IMAGING NEURAL RESPONSES TO PAIN RELATED STIMULI IN PATIENTS CHRONIC PAIN

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We were unable to complete the study examining patients with chronic non malignant pain pre and post a pain management programme. Unfortunately, the pain management programme that we are using for the study was at risk of closure and referrals were extremely low and despite enrolling Bath Pain Management Programme as another centre we were unable to recruit. We did scan 4 patients but nothing of statistical significance was seen pre and post the pain management programme; probably due to the study being underpowered. We sought approval to NIAA to look at neural correlates of non painful, pain related stimuli and also examined an attention task to probe Default Mode Network, voxel based morphometry (VBM), cerebral blood flow (CBF) and resting BOLD, and this was agreed.

INTRODUCTION

The management of chronic non-malignant pain (CNMP) is difficult and despite an increased understanding of the factors contributing to the maintenance of pain and disability through behavioural research, there has been only a moderate improvement in treatment outcomes over the last decade [15, 16]. Significantly interventions have shown at best, only moderate effects in reducing pain and disability in those suffering with chronic pain (CLBP) [17].

The main focus of this research is chronic musculoskeletal pain (CMSKP), including chronic low back pain (CLBP). The reason for this focus is that the largest proportion of patients with CNMP, have CMSKP and/or CLBP and the costs to the individual, society and the health system are great. Approximately 5% of patients develop CLBP following an initial acute back episode and yet these account for 75% of the costs associated with low back pain [1]. Based on the latest available statistics from the HSE [18] the total number of people with musculoskeletal disorders in 2010/11 was 508 000 out of a total of 1 152 000 for all work-related illnesses with 158,000 new cases a year.

Pain interrupts, demands attention, and is difficult to disengage from [7]. An attentional bias can be considered as selective attention towards specific information and typically, but not always, these biases are explored in relation to threat and may illustrate a predisposition towards threatening

information [21]. In an acute situation, pain related-attentional bias is wholly appropriate and serves as a strong survival mechanism, but in people with CNMP it appears not to serve a useful function and can cause harm in itself.

Several factors are thought to be involved in moderating the attentional demands of pain, the strongest and most consistent effects relate to fear, anxiety, and catastrophising [7]. Attentional vigilance for pain-threatening information results in a greater chance of detecting potential sources of threat, exacerbating pain, disability, deterioration in physical health, social isolation and work loss [21]. Attentional bias to pain may illustrate a lack of acceptance of having CNMP and may be detrimental to management; acceptance is beneficial in terms of patient functioning [28, 29].

Pain related fear refers to an excessive and debilitating fear of physical movement and activity resulting from a feeling of vulnerability to pain [30]. Pain-related fear and catastrophising are associated with increased attentional interference, awareness of pain, impaired disengagement from pain, and can moderate the effects of attentional coping attempts [8, 31-35]. Disability and depression may result from activity avoidance, [28, 36-39]. Pain related fear accounts for between 7-31% of the variance in pain severity [40].

The Fear Avoidance model (FA model) [41], is commonly accepted as one which integrates the fear-related themes above. It proposes that dysfunctional interpretations give rise to pain-related fear, and associated safety seeking behaviours such as avoidance/ escape and hypervigilance. It also suggests that if the injury/pain experience is perceived as non-threatening, patients positively adapt and cope with their pain [42].

Early work with clinical populations indicates considerable promise for fMRI methods to be used in pain diagnosis and therapy [64-66]. Recent advances in functional imaging have transformed the understanding of central processing of pain. Unfortunately, current clinical classifications of CNMP have been so far unhelpful in understanding how pain is processed [64]. Functional imaging has already redefined chronic pain as a degenerative disease [67, 68], and has shed some light on complex diseases such as fibromyalgia [54]. Therefore, the application of functional imaging may improve the categorisation of pain conditions in an objective manner based on a better understanding of central mechanisms and may lead to improved diagnosis and the identification of more appropriate treatment regimens [64].

