

## Background

Peripheral nerve fibres in the skin that respond to mechanical stimulation can be divided into two broad categories; high threshold mechanoreceptor afferents (HTMAs), which are nociceptors that encode for noxious range mechanical stimulation, and low threshold mechanoreceptor afferents (LTMAs) which encode the discriminative and affective aspects of light touch. Recently a class of unmyelinated LTMA has been recognised in humans, C-tactile afferents (CTs), which signal light pleasurable affiliative touch. CTs are also thought to play a pain modulatory role although the nature of this may be state-dependent. In general stimulation of CTs has analgesic effects but in neuropathic pain states their stimulation may cause pain/allodynia. Harnessing the analgesic effects of CTs represents a valid treatment target through pharmacological agents and neuromodulation.

It has been shown using functional MRI that the signals from CTs project to the insula cortex, a region of the brain that is also important for processing emotional aspects of pain. To establish if signals from CTs interact with the pain signalling pathways in spinal cord we investigated the psychophysical effects of cordotomy on pain and gentle touch. The cordotomy procedure treats cancer related pain by interrupting pain pathways in the spinothalamic tract of the spinal cord. Preliminary data from 20 cordotomy patients showed only very subtle changes in gentle touch perception but dramatic deficits in classical spinothalamic modalities along with resolution of pain.

The aim of this project is to further evaluate the central pathways of CTs and their interactions with pain processing. To verify and extend the preliminary psychophysical findings we are studying the behavioural consequences and sensory deficits in patients following cordotomy. This behavioural data will be correlated with

- 1) Lesion location and extent in the spinal cord as defined using structural MRI
- 2) The pattern of brain activity with fMRI in response to CT touch and painful mechanical stimulation
- 3) Automatic physiological consequences (psychophysiological) such as heart rate variability and galvanic skin response

## Progress

The project has had a significantly delayed start date. This was due firstly to the length of time needed to obtain approval through the NHS ethics system and secondly the time taken for the recruitment process for the Research Assistant. The project formally started 01/09/2018. The initial goal was to set up the functional imaging protocol at The Walton Centre. There were initial teething problems with the paradigm, which is to be expected, but the design and statistical plan has been formalised. The fMRI study design is shown below. Recruitment then started and we received a no cost extension. A further 4 patients were recruited and underwent formal psychophysics and autonomic testing. A further 2 underwent cervical spine imaging but unfortunately we did not have the opportunity to use the fMRI paradigm. Unfortunately we have had further unavoidable delays due to the COVID-19 pandemic.

