SECOND YEAR REPORT

STUDY TITLE: IMAGING NEURAL RESPONSES TO PAIN RELATED STIMULI IN PATIENTS WITH CHRONIC NON-MALIGNANT PAIN (CNMP) PRE AND POST A PAIN MANAGEMENT PROGRAMME

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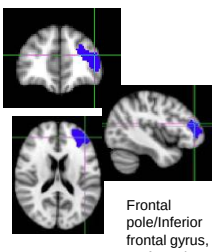
Imaging neural responses to pain related stimuli in patients with chronic non malignant pain pre and post a pain management programme is not running to time. Currently, 4 participants have been enrolled and have completed the study but 15 participants are required. Unfortunately, the pain management programme that we are using for the study is at risk of closure as Health Boards are attempting to save money in Wales and as a result a number of programmes have been cancelled and recruitment to those that are running have dropped from 12 to 4. The Bath Pain Management Programme has now been recruited but only one enquiry has been received to date.

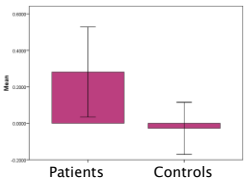
However, the previous pilot project has led to a number of interesting findings and we have enclosed some of the data presented to the Anaesthetic Research Society Meeting on the 30th June 2011 and which we anticipate will be published in the British Journal of Anaesthesia. This pilot investigated neural activity in affective and attentional regions in chronic pain patients versus healthy controls, as assessed by fMRI using a non-painful stimulus. The reason for using non-pain stimulus is that the meaning of pain, in terms of its perceived physical and psycho-social causes and consequences, is different in CNMP compared to acute pain. This can affect the threat value of pain and the way in which it demands attention. There is a need to develop methods to investigate naturally occurring changes in chronic pain and responses to pain cues. The majority of functional Magnetic Resonance Imaging (fMRI) studies to date have focused on experimental acute pain and then made inferences about CNMP.

Fifteen CNMP patients with predominantly musculoskeletal pain were recruited and age and gender matched to healthy controls. The average age was 58 (age range 25-83), 20 participants were female and the average pain score for the pain group was 88 on a visual analogue scale from 0 (no pain) to 100 (worst possible pain). All participants initially had a practice run in the mock scanner before scanning was performed on a 3T MR Scanner (GE Healthcare). During one acquisition (T2*-weighted for blood-oxygen level dependent contrast), subjects were shown activity of daily living photographs taken from the Photograph Series of Daily Activities database, a validated tool for assessing kinesiophobia. These photographs had already been validated in a previous study by the authors. Patients were asked to think about how they would feel, mentally and physically, if asked to undertake this activity and rate their anxiety using a button box. Additionally, a T1-weighted structural scan was acquired for data processing. Participants were also asked to complete a number of questionnaires on pain, function, fatigue and mood. Data was analysed using FEAT query and the significant voxels illustrated below show patients>controls.



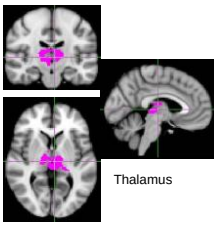
Frontal pole/Inferior frontal gyrus, prefrontal cortex

Bar graph showing responses in Area 4 with error bars 95% confidence Intervals



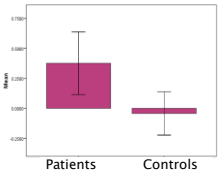
Activation area 4

Group	Means	SDev	p Value
Patients (1)	0.281	0.446	**0.030**
Controls (2)	-0.027	0.246	



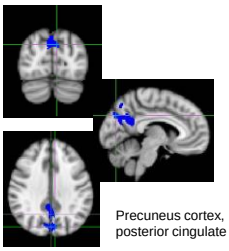
Thalamus

Bar graph showing responses in Area 3 with error bars 95% confidence Intervals

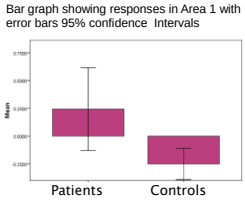


Activation area 3

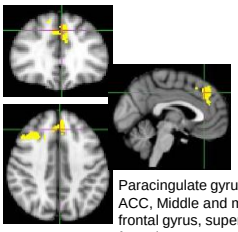
Group	Means	SDev	p Value
Patients (1)	0.375	0.471	**0.009**
Controls (2)	-0.426	0.312	