Functional MRI is a technique that can detect the changes in perfusion caused by brain activity. In fMRI, the capillary changes in blood flow and volume result in a change in deoxyhaemoglobin concentration. The change is reflected in an increase in image intensity at the location of the activity and is called the blood oxygenation level-dependent (BOLD) signal. It does not measure absolute states, rather it needs a reference state to compare to, for example pain needs to be evoked or modulated during an fMRI scan to localize brain activation but it can be used repeatedly in subjects and therefore can be useful in longitudinal studies [69].

Neuroimaging has improved our understanding of how cognition, emotion and context can influence pain perception [69, 73-75]. However, to date, it has not been well utilised in the CMSKP population and this area of research appears to be still in its infancy where there are methodological and ethical challenges that need to be addressed [76]. The majority of fMRI work to date has focused on acute, experimentally induced pain in healthy volunteers, where the meaning of pain is different from CMSKP [8, 33] and the pain-related changes in brain structure and functioning [67, 68] seen in chronic pain patients are not present in the healthy volunteers. Studies using functional Magnetic Resonance Imaging (fMRI) in acute pain populations have been successful in demonstrating the effects of manipulating attention (primarily distraction), expectation and anticipation, paradoxical sensations and control [64].

It has long been proposed that a 'neural matrix' for pain exists which described the dynamic role of networks within the brain responsible for the experience of it. This model suggests that although the processing of pain by the brain is genetically specified, processing is modified by experience [77-79]; factors increasing the sensory flow of pain signals may alter the excitability of central thresholds over time resulting to sensitivity to pain. Therefore, psychological factors thought to amplify pain signals, such as attention, fear and catastrophising may lead to changes in central neural mechanisms leading to central sensitisation and a chronic hyperalgesic state [77-79]. Previous studies have shown that people who are fearful and catastrophise attach more threat or harm to non-painful stimuli, such as innocuous electrical currents [80, 81] and the neural correlates of this are not clear.

Given that treatment for CMSKP has not advanced for many years and behavioural research has not achieved consistent results, fMRI methods may help to provide further understanding of how pain-related attention, fear and catastrophising affect patients. A number of approaches have been used to study pain in fMRI studies, including block design [82], event-related [83] and percept-related [84] paradigms.

AIMS

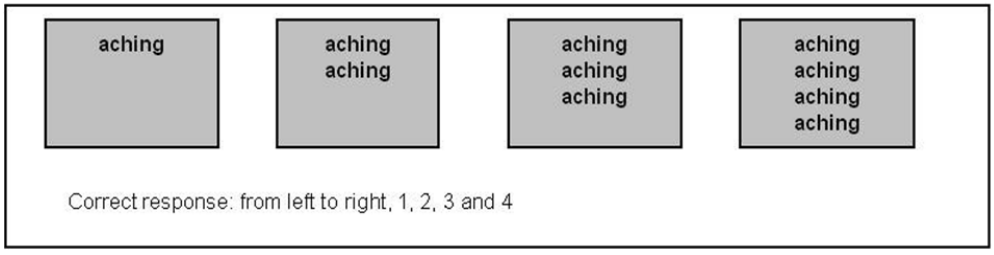
The aim of the research is to explore Blood Oxygen Level Dependent (BOLD) signal changes in response to viewing non-painful pain-relevant stimuli. It is also intended to examine resting BOLD data and voxel based morphometry in the chronic low back pain group compared to their matched controls. The reasons for undertaking research within this field included the fact that much of the research to date has looked at the impact of nociception in healthy volunteers and inferences are then made about how people with CMNP process painful stimuli. However, patho-physiological processes, such as responses to nociception, do not adequately explain the levels of pain and disability that patients with CNMP report [89-91]. The research that has been undertaken in fMRI studies has revolved around factors such as attention, fear and catastrophising in healthy populations and has not examined the role of these within the CNMP population in any great depth. Therefore, the research approach in these studies is exploratory and the studies have not been scaled or designed to test hypotheses. The studies included have research aims to reflect the exploratory nature.

