Project Details	
Project Code	NMH27Ca Tackley
Title	Pain as neurobiological surprise: Using human brain imaging and animal studies to advance new concepts in persistent pain.
Research Theme	Neuroscience & Mental Health
Project Type	Other
Summary	We experience surprise when our best guess about the immediate future turns out to be wrong. This can be dangerous: it might mean tripping on an unexpectedly loose stone, or underestimating the temperature of a saucepan and burning your hand. Thus, to survive, animals are constantly in the business of minimising surprise. This PhD will test the idea that pain is a form of neurobiological surprise, specifically signalling unexpected threat or damage. This will be explored using human neuroimaging and rodent studies, evaluating the influence of conscious and unconscious predictions, and investigating the maintenance of persistent (chronic) pain states.
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 . Recent in-vivo imaging of the spinal cord of awake, behaving, healthy rodents has demonstrated that nociceptive pathways are nearly continuously active providing critical evidence that these pathways are active during non-painful behavioural states. Whilst this raises many new questions, this is intrinsically important to an old one: When and how does nociceptive signalling become painful? Melzack and Wall hypothesised over half a century ago that pain is actively regulated and constructed via gating of nociceptive signalling at the level of the spinal cord, and whilst subsequent decades have refined the details, their broad thesis remains central to our understanding of pain. Building on this long-established foundation, we suggest that pain is only "allowed through the gate" when a nociceptive signal is sufficiently surprising. In this model, the predominantly unconscious surprise (or to use predictive coding terminology: prediction error, PE) only becomes conscious (i.e. painful) if it is elevated to consciously available processes. Even when pain is felt (consciously), the internal model generating the PE may be largely or wholly unconscious. An intuitive parallel is the familiar visceral jolt experienced when stepping onto an unmoving escalator: conscious surprise (the visceral jolt) results from erroneous unconscious predictions (that the escalator is moving). 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'. Our hypothesis is in essence another predictive coding hypothesis of pain but with a distinct emphasis. 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 and testable predictions, including: a. If nociception is accurately predicted, no PE results and thus no pain is experienced; b. Whilst we can consciously anticipate pain, complex unconscious predictive models about our future sensory state do not predict pain, only nociception; c. Pain exists only in the conscious sphere and represents escalated nociceptive PEs from lower levels; d. Pain is a conscious manifestation of a nociceptive PE: it drives prediction updates but it does not form part of that prediction; 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 motor task (developed by the student) associated with a mildly noxious stimulus. 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 assessing cerebellar-PAG connectivity). Flexible / 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, psychophysics, as well as sophisticated rodent experimental environments.
Can be completed part time?	Yes
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