Project Details	
Project Code	MRCNMH25Ba Bultitude
Title	Brain stimulation and neurophysiological investigations of central nervous system changes in pathological pain, and their augmentation by treatment.
Research Theme	Neuroscience & Mental Health
Summary	Chronic pain can involve changes throughout the central nervous system (CNS). Some treatments aim to alter CNS function, with limited results. This could be because research often investigates only one part of the CNS (e.g. cortex or spinal cord). This PhD will use brain stimulation, sensory testing, and neurophysiological methods to build an integrated understanding of changes in different levels of the CNS in chronic pain, and their modification by treatment.
Description	Many chronic pain conditions cannot be explained by pathology in the painful body part, and are driven by central nervous system (CNS) changes at multiple levels (e.g. the brain, brainstem, and spinal cord). These can include changes in the motor and somatosensory systems, and in top-down endogenous pain modulation (the CNS mechanisms that augment pain signals from the limb to the brain via the spinal cord). Some treatments, such as spinal cord stimulation, aim to relieve pain in a limb by altering another part of the CNS. However, this requires invasive surgery. Other approaches recondition the motor system through behavioural training, however these are intensive and often provide little pain relief. A limitation in the current understanding is that CNS changes in pathological pain are usually measured in only one part of the CNS. A greater understanding of changes throughout the entire CNS, how these relate to activity in endogenous pain modulation systems, and how these are affected by CNS-targeting interventions, could help refine treatments. This PhD will address these gaps with a view to informing treatment. Complex Regional Pain Syndrome (CRPS) will be our sample population because symptoms are severe but limited to one limb. This means the equivalent unaffected limb and corresponding nerves and brain areas can be used to collect within-subjects control data in addition to comparisons to pain-free controls. In study 1, the student will examine changes to cortical function, central pain processing, and somatosensory and motor function in 50 people with CRPS and 50 pain-free controls. They will choose the measures during the 'prep' period. Likely candidates are: - Transcranial Magnetic Stimulation (TMS) to measure the size and responsiveness of the representation of the affected limb on primary motor cortex (M1). - Established protocols (e.g. conditioned pain modulation, temporal summation of pain) for assessing endogenous pain modulation. - Quantitative Sensory Testing (QST) to gain an understanding of changes to somatosensory and pain processing. QST is a highly standardised psychophysical approach to measuring sensitivity to mechanical and thermal stimuli.

	We expect that in CRPS (versus pain-free controls): 1) M1 for the affected limb will be smaller and more excitable, 2) there will be diminished endogenous pain inhibition, and 3) the affected limb will have greater QST sensitivity. The student will also examine multivariate relationships between these measures, led by hypotheses generated during the 'prep' period. Study 2 will be a pilot Randomized Controlled Trial to examine the effects of a CNS-targeting intervention on the same measures as used in study 1. The intervention will be 5 repeated daily sessions of transcranial direct current stimulation (tDCS) to M1. TDCS is thought to alter the resting membrane potential in the underlying cortex, increasing or decreasing the likelihood of action potentials. Daily tDCS to M1 may activate corticospinal and corticothalamic projections, which in turn influence the activity of regions of deeper brain areas, the brain stem, and the spinal cord involved in pain modulation mechanisms. However no study has investigated the effects of tDCS throughout multiple levels of the CNS. Also, daily sessions of tDCS to M1 decreases pain in people with chronic pain, although there are no mechanism-driven studies in people with CRPS. Twenty people with CRPS will be randomized to receive tDCS to M1 contralateral to their affected limb, or sham (placebo) stimulation. We hypothesise that tDCS will reduce pain (compared to sham). Exploratory analyses will investigate which CNS changes recover after treatment and whether any of these predict pain outcome. This study will lead to a better understanding of the CNS mechanisms of tDCS treatment; the predictors of the effectiveness of the treatment; and the relationships between the motor, somatosensory, and endogenous pain modulation systems.
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