OUTCOMES

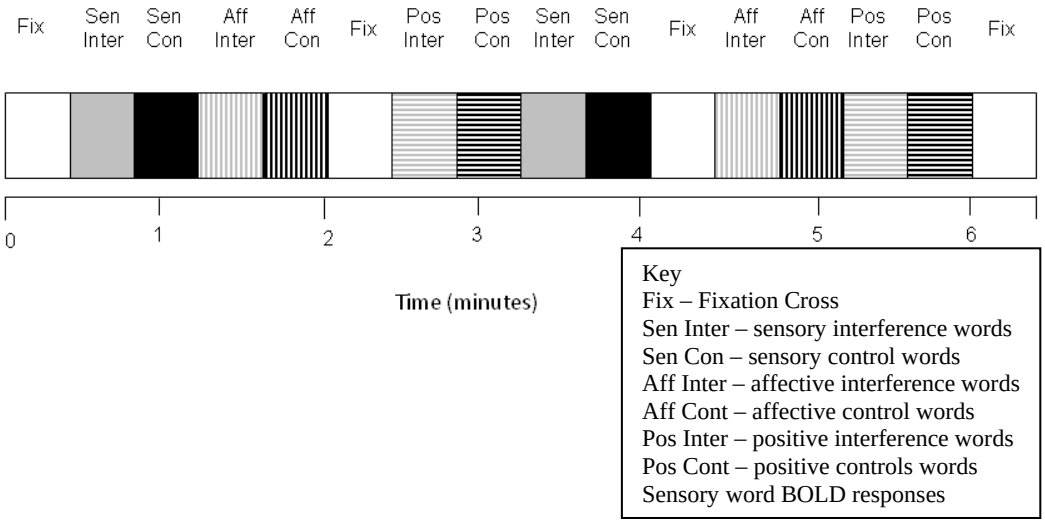
We are currently working on four papers, the Stroop study has been submitted to a peer reviewed journal, the chronic musculoskeletal pain (CMSKP) paper using a pictures of daily living and imagination task is being submitted to a peer reviewed journal. The chronic low back pain (CLBP) study also using the picture and imagination task and including VBM and resting BOLD and the cerebral blood flow paper is being written at the time of this report. We recruited 15 CMSKP patients and 15 matched controls for the Stroop and Picture/Imagination Task and 20 patients and 20 controls for the CLBP Picture/Imagination task, N-Back, CBF and VBM. The key findings include:

1. Stroop: BOLD fMRI differences on presentation of pain-related words during a Stroop task are reported in regions involved in pain perception and emotion revealing heightened attentional and emotional processing. However, no behavioural response time differences were seen; fMRI appears to reveal differences in brain activity that are not apparent in behavioural data.

Example of 4 individual trials

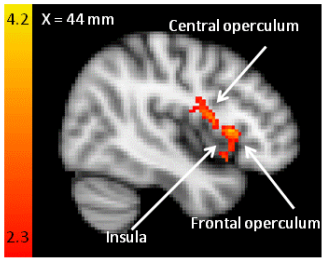


Block design for the pain related and emotional Stroop tasks



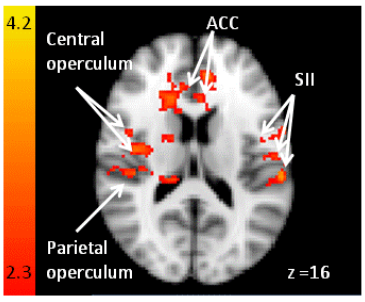
Responses to sensory pain word category(patients>controls)

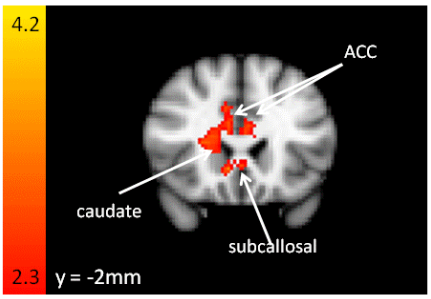
BOLD signal changes during pain related Stroop task comparing sensory words to the control words differences between the patient and control groups. This z-statistic map represents these group differences in a whole brain analysis and the z-statistic map is shown in standard MNI space. The color bar shows the scale of the z-statistic (2.3 – 4.2). Cluster correction for multiple comparisons was performed at $p<0.05$.

