Project Details	
Project Code	MRCNMH26Ca Tackley
Title	Pain as neurobiological surprise: Using human brain imaging and animal studies to advance new concepts in persistent pain.
Research Theme	NMH
Project Type	Wet lab
Summary	Complex nervous systems attempt to minimise surprise and aid survival by forming predictions about the world. Surprise signals danger: it is evidence that the future was poorly predicted. Short-term (acute) pain has a lot in common with surprise. We propose that pain too signals a poorly predicted future, specifically poorly predicted damage. Using human neuroimaging and rodent studies, this project will explore conscious and unconscious predictions, asking whether a reconceptualisation of pain as surprising damage is valid. For some individuals, pain networks malfunction causing persistent (chronic) pain and we believe our reconceptualisation could revolutionise the understanding of this debilitating state.
Description	**BACKGROUND** Human tissue damage does not always lead to pain. There are circumstances in which damage-responsive (nociceptive) "pain" pathways are active and yet minimal, or no pain is felt. The placebo effect is one example, as are reports of soldiers feeling no pain from battle-related injuries [Best 2014]. Recently, in-vivo imaging of the spinal cord of awake, behaving, healthy rodents demonstrated that painless nociceptive pathway activity is nearly continuous [Ahanonu 2024] and suggests that nociceptive pathways are being utilised during non-painful behavioural states. Whilst this raises many questions, one is: When and how does damage information processing become painful? One possibility is that pain is felt only when a nociceptive signal is sufficiently surprising. And not simply the surprise of violating a consciously available expectation. Whilst conscious nociceptive surprise is part of the system, hierarchical models of pain place this as the uppermost link in a multi-level chain of unconscious nociceptive surprise evaluation, from peripheral nociceptive circuits, through to spinal cord networks and subcortical and cortical areas [Friston 2022]. In this model, the predominantly unconscious surprise (or prediction error, PE) only becomes conscious (we posit: as pain) if it is passed all the way to the top. Even when pain is felt (consciously), the internal model generating the PE may be largely or wholly unconscious. An intuitive parallel is the PE experienced when stepping onto an unmoving escalator [see Gomi 2014]. ---------- Our hypothesis, then, is that nociceptive ('damage') information is only experienced as pain to the degree that the damage is unexpected (or surprising = PE); We propose that this is faulty in chronic pain, leaving people in a state of constant nociceptive 'surprise' [van Ettinger-Veenstra 2019]. ----------

	Our hypothesis is in essence another predictive processing hypothesis of pain but with an important distinction. Previous hypotheses have enshrined pain as the sensory phenomena that is modelled and predicted; In our hypothesis, damage (nociception) usurps pain and instead posits that pain arises only where damage is underestimated. This new conceptualisation leads to some unexpected predictions, including: a. Whilst we can consciously anticipate that something will be painful, complex unconscious predictive models about our future sensory state do not predict pain, only nociception; b. Pain exists only in the conscious sphere and represents elevated nociceptive PEs from lower levels; c. Pain can be considered equivalent to conscious PE: it drives prediction updates but it does not form part of that prediction; d. If nociception is accurately predicted, no error results and no pain is experienced; e. Because pain can be considered conscious PE, conscious anticipation of pain is an awareness of the uncertainty (error-fullness) of nociception predictions. **KEY RESEARCH QUESTION:** Is pain a conscious prediction error resulting from inaccurate nociceptive predictions? **OBJECTIVES:** 1. Behavioural. Aim: to create a model of nociceptive prediction error that translates between humans and rodents. Approach: This could take the form of a door opening task that is ecologically associated with a mildly noxious stimulus (thermal or punctate) at the point of door contact. The stimulus would be calibrated prior to the task, outside of the task paradigm, to produce reports of mild pain in humans and minimal nocifensive behaviour in animals. If sufficiently ecologically valid, training may not be needed to reduce or abolish pain percept / nocifensive behaviour. Reversal of the expected contingency, e.g. by altering the noxious intensity of the stimulus would provide insight into nociceptive prediction-error model updating and pain experience. 2. Assessing CNS function. Aim: to perform imaging in humans and lesions/modulation in rodents that provides neurobiological underpinnings of the behavioural model. Approach: Using the suggested behavioural model above, rodents with lesions of CNS Candidate areas for prediction error processing (e.g. the PAG / RVM / cerebellum) can be tested to determine rate of model updating. This might also be tested in chronic pain patients, or a selection of participants enriched for slower model updating. Human participants can then undergo functional MRI imaging to determine if the same candidate areas are implicated (e.g. via cerebellar-PAG connectivity). **STUDENT-LED COMPONENTS** Having reviewed the literature, in liaison with the supervisors, the student will have the opportunity to use their knowledge to update the hypotheses and research question. Across the two Universities and our

	three departments (see details in the 'Research Environment' section below) we have access to a range of state-of-the-art equipment and facilities. Once familiarised with these and the current state of field, the student will be able to develop novel paradigms to explore the research question and test hypotheses. These could include use of virtual reality, a split-belt instrumented treadmill that moves in pitch and sway, the latest single-unit EMG recording, MRI, EEG and MEG, as well as sophisticated murine experimental environments.
Supervisory Team	
Lead Supervisor	
Name	Dr George Tackley
Affiliation	Cardiff
College/Faculty	Biomedical and Life Sciences
Department/School	Psychology
Email Address	tackleyg@cardiff.ac.uk
Co-Supervisor 1	
Name	Dr Jennifer Davies
Affiliation	Cardiff
College/Faculty	College of Biomedical and Life Sciences
Department/School	Healthcare Sciences
Co-Supervisor 2	
Name	Dr Charlotte Lawrenson
Affiliation	Bristol
College/Faculty	University of Exeter Medical School
Department/School	Clinical and Biomedical Sciences
Co-Supervisor 3	
Name	
Affiliation	
College/Faculty	
Department/School	