Aims: To develop ultra-high field (UHF) MRI methods that will determine (a) the relationship between structure and function in pBA3c and (b) the dynamic connectivity of pBA3c within S1. This information will be used to define the role of pBA3c in both nociception and chronic pain and whether the region is a legitimate target for clinical pain treatment. High spatial resolution imaging is essential to delineate its structure, function and connectivity, therefore the focus of this application was to develop UHF (7 Tesla) MRI protocols that will subsequently be used to test hypotheses about the role of pBA3c in pain perception and chronic neuropathic pain, as well as defining whether it represents a valid target to treat chronic pain with neuromodulation. In development of the protocol, the measures were expanded to provide detailed study of vibratory stimulation, as a comparator and to aid definition of sub-areas of S1.

Methods:

Development and study set-up: First, on the Philips Achieva 7T scanner, the optimal radiofrequency (RF) coil (standard Nova vs. high density surface coils) and MRI sequences for the collection of high spatial resolution over primary somatosensory cortex (S1) was assessed for the acquisition of (1) structural and (2) resting state (RS) functional MRI (fMRI) and task-based data within S1. MRI sequence parameters were compared for 2D EPI parallel acceleration factor (SENSE) and multiband (MB) factor, against 3D EPI. Next, the use of the two thermode devices, the MEDOC (Pathway Model CHEPS (to deliver contact heat which has a single probe) and QST.Lab (which can drive multiple small probes to deliver thermode patterns) were assessed on the 3T Philips Ingenia scanner and 7T scanner. It was noted that the QST.Lab induced significant eddy-current induced vibrations inside the 7T, which was discussed with the company and methods to reduce this vibration were explored, however these did not dampen the effects at 7T so this device was limited to use at 3T. The optimal protocol for thermal data collection was then assessed to compare the benefits of protocol collected fMRI datasets involving thermal stimulation to the forearm and hand, at both 3T and 7T using the MEDOC, and performing a thermal grill task on the hand at 3T using the QST.lab. The acquisition of simultaneous galvanic skin reactance (GSR) data alongside the thermal grill stimulus was also assessed. Methods for high-resolution structural data was also using MPRAGE and PSIR data sets, as well as T_1 mapping and T2* weighted data of the cortical laminar anatomy. In addition protocols were set up to map mechanoreceptive responses, non-noxious vibrotactile stimulation is delivered to digits in contralateral S1. The protocol was further expanded to study changes in pain processing by imaging subjects following delivery of Capsacian, a potent algogen which results in high frequency firing of TRPV1 expressing C-fibre nociceptors.

Study protocol:

Following optimisation of the imaging acquisition described above, to date data has been collected on seven healthy subjects, (2 female, Mean age 30 (standard deviation 5.1)) and 1 pain-free individual. Prior to the MRI scan session, all subjects underwent a behavioural session involving measuring piezo-stimulation thresholds, such that the piezo-stimulation intensity was set to 3.16 dB multiplied by their amplitude threshold; and thermal thresholding to determine their heat pain limits.

The protocol at 7T comprised the following measures over primary somatosensory cortex (S1):

(i) Each participant underwent resting state scans (each 5 mins, 24 slices, MB3, TR 1.5s).

(ii) Thermal stimulation was performed using teh MEDOC on the hand/thenar with two repeats, (each 5mins, 34 slices, MB2, TR 2s), followed by x1 scan of piezo

stimulation (200 Hz) of the same location in a block design (same scan parameters as thermal stimulation).

(iii) Next, thermal stimulation was performed using the MEDOC on the inner forearm with two repeats, followed by piezo stimulation for x1 scan on the hand/thenar.

The subject exited the scanner, and the inner forearm area was kindled using thermal stimulation for 5 mins, set at their heat pain limit threshold. Capsaicin Cream (Axsain 0.075%w/w cream) was then applied to the inner forearm. This was allowed to develop for 30 minutes and then wiped off prior to scanning. The subject's heat pain thresholds were re-tested, and the degree of allodynia evoked by soft brushing following injection recorded using a VAS (0-100). The subject re-entered the scanner for:

(iv) resting state scan was performed

(v) thermal stimulation on the arm (same location as Capsaicin was placed) for x2 scans, and x1 piezo-stimulation scan was performed on the inner forearm.

(vi) Whole brain structural measures were also collected on all subjects.

(vii) In addition, in a separate scan session each subject had a highly detailed digit mapping fMRI session to reliably map D2,D3,D4 and D5 in primary somatosensory cortex, as well as collect within digit maps.

The protocol at 3T comprised the following measures in which data was collected at lower resolution (2.5 mm isotropic) over the whole brain:

(viii) Thermal stimulation was performed using the MEDOC on the inner forearm with two repeats using whole brain fMRI of the forearm/Hand - 5 mins x 2.

(ix) Thermal grill stimulation of the forearm/Hand – 5min x 2

(x) Thermal grill with S1 and subcortical fMRI – high resolution. Forearm/Hand – 5 min x 2

(xi) Resting fMRI whole brain

(xii) T1mapping slice shifted.

