

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.

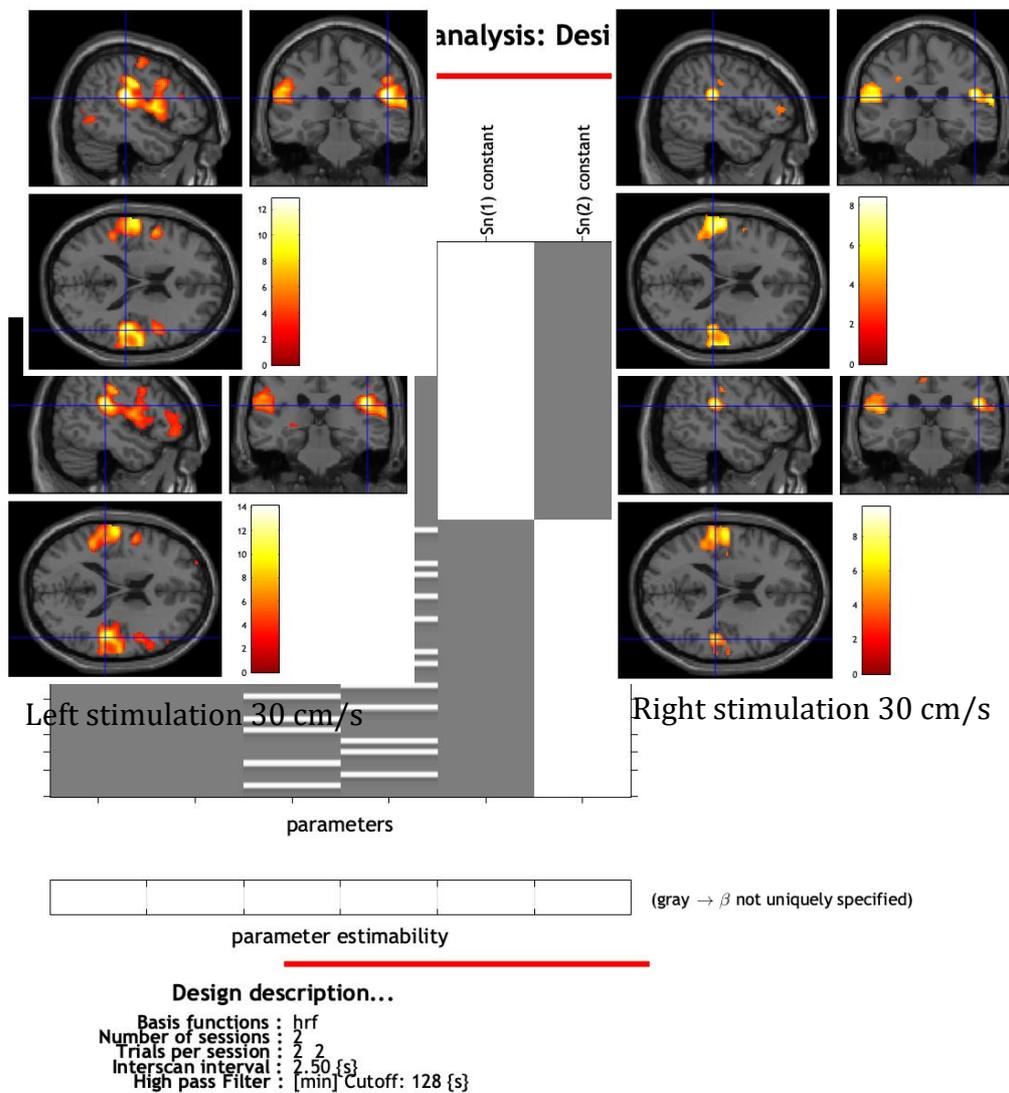
It has been shown using functional MRI that the signals from CTs project to the insula cortex, a region of the brain that is also important for processing emotional aspects of pain. To establish if signals from CTs interact with the pain signalling pathways in spinal cord we investigated the psychophysical 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.

