Project Details	
Project Code	NMH27Br Dunham
Title	What drives the pain? Exploring the peripheral component in models of central sensitisation.
Research Theme	Neuroscience & Mental Health
Project Type	Wet lab
Summary	Chronic primary pain affects 8 million UK adults, but we still do not understand what drives pain when there is no identifiable injury or disease. Most research has focused on changes in the spinal cord and brain, but emerging evidence suggests that peripheral 'pain' nerves may also become sensitised and overactive. During this PhD, you will learn microneurography, a rare technique that records directly from individual human pain nerves. You will investigate how pain nerves change during experimental pain models and whether similar changes occur in patients with fibromyalgia, challenging current theories and identifying mechanisms that could inform better treatments.
Description	Chronic primary pain is pain for more than three months without an identified underlying injury or disease that explains its severity. It affects millions of people and is difficult to treat. Medicines are often of limited benefit. Developing better treatments requires a clearer understanding of the biological mechanisms that cause pain to persist. Most current theories focus on changes within the central nervous system, the spinal cord and brain. These include increased responsiveness of pain-processing neurons (central sensitisation), reduced activity of the brain's own pain-control systems, and amplification of pain-related signals within the brain. However, emerging evidence suggests that the peripheral nervous system may also contribute. Nociceptors are specialised sensory nerves that detect damage and provide the signals that can give rise to pain. In healthy people, nociceptors are silent in the absence of tissue damage. Recent studies have identified abnormal ongoing activity and increased sensitivity of peripheral nociceptors in conditions including fibromyalgia and Long Covid. Experimental pain models in healthy volunteers provide an important way to investigate how peripheral and central mechanisms interact to produce persistent pain hypersensitivity. Capsaicin applied to or injected into the skin and high-frequency electrical stimulation (HFS), for example, can produce increased pain in response to stimulation outside the treated area. This secondary hyperalgesia is generally interpreted as evidence of increased responsiveness within central nociceptive pathways. However, there is an important problem. In the well-characterised capsaicin model, an intense barrage of nociceptor activity initiates central sensitisation, while continued peripheral nociceptor activity contributes to its maintenance. Neither feature fits comfortably with conventional theories of chronic primary pain, in which substantial ongoing peripheral nociceptor input is generally assumed to be absent. Emerging evidence of abnormal nociceptor activity in patients challenges this assumption, but there is little reason to believe that chronic primary pain is initiated by the intense, acute nociceptor barrage used in the capsaicin model.

	HFS provides an important opportunity to investigate this problem. Like capsaicin, HFS produces prolonged secondary mechanical hyperalgesia that is widely attributed to sensitisation of central nociceptive pathways. Unlike capsaicin, spontaneous pain and visible signs of peripheral inflammation diminish rapidly following stimulation. HFS is therefore often considered a model in which prolonged pain hypersensitivity is maintained predominantly by changes within the central nervous system. But a fundamental assumption remains untested: does peripheral nociceptor activity really return to normal after HFS? Resolving this question is important for both experimental and clinical pain research. If nociceptor activity remains altered after HFS, peripheral input may contribute to hypersensitivity currently attributed to central sensitisation. Conversely, if nociceptor activity normalises while hypersensitivity persists, HFS would provide a powerful model for investigating centrally maintained changes in pain processing. Comparing these findings with direct recordings from patients with chronic primary pain will establish whether either experimental state resembles mechanisms present in patients. This PhD will determine how the activity of individual human sensory nerve fibres changes during the development and maintenance of HFS-induced pain hypersensitivity and compare these changes with nociceptor activity recorded from patients with fibromyalgia. The project will use microneurography, a rare technique that allows electrical activity to be recorded directly from individual sensory nerve fibres in awake human participants. A fine, insulated microelectrode is inserted through the skin into a peripheral nerve, allowing individual C- and A-fibre nociceptors to be identified and characterised. During the first year, the student will develop expertise in microneurography and characterise the sensory changes produced by HFS, including changes in heat sensitivity and responses to punctate and dynamic mechanical stimulation. The student will then combine these approaches to determine whether, and how, different populations of sensory nerve fibres contribute to the development and maintenance of HFS-induced pain hypersensitivity. In parallel, the student will record from nociceptors in patients with fibromyalgia, characterising abnormalities in peripheral nerve activity and comparing these with changes observed in experimental pain models. The project will also draw on CUBRIC's advanced neuroimaging expertise and facilities to investigate brain and spinal cord activity associated with HFS-induced sensitisation. By studying peripheral nerve activity, sensory perception and central nervous system processing within the same experimental framework, the project aims to determine how peripheral and central mechanisms interact to produce persistent pain hypersensitivity. The later direction of the PhD will be shaped by the findings and the interests of the student. Possible directions include directly comparing HFS with the capsaicin model, investigating alternative methods of inducing prolonged nociceptor activity, or determining whether

	mechanisms identified in experimental models are present in other chronic primary pain conditions. Overall, this project will provide interdisciplinary training in human sensory neuroscience, pain physiology, microneurography, psychophysics and neuroimaging. It will address a fundamental and unresolved question in pain research: to what extent is persistent pain hypersensitivity maintained by ongoing activity in peripheral sensory nerves, changes within the central nervous system, or interactions between the two?
Can be completed part time?	Yes
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