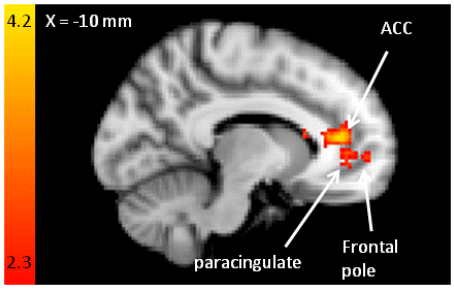


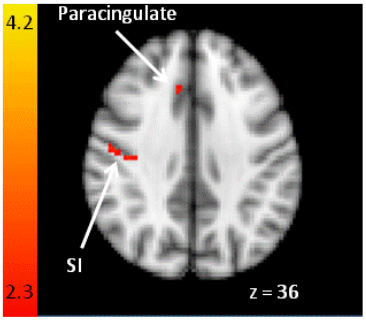
Maps comparing activation during pain-related Stroop task

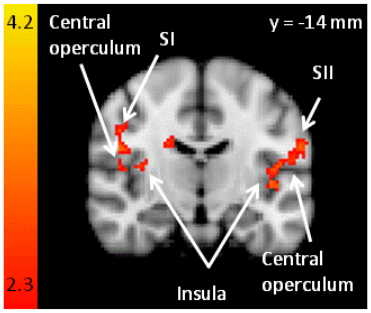
Maps comparing activation during pain-related Stroop task contrasting sensory and affective pain words compared with control words between the patient and control groups. Patients with CMSKP have significantly different BOLD signal responses in sensory-discriminatory pain related regions, the affective-motivational dimention and the cognitive evaluative dimension . Each *z*-statistic map represents these group differences in a whole brain analysis. The color bar shows the scale of the *z*-statistic (2.3 – 4.2). Cluster correction for multiple comparisons was performed at $p<0.05$.







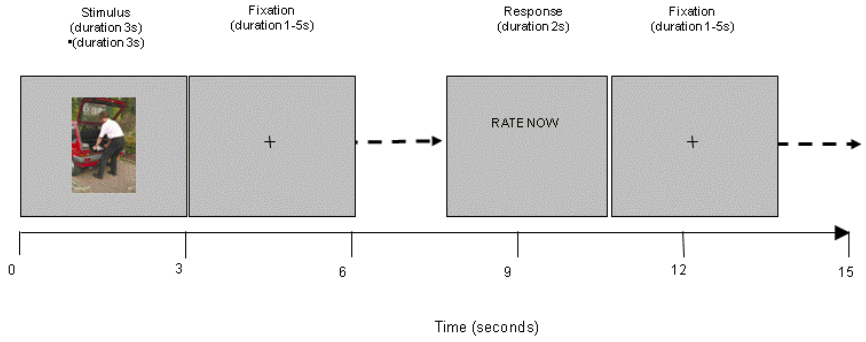




2. CMSKP and picture/imagination task (methods paper): This study developed a functional magnetic resonance imaging (fMRI) tool, Picture Imagination Task, to elicit neural networks associated with pain-related fear. A network of a priori brain regions including the amygdala and insula were subsequently identified in patients but not controls; regions involved with the processing of fear. Regions associated with the affective-motivational dimensions of pain and associated with anxiety scores supported the salience of the tool in people with CMSKP. The results indicate that this tool can accurately identify regions known to process fear in patients with CMSKP.