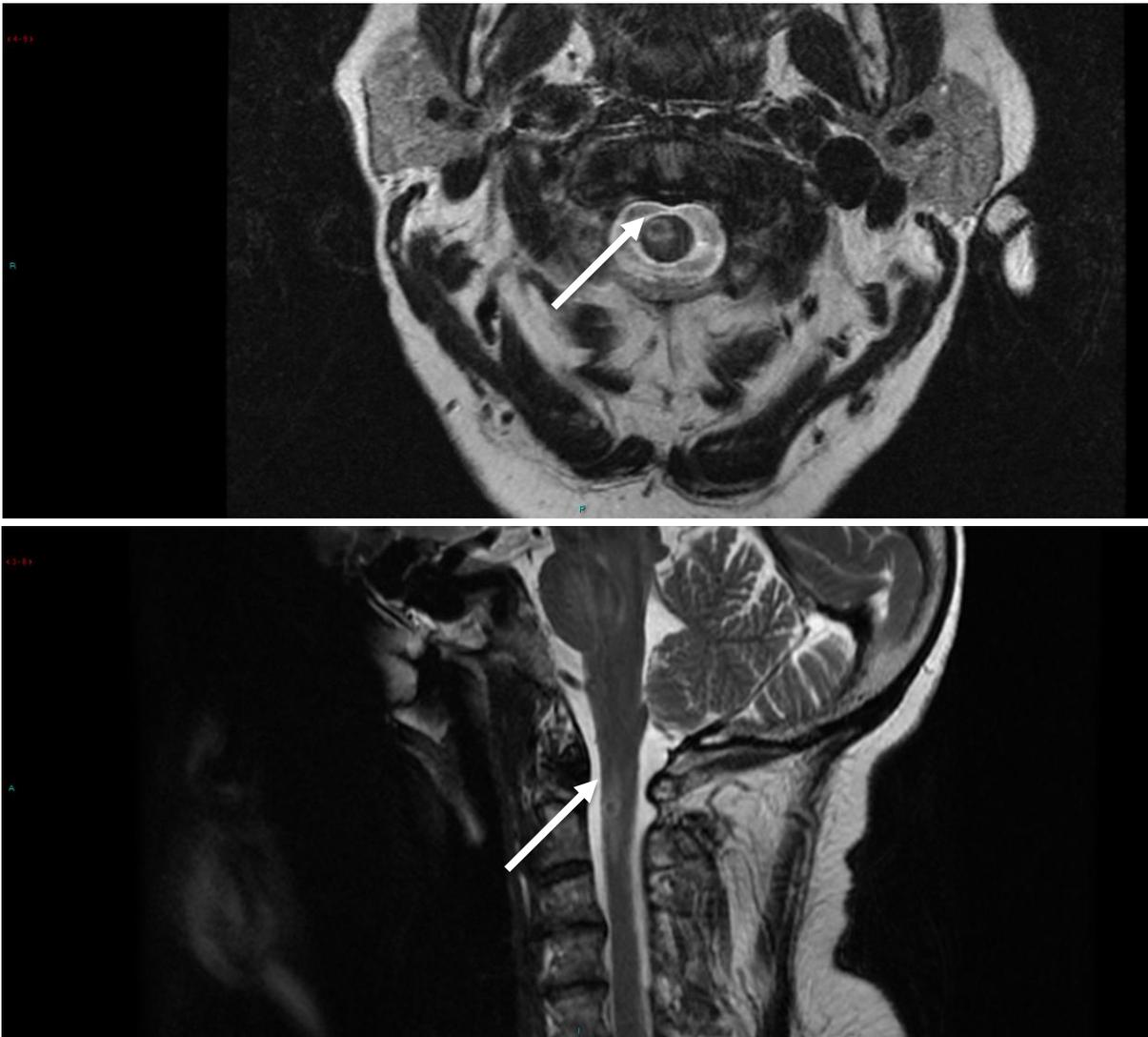


Left stimulation 3 cm/s

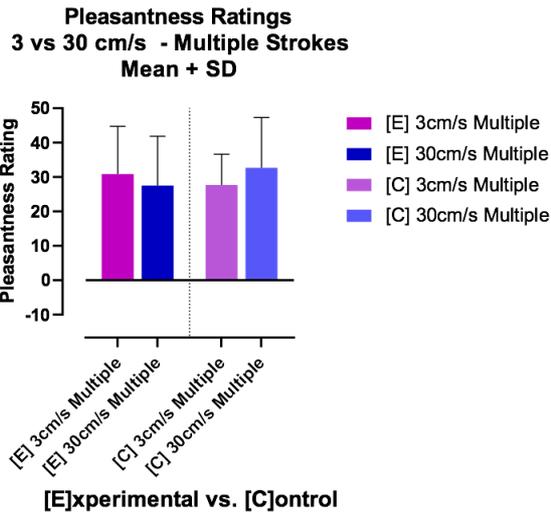
Right stimulation 3 cm/s

In addition structural imaging of the cervical spine as well as psychophysics and psychophysiology have been performed in 3 cordotomy patients. Representative images showing sagittal and