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RUNNING HEAD: PAIN ANTICIPATION IN CHRONIC LOW BACK PAIN

Brain areas involved in anticipation of clinically-relevant pain in low back pain populations with high levels of pain behaviour

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ABSTRACT

The purpose of this study was to identify neural correlates of pain anticipation in people with non-specific low back pain (NSLBP) that correlated with pain-related distress and disability, thus providing evidence for mechanisms underlying pain behaviour in this population. Thirty NSLBP sufferers, with either high levels of pain behaviour (WS-H) or low levels (WS-L) based on Waddell Signs (WS), were scanned with functional Magnetic Resonance Imaging (fMRI) whilst a straight-leg raise (of the side deemed to cause moderate pain in the lower back) was performed. On each trial coloured stimuli were presented and used to indicate when the leg definitely would be raised (Green; 100% certainty), might be raised (Yellow; 50% certainty) or would definitely not be raised (Red; 100% certainty). In response to expected vs. unexpected pain the group difference in activation between WS-H and WS-L co-varied as a function of anxiety scores in right insula and pregenual anterior cingulate cortex and as a function of catastrophizing in prefrontal and parietal cortex and hippocampus. The results suggest NSLBP populations with the highest levels of pain-related distress are more likely to attend to and infer threat from innocuous cues, which may contribute to the maintenance of pain behaviour associated with some chronic pain states.

Perspective: This article demonstrates a likely neural network for exacerbating pain anticipation in NSLBP contributing to high levels of pain behaviour in some people. This information could potentially help clinicians and patients to understand how anticipation of pain may contribute to patient pain and disability.

KEYWORDS: anxiety; catastrophizing; non-specific low back pain (NSLBP); pain behaviour; Waddell Signs

INTRODUCTION

Fear of pain, driven by anticipation (and not actual sensory experience), is suggested to be a strong negative reinforcer for persistent avoidance behaviour and functional disability in some chronic low back pain (cLBP) populations.[31,61,69] According to this fear-avoidance model,[62] anticipation of pain often results in poor task performance that cannot be accounted for by pain severity[12] and this has been empirically demonstrated in several studies showing lower levels of performance in patients who anticipated pain induced by a task (such as leg-raising or lifting a heavy sack[39,61]) than those who didn't. The underlying neural mechanisms of such behaviour are, however, unknown. The purpose of this study was to determine which neural structures mediate the anticipation of pain in patients with non-specific low back pain (NSLBP) and furthermore, whether there is a different level of brain activation, detectable with functional Magnetic Resonance Imaging (fMRI), in those patients with NSLBP and the highest levels of pain-related fear and disability.

Human neuroimaging studies have identified several areas putatively involved in the anticipation of experimental pain in healthy controls including anterior cingulate cortex (ACC; BA32'/24'), cerebellum, ventral premotor (vPM) and ventromedial prefrontal cortex (vmPFC), periaqueductal grey (PAG) and hippocampus.[24,7,46,47,48] A key psychological factor in the subjective experience of anticipated pain is its predictability: Noxious stimulation that is unpredictable in either its occurrence or intensity, can increase anxiety and cause hyperalgesia with increased activity seen in vmPFC, mid-cingulate cortex and hippocampus, whilst knowledge that noxious stimulation is certain to occur involves activation of rostral-cingulate cortex, anterior insula and cerebellum.[46,47,41]

In patients with NSLBP and the highest levels of pain-related anxiety, fear, and disability, the psychological consequences of anticipation and perception of pain should be most apparent. To determine which patients with NSLBP had such a profile we performed a clinical examination using the Waddell Signs[68] and used a series of questionnaires designed

to measure these factors (see Methods for details). The Waddell Signs (WS) are a series of physical signs frequently found in patients with cLBP, which may draw attention to the possibility of 'maladaptive overt illness-related behaviour which is out of proportion to the underlying physical disease and more readily attributable to associated cognitive and affective disturbance'.[67] The aim of the current study was to investigate whether differences in brain activity would be apparent in patients with NSLBP who have the highest levels of pain behaviour, assessed using WS, and scores on psychometric measures of pain-related distress and disability (compared to a control group of NSLBP patients without such traits) in response to a certain (i.e., predictable, occurring on 100% of all trials) or an uncertain (i.e., unpredictable, occurring on 50% of all trials) painful event. Rather than use an experimental pain stimulus we adapted the 'straight-leg raise' (SLR), the common clinical test employed in the diagnosis of sciatica, to exploit the common feature seen in cLBP patients whereby this simple manoeuvre frequently provokes pain in the lumbar region. Such pain is probably generated in paraspinal muscles that in electrophysiological tests show abnormal activation patterns during flexion/extension movement.[1] We chose to use this model because it is a reliable method for eliciting pain,[39] can be used safely in the scanning environment, and provides unique information on the brain regions involved in anticipating a clinically-relevant pain in patients with significant pain-related distress. We predicted that participants with the highest levels of pain behaviour (as measured through WS) would show increased activity in response to both a certain painful event (in rostral-cingulate cortex, anterior insula and cerebellum) and uncertain pain (in vmPFC, mid-cingulate cortex and hippocampus), which furthermore correlates with psychometric measures of pain-related distress and disability compared to a control group of NSLBP patients without such traits.

