Key research questions: This PhD project aims to identify translationally relevant behavioural biomarkers of pain susceptibility and to determine whether non-invasive modulation of pain-related neural pathways in rodent models can alter susceptibility to pain. To predict pain phenotypes, translational methods that can bridge human and rodent models must rely on quantitative measures that go beyond psychological questionnaires of fear and anxiety in humans. Behavioural measures of emotional prediction error (where there is a mismatch between expected versus actual outcomes) might provide a method for non-invasively identifying how individual flexibility relates to

	the pain experience. Flexibility of emotionally related prediction error signals may provide direct insight into flexibility of internal pain models. Work package 1 (months 0-24): Supervised by Dr Charlotte Lawrenson the student will conduct research in male and female rodents to investigate emotional susceptibility to chronic neuropathic and inflammatory pain. Cued and contextual conditioning studies will provide insight into emotional flexibility by investigating individual measures of learning and extinction. A variety of paradigms will be assessed for their predictive power in pain phenotypes. Initial training will be required to obtain a PIL qualification, and further training will be conducted to learn surgical techniques and behavioural handling. Work package 2 (months 12-24): In collaboration with Dr Daniel Whitcomb (Bristol) the student will use targeted TUS, a non-invasive neuromodulatory technique, to target known pathways involved in emotional control to assess effects on neuropathic and inflammatory pain susceptibility. Work package 3. (Months 18-42): The student will use human pain models and quantitative sensory testing supported by co-supervisor Dr Sam Hughes to explore the relationship between pain and fear learning paradigms to assess emotional flexibility that parallels the studies carried out in work package 1. This will be carried out in collaboration with co-supervisor Dr Tom Barry at the University of Bath, who will advise on the use of fear conditioning and extinction in humans to monitor emotionally related prediction error signals. The initial months (18-24) will involve experimental design, pre-registration and ethical approval before conducting studies. Work package 4. (Months 24-42): Neuroimaging (fMRI) will be integrated with experiments in WP3 to investigate CNS regions that correlate with emotionally related prediction error signals and their relationship with pain specific activity. Target regions of interest will span the cortical-brainstem-spinal pain networks (with the support of co-supervisor Dr George Tackley) to include (but not limited to) the periaqueductal grey, the cerebellum and spinal dorsal horn. Student ownership In the first three months of study the student will conduct a literature search to assess translational methodologies for investigating emotional flexibility. They will also gain background knowledge of pain models and related CNS networks to identify pathway targets of interest relevant to both rodents and humans. The student will use results from this work to create models, using machine learning and AI, to predict future pain outcomes.
Can be completed part time?	No
Supervisory Team	
Lead Supervisor	
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