transverse sections of the cervical spine on MRI are shown below. The lesion is marked with a white arrow. Analysis will be

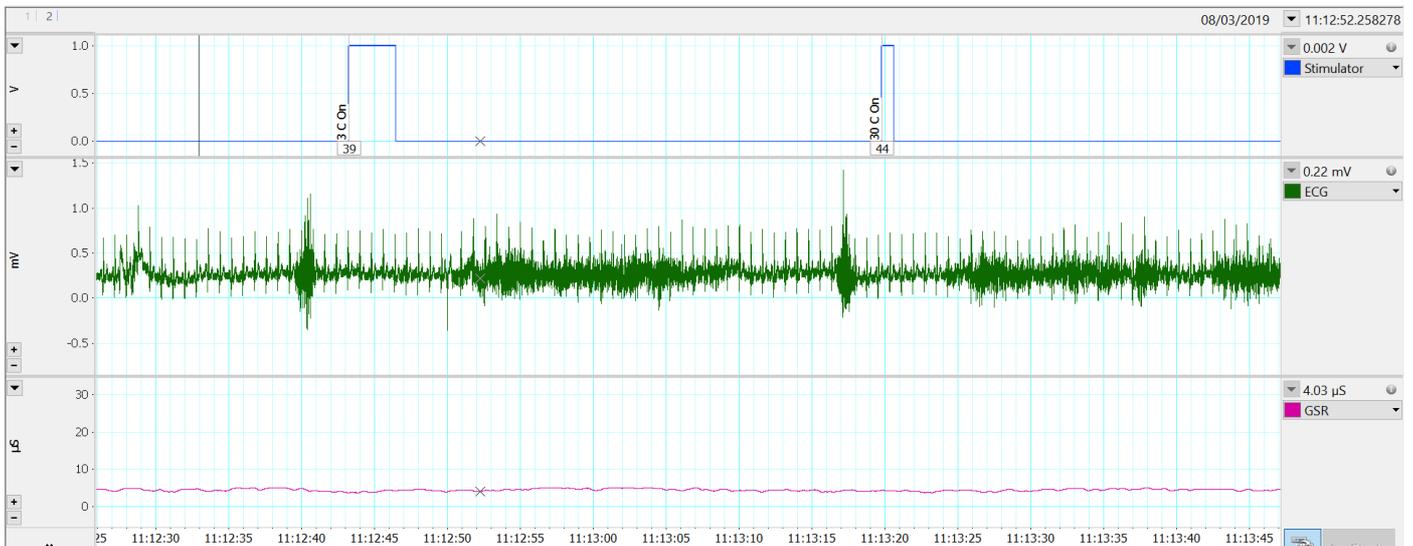
directed towards quantifying lesion location and volume so that this can be correlated with sensory deficits, pain relief and psychophysiological findings.