METHODS

Participants

Thirty participants with NSLBP (16 male and 14 female), aged between 21 – 67 years (with a mean age of 45 years; SD = 12.4) were recruited. Due to excessive head movement, 1 participant was removed from the final analysis and data are presented for the remaining twenty-nine participants (Note: The participant was removed based on the criterion for acceptable head motion set by[29] who performed fMRI in 11 failed back surgery syndrome patients and 14 healthy controls. We can confirm that head motion in our study did not exceeded 2mm in any data set and there was no difference in head motion between groups (WS-H = .062mm vs. WS-L = .068mm; p = .527). However, one participant still had a mean absolute displacement of more than 2SDs from the overall group mean and we have therefore chosen to exclude this person's data on this basis). The study protocol was approved by the local NHS Research Ethics Committee (REC) and the University of Liverpool ethical review board and was conducted in accordance with the Helsinki Declaration (1989). Participants gave fully informed written consent of their willingness to participate. The patient inclusion criteria were: pain over 6 months; mechanical back pain without sciatica; no previous operations for back pain (including facet denervation); MRI showing no structural spinal abnormality other than degenerative change in no more than three lumbar discs and SLR associated with back pain (not leg pain).

In order to differentiate participants with NSLBP on the basis of their pain-related behaviour, each patient underwent a clinical examination by two specialists (spinal surgeon, pain physician) independently, which included the assessment of Waddell Signs (WS). The aim was to identify those participants with a high number of signs (WS-H) vs. those with a low number (WS-L). Any discrepancy in scoring between assessors was resolved by consensus. The WS are a series of validated clinical signs found in patients with cLBP[61] as follows: Tenderness (superficial skin tender to light touch or non-anatomic deep tenderness

not localised to one area); Simulation (axial loading pressure on the skull of a standing patient induces lower back pain, or rotation of the shoulders and pelvis in the same plane induces pain); Distraction (difference in SLR in supine and sitting positions); Regional (weakness in many muscle groups i.e., 'give-away weakness' or where the patient does not give full effort on minor muscle testing or sensory loss in a stocking or glove distribution i.e., non-dermatomal); and Over-reaction (disproportionate facial or verbal expression i.e., pain behaviour).

WS have been shown to have good construct validity[3] and are suggested to be a reliable basis for identifying patients with cLBP[4]. Unfortunately, a "validated" cut-off and data on the sensitivity/specificity of WS are lacking. However, Waddell et al.,[68] originally suggested that the presence of 3 or more signs represents a positive nonorganic test and this definition has been used in most previous studies (e.g.,[20]). In the present study, we chose to use a more conservative definition to secure two distinct NSLBP populations, namely the presence of 4 or more positive symptoms as the cut-off for the WS-H group and the presence of 1 or 0 positive signs as the cut–off for WS-L group. Thirteen participants (6 females) formed the WS-H group whilst the WS-L group comprised the remaining 16 participants (7 female). The difference in age between groups was non-significant (WS-H mean = 45 years, SD = 10.2; WS-L mean = 47 years, SD = 13.1; $p = .671$; independent t-test comparison) as was the difference in mean duration of LBP (WS-H mean = 114 months; WS-L mean = 112 months; $p = .965$; see Table 1). All participants were on stable medication at the time of scanning. On-going medication did not differ substantially between groups with most taking NSAIDS and paracetamol (acetaminophen up to 4000mg/day. Note: Information concerning medication use was not collected for 6 participants who were not receiving hospital care at the time of the investigation and who were recruited by another route). Seven patients in each group were on low doses of opioids (morphine equivalent dose up to 12mg/day; one patient in the WS-H group was on stable modified release morphine sulphate at 60mg/day), three

patients in the WS-H group were on low doses of antidepressants (25mg/day; one patient in the WS-H group was on citalopram at 40mg/day). None of the participants reported taking medication in excess of recommended doses and there is no evidence to support the idea that pain medication, at the low doses our participants were taking, has any effect on the BOLD signal.[43]

INSERT TABLE 1 ABOUT HERE

Apparatus and materials

Three colours (Red, Green and Yellow) were used to indicate the type of stimulation participants received on a trial-by-trial basis. The timings of the colours were controlled via E-Prime® software (Psychology Software Tools, Inc PA) running on a Dell laptop and projected onto a screen at the foot of the scanner bed via a LCD projector (Epson LMP7300). Participants were able to see the images on the screen through a tilted mirror in the head coil, which reflected the field of view 90º to the horizontal plane.