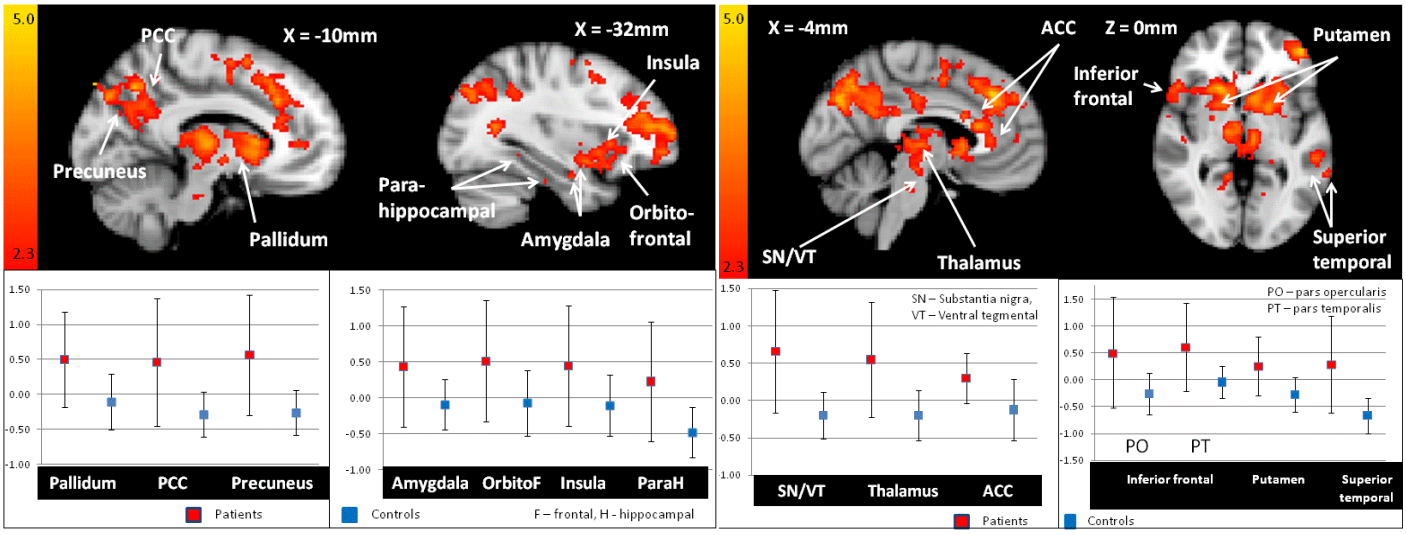
Trial timing

Each trial in the task lasted 7-15 s and was composed of 4 different screens; a photo from either PHODA or a neutral activity, a fixation cross, a screen to indicate the subject should respond and ended with a second fixation cross.



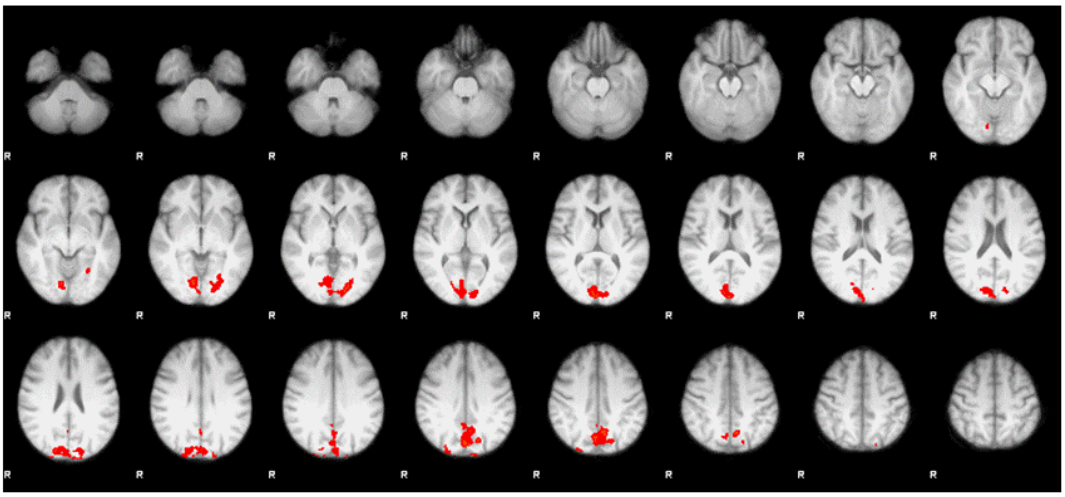
Maps illustrating regions known to be involved in phobia and fear conditioning