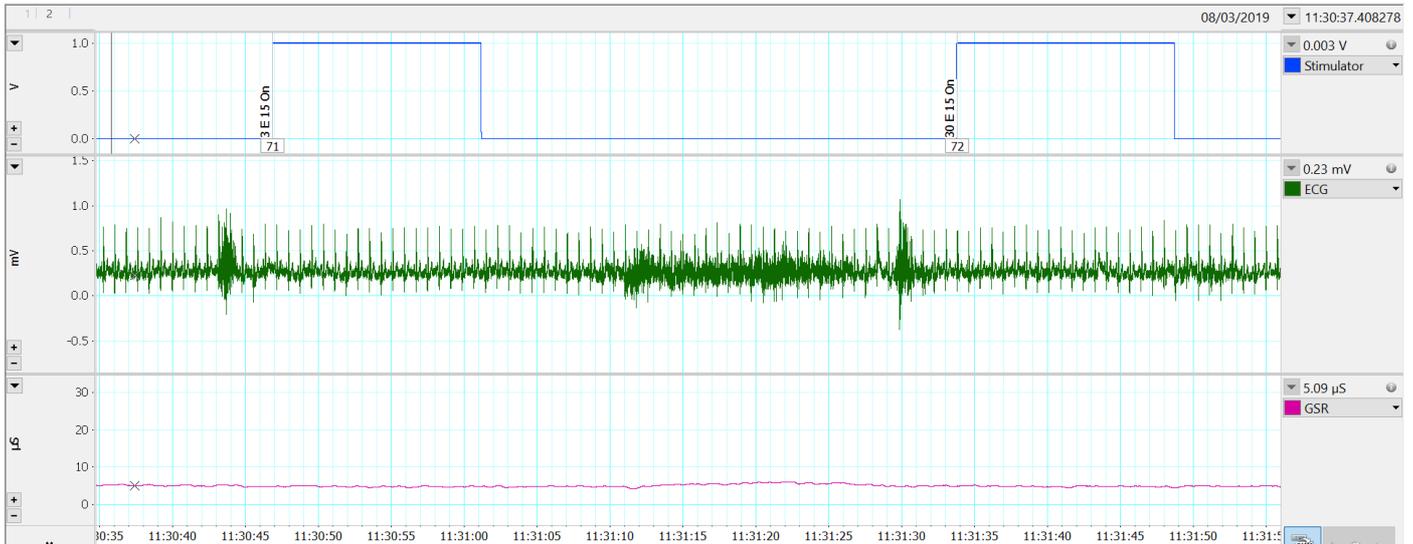
Psychophysical testing in the small number of patients tested to date has revealed clear cut evidence of canonical spinothalamic modality deficits in innocuous temperature, thermal pain and noxious mechanical pain perception (not shown). These findings accompany the immediate relief from cancer associated pain. Ratings of pleasantness for soft brushing on forearm hairy skin show subtle differences between the pain affected (Experimental) and unaffected (Control) sides post-cordotomy - see image below. The participant numbers are currently too small to detect statistical significance or to correlate with imaging and psychophysiological data.



Psychophysiological data was collected at the same time as psychophysical ratings and noxious temperature detection. This includes heart rate variability and the galvanic skin response (GSR). Raw traces to stroking on the pain affected and unaffected sides are shown below. This data is undergoing formal analysis and will be correlated with imaging and psychophysics. It is anticipated that on the side affected by cordotomy the GSR and change in heart rate will be lowered in response to stimulation with noxious temperature as well as soft brushing with CT optimal velocities.



Brushing (Single) + ECG + GSR
[C]ontrol Site



Brushing (Multiple) + ECG + GSR
Pain affected Side

Conclusion

Although process has been slow, largely due to delays in start up, data is now being collected and all investigative methods are working as per the original proposal. The aim over the coming 6-9 months will be to recruit more patients and initiate formal analysis of psychophysiological and imaging data obtained. Clearly this will depend upon a stream of referrals in to Dr Sharma's cordotomy service.