Project Details	
Project Code	MRCNMH24Ca DaviesJ
Title	Physical fatigue and the neural control of muscle activity in health and disease: Unravelling mechanisms and implications
Research Theme	Neuroscience & Mental Health
Summary	Fatigue can be explained as the feeling that we should stop or not start something. It normally subsides with rest but in many medical conditions this doesn't happen. Chronic fatigue is a troubling symptom across conditions with substantial impact on quality of life. Movements feel more effortful, reducing motivation to move. Why is this this case? This project will use start-of-the-art techniques to investigate control of movement in patients with chronic fatigue.
Description	When we are physically fatigued, movements feel more effortful. In this studentship you will use start-of-the-art neurophysiology techniques to explore why this might be the case and how this knowledge can improve our treatment of chronic fatigue across clinical conditions. Muscle contraction is controlled by spinal motor neurones, the firing of which is controlled by a combination of synaptic inputs that converge onto the cell from multiple levels of the motor system and neuromodulatory inputs that determine the intrinsic properties of the motor neurone. Neuromodulators are altered in many conditions that involve chronic fatigue. The impact of these changes on the neural control of movement is multifaceted, complex and not well studied. However, evidence from activity-induced (transient) fatigue in healthy individuals suggests that it is likely significant and potentially modifiable. Objective 1 will examine the intrinsic properties of motor neurones. If these are altered such that the neurones become more hyperpolarised in their resting state, a greater level of depolarisation from synaptic inputs would be necessary to initiate and execute muscle contractions. This would result in movements feeling more effortful– a hallmark of chronic physical fatigue. The intrinsic properties of motor neurones are strongly influenced by dendritic channels that create a persistent inward (depolarising) current. A decrease in the concentration of neuromodulators within the central nervous system would reduce these currents. Greater synaptic input would then be required to initiate and execute muscle contractions, leading to a heightened sense of effort. Objective 1 is to quantify the magnitude of persistent inward currents in spinal motor neurones in people with and without chronic fatigue. These currents will be quantified using paired motor unit analysis technique and the incidence of self-sustained firing, derived non-invasively from decomposition of high-density surface electromyography signals. Objective 2 will examine synaptic inputs to motor neurones. If the balance of inhibitory and excitatory inputs to the motor neurone is altered in the favour of more inhibition, more excitatory synaptic inputs would be necessary to initiate and execute muscle contractions. This would again result in movements feeling more effortful. Objective 2 is to quantify the excitability of spinal motor neurones, or the balance of inhibitory and excitatory inputs onto motor neurones, in people with and without chronic fatigue. You will be supported to select a focus for this objective based on your own interests. This is likely to include peripheral nerve and/or transcranial magnetic stimulation to probe a

	selected pathway within the motor system and using electromyography to record the response to this stimulation. You will be encouraged to consider cortical, brainstem, and spinal pathways involved in motor control and supported to develop a comprehensive understanding of the neural control of movement. Throughout the studentship you will work with people with lived experience of chronic fatigue to co-develop the details of the experimental protocol including the specific muscles and activities studied. You will explore how these mechanisms are related to reported fatigue levels and work with clinical trial methodologists to translate the mechanistic knowledge into novel interventions that can be tested in clinical populations with fatigue. This project is highly interdisciplinary and will cross physiology, neuroscience and applied clinical sciences. You will join the GW4 community studying fatigue in people with multiple long-term conditions. You will be part of a network of academics and clinicians working towards understanding the mechanisms of fatigue across clinical conditions and developing and testing novel targeted interventions for fatigue in people with multiple long-term clinical conditions
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