Statistical maps comparing activation during the picture and imagination task between the patient and control groups. Patients with CMSKP have significantly different BOLD signal differences in regions known to be involved in phobia and fear conditioning. Each z-statistic map represents these group differences in a whole brain analysis. The graphs show the percentage signal change with the error bars representing standard deviations across subjects. The images are a combination of anatomical and functional data and the graphs represent the direction and magnitude of the signal change within the region and were therefore not tested for statistical significance. The colour bar shows the scale of the Z-statistic (2.3 – 5.0). The circles represent the anatomical location of the corresponding coloured region in the graph. Slice location is identified in white on the figures and presented in millimeters.



Maps illustrating across group correlations with anxiety

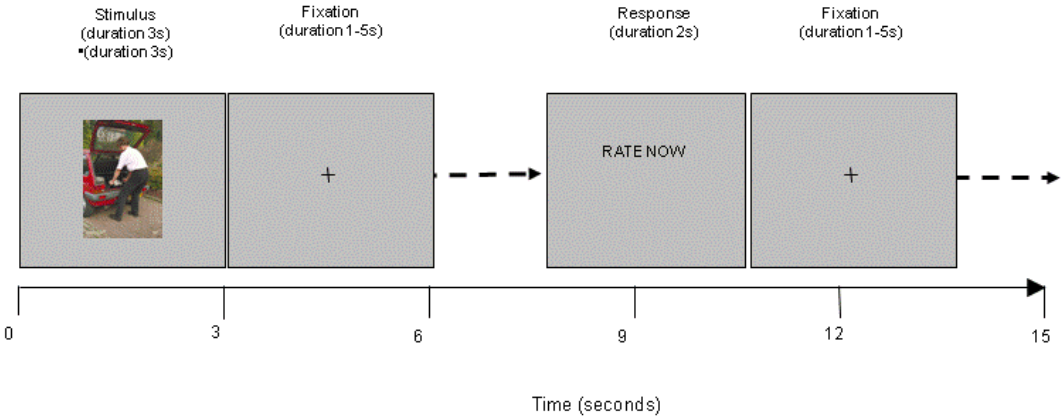
De-meaned anxiety scores were regressed into a covariate statistical model at the group level in which the FEAT analysis was run independently for each. Each z statistic map represents these group differences in a whole brain analysis. The images are a combination of anatomical and functional data. The scale of the Z-statistic (2.3 – 7.0).



3. CLBP and picture/imagination task (validation paper): The task resulted in BOLD differences in brain regions associated with fear conditioning, emotional and sensory pain processing. Higher kinesiophobia and catastrophising scores resulted in BOLD differences in regions associated with fear and negative emotion processing. Increased BOLD responses were also seen in patients and not controls in areas that are deemed to be part of the default mode network activity; posterior cingulate cortex, precuneous, angular gyrus and middle frontal cortex when completing the picture activity. There were no differences between patients and controls in grey matter density (VBM analysis), but there were differences in resting state connectivity (dual regression and seed region analyses).