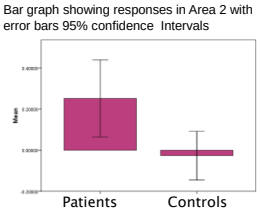
Precuneus cortex, posterior cingulate



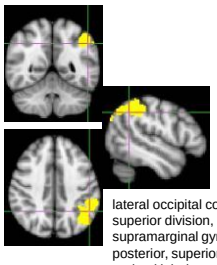
Activation area 1			
Group	Means	SDev	p Value
Patients (1) Controls (2)	0.244 -0.250	0.670 0.245	**0.015**



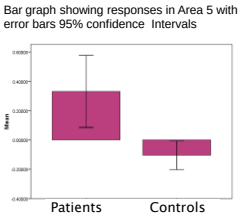
Paracingulate gyrus, ACC, Middle and medial frontal gyrus, superior frontal gyrus



Activation area 2			
Group	Means	SDev	p Value
Patients (1) Controls (2)	0.251 -0.262	0.337 0.204	**0.013**



lateral occipital cortex, superior division, supramarginal gyrus, posterior, superior parietal lobule



Activation area 5			
Group	Means	SDev	p Value
Patients (1) Controls (2)	0.331 -0.104	0.443 0.168	**0.002**

Various well-established pain regions showed significant activation in the patients compared to the healthy control subjects. The CNMP patients also showed significant activation in the default mode network (DMN) during the task; the DMN is typically characterised as regions of the cortex which are inactive during a task and active at rest in healthy subjects. The behavioural questionnaires illustrated that CNMP significantly affected the quality of patients' lives.

These findings demonstrate that chronic pain has a widespread impact on overall brain function, and aberrant DMN activity may underlie the cognitive and behavioural impairments accompanying chronic pain. This aberrant activity is thought to lead to the frontal lobe cortical loss and abnormal brain ageing seen in patients with CNMP. Using this method, we have assessed the impact of CNMP without inflicting acute, experimental pain and established a method that could be used in future research to examine whether these brain changes can be reversed.

A Stroop task was also used. This task posted words which were either pain affect, pain sensory, positive words or household objects matched for valience and usage in the English language, and the participants had to indicate on a button box how many times the word was presented. The theory behind the counting Stroop is that there will be a delay in response for those words that are meaningful to the individual. A paper is being prepared at present for the journal Pain.

With agreement from the NIAA, we are now expanding on this pilot. From the initial pilot, 9 patients (those that had chronic low back pain) and their controls will be used and there are another 21 chronic low back pain patients recruited with controls (14 patients and 3 controls have been completed) with September 2011 anticipated to be the end of data collection. PHODA will be used for all patients as well as the structural scans investigating cortical thickness and blood flow. In the new group, the following is being undertaken:

- N-back task specifically to study the differences between the Default Mode Network in healthy volunteers and patients with chronic pain
- Undertake resting BOLD measures to assess altered functional connectivity in chronic pain patients. Recent evidence in the literature suggests that there may be altered communications between brain regions at rest in these patients, relevant to the pain condition
- Undertake Diffusion Tensor Imaging to examine differences in tissue (white matter) microstructure between our pain patients and healthy controls. Recent evidence suggests a previously unexpected degree of structural plasticity in chronic pain which may provide a predictor of outcome following treatment.

Participants who agree to be recruited and are undertaking a pain management programme will continue to be scanned but it is anticipated that the grant awarded will be used for the extended programme of activity examining structural and functional differences between patients with chronic low back pain and healthy, age and gender matched controls.