Image analysis and questions to be addressed

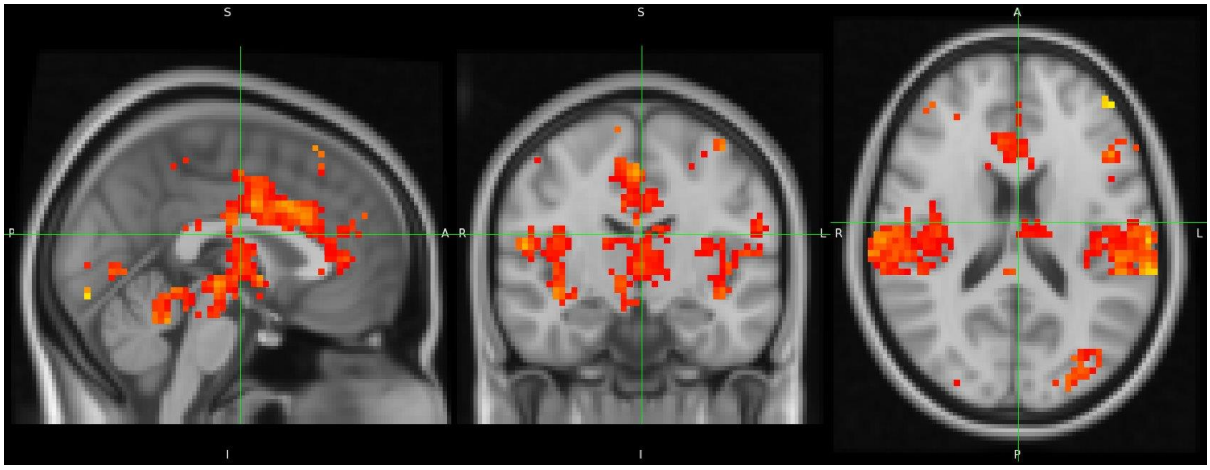
Distortion correction scans were collected for all fMRI runs. A noise scan was also collected for each fMRI run to perform thermal noise removal using NORDIC PCA in post-processing. Structural scans were collected and segmented via Freesurfer to obtain surfaces and flattened cortical patches, as well as to delineate Brodmann areas. Primary data analysis has been performed to generate maps of responses to stimulation, and comparison of measures at 3 and 7T. We are now finalising analysis to address the following hypotheses:

(a) Does a distinct structure-function relationship exist in nociresponsive S1: We will compare the location of pBA3c and touch responsive S1.

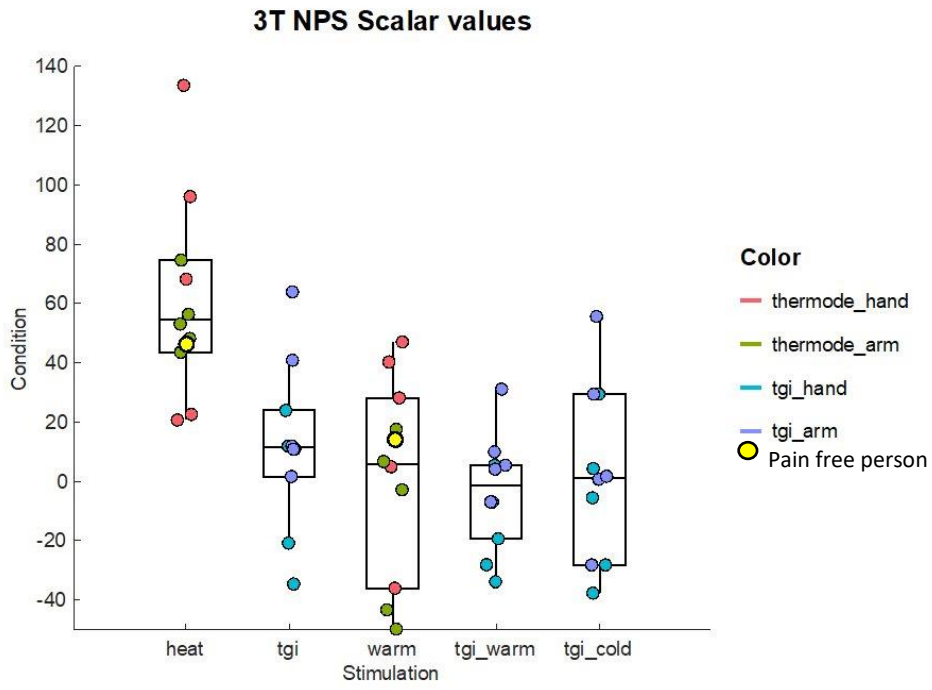
(b) How are responses altered dynamically altered by pain. We will study task-based responses and whether changes in functional connectivity occur. it is predicted that capsaicin will initiate a C-fibre nociceptive barrage to pBA3c that results in a prolonged increase in spike firing in nociresponsive pBA3c neurons causing a dynamic change that will be associated with the development of tactile allodynia.

fMRI in pain-free person (a) and normal values for neurological pain signature (b)

(a)



(b)



Representative 7T and 3T scans showing activation of 3a by noxious heat stimulation (c)

(c)