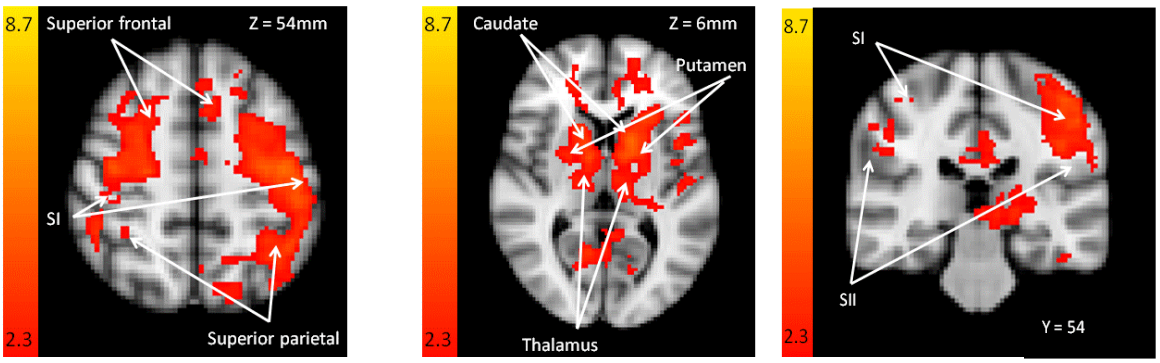
Trial timing

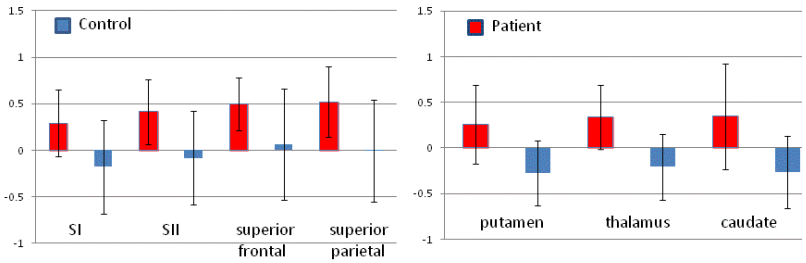
Each trial in the task lasted 7-15 s and was composed of 4 different screens; a photo from either PHODA or a neutral activity, a fixation cross, a screen to indicate the subject should respond and ended with a second fixation cross.



Regions implicated in the sensory-discriminative dimensions of pain

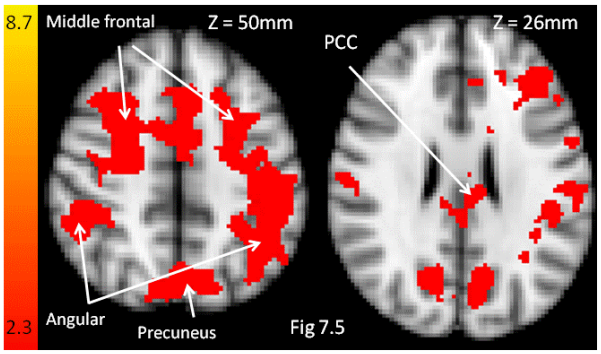
Statistical parametric maps comparing activation during the PHODA-LBP task between the patient and control groups. Patient with CLBP have significantly different BOLD activation in main sensory discriminative pain regions (ACC and Insula are presented in Fig 7.3) when undergoing the task and imagining undertaking the activity depicted in the photograph. Each z-statistic map represents these group differences in a whole brain analysis. The colour bar shows the scale of the *z*-statistic (2.3 – 8.7). The images are a combination of anatomical and functional data and the graphs represent the direction and magnitude of the signal change within the region and were therefore not tested for statistical significance. The graphs show the percentage BOLD signal change with the error bars representing standard deviations across subjects.

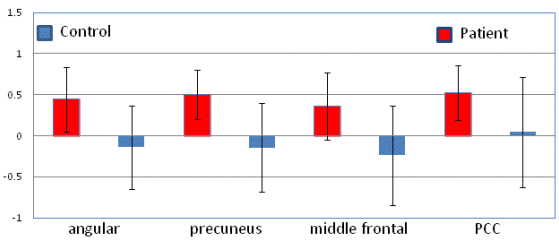




DMN Regions

Statistical parametric maps comparing activation during the PHODA-LBP task between the patient and control groups. Patient with CLBP have significantly different BOLD activation in regions known to be involved in DMN when undergoing the task and imagining undertaking the activity depicted in the photograph. Each z-statistic map represents these group differences in a whole brain analysis. The colour bar shows the scale of the *z*-statistic (2.3 – 8.7). The images are a combination of anatomical and functional data and the graphs represent the direction and magnitude of the signal change within the region and were therefore not tested for statistical significance. The graphs show the percentage signal change with the error bars representing standard deviations across subjects.

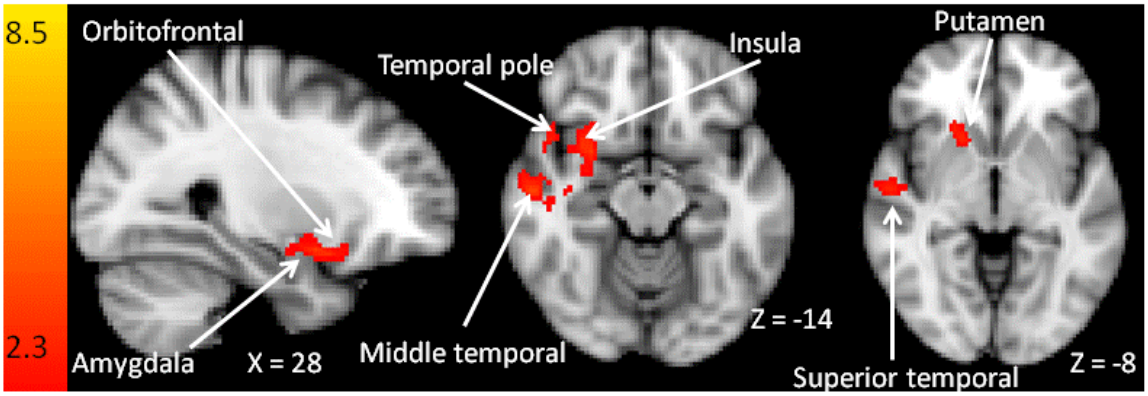




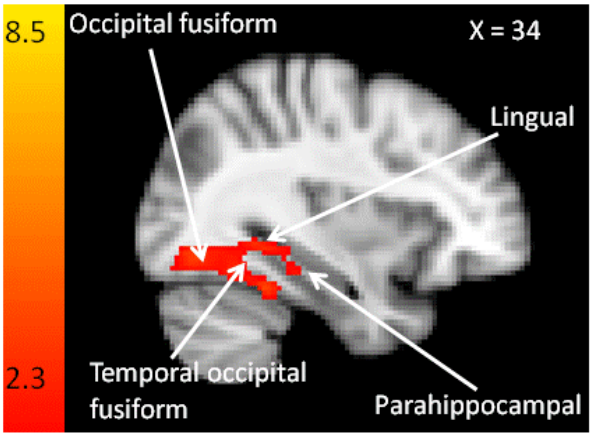
Statistical parametric maps illustrating BOLD signal changes with higher catastrophising and TSK scores

Maps illustrating activation during the PHODA-LBP task in regions associated with higher catastrophising (A) and TSK (B) scores. Each z-statistic map represents these group differences in a whole brain analysis. The colour bar shows the scale of the *z*-statistic (2.3 – 8.7) and the slice co-ordinate is stated.

A. Catastrophising scores



B. TSK scores



4. N-Back: This was used to tap into the differences in the Default Mode Network in more depth but there were no statistically significant differences in patients compared to controls. The behavioural results showed large errors in the responses given in the patient group compared to the control group and this may have resulted in the lack of neuroimaging differences between the groups

5. CBF: CBF was assessed using arterial spin labelling (ASL) in a cohort of 13 patients with chronic low back pain and compared with CBF in 14 healthy controls. Additionally, voxel-based morphometry was used to compare grey matter density between the two groups. Significant regional increases in CBF in the patient group were detected and include parts of the thalamus, posterior cingulate, hippocampus/parahippocampus, insula, brainstem, caudate, pallidum, putamen, supramarginal gyrus, cuneus, precuneus, inferior temporal gyrus, occipital lobe and the central and

parietal operculum. No regions of significantly decreased CBF in the patient population compared to the controls were detected. No significant differences in grey matter density between the patients and controls were detected. While many of the regions showing increased CBF have also been reported for other pain types (acute pain, tonic pain, post-surgical pain) some of the regions found in this study may be unique to chronic pain, such as portions of the central operculum and intracalcarine cortex.

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