Design and procedure

Immediately prior to fMRI scanning, we first established from the participant which leg caused the maximum discomfort to the lower back by manual vertical elevation (right leg for 10 participants in the WS-L group and 7 participants in the WS-H group). We then established the maximum elevation the leg could be lifted in this vertical direction so that the person felt moderate but distinct pain (not exceeding 7/10 on a numerical pain rating scale) and without incurring excessive head movement. To further reduce head movement, participants lay in the MRI scanner with the opposite leg slightly bent at the knee (the leg not used for testing) to absorb any movement from the SLR into the hips. Participants were informed that this level of elevation would be used in the subsequent fMRI scan. In practice,

the leg was never raised above 60º, with 75% of WS-H patients tolerating a leg-raise of 30º or less. In none of the participants tested did the pre-scan SLR lead to prolonged pain. The advantage of this method is that the pain is seen as naturally occurring by the patient, and the visual cues signalling movement of the leg are more likely to be interpreted as a clinically-relevant threat.

The colours used to signify expectation of movement to the pre-determined level (thus incurring moderate pain) were: Green – expect that the leg will be moved on this trial (100% probability); Red – expect that the leg will definitely not be moved on this trial (100% probability) and Yellow – the leg may or may not be lifted on this trial (actual probability 50% but this was not communicated to the patient). Each colour was presented five times for 15 secs each time (interspersed with 15 secs of rest) in a pseudo-randomised order. This epoch was further divided into 10 secs of colour observation (no movement of the leg) followed by 5 secs during which the leg was potentially raised (with only one lift in the 5 sec window). Total scan time was 7 mins 30 secs. Participants were instructed to focus on the colours and what they signified throughout the scan and not to actively move the leg.

Prior to fMRI scanning each participant was asked to complete several questionnaires. This included recording using a visual analogue scale[49] (VAS; i.e. a 10cm horizontal line on which patients made a vertical mark) how much LBP they were currently experiencing (VAS_{now}) and the average pain they had experienced in the last 5 days (VAS_{5Day}); the Pain Catastrophizing Scale[56] (PCS), which indicates whether people have negative thoughts about pain and, if so, what form these thoughts are likely to take (i.e., rumination, magnification, helplessness) as well as the Fear-Avoidance Beliefs Questionnaire[69] (FABQ), which tests patients' beliefs about how much pain interferes with their normal work and social activities and finally the Hospital Anxiety and Depression Scale[75] (HADS).

Scanning procedure

MR data were acquired using a 1.5 T Signa LX/Nvi neuro-optimised system (General Electric, Milwaukee, WI). FMRI was performed with a blood oxygenation level-dependent (BOLD) sensitive T_2^*-weighted multi-slice gradient echo EPI sequence (TE = 40 ms, TR = 3 secs, flip angle = 90º, FOV = 19 cm, 64 x 64 matrix). Twenty-four contiguous 5-mm thick axial slices were prescribed parallel to the AC-PC line and covered the whole brain. After acquiring a short series of EPI volumes to produce saturation, a total of 150 EPI volumes were collected during the fMRI experiment. For the purpose of anatomical referencing and visualisation of brain activation, a high-resolution T_1-weighted 3D inversion recovery prepared gradient echo (IRp-GRASS) sequence was acquired (TE = 5.4 ms, TR = 12.3 ms, TI = 450 ms, 1.6-mm slice thickness, FOV = 20 cm, 256 x 192 matrix), with 124 axial slices covering the whole brain.

Data analysis

Questionnaire data were collected from all patients prior to fMRI scanning and entered into SPSS v21 (SPSS Inc., Chicago, IL) to calculate group mean differences (independent t-tests). Missing questionnaire data were imputed using the multiple imputation tools in SPSS. In particular, using Little's Missing Completely at Random (MCAR) Test we first ensured the missing data were randomly distributed (χ^2=25.800, $p > 0.05$) after which we were able to do a Fully Conditional Specification, which generates a multivariate model based on condition models for each missing variable. SPSS uses the Markov Chain Monte Carlo procedure to create a probability distribution used for the Fully Conditional Specification. As suggested by Marshall et al (2010)[37] we used Predicted Mean Matching (PMM), which picks a random value from the model most likely to fit the missing value, ensuring the imputed values are plausible. The resulting five multiple imputation values for each missing value were aggregated to create a mean imputed value to fit the expected data.

All fMRI image processing and statistical analysis was performed using FEAT v6.00 software (FMRI Expert Analysis Tool, Oxford Centre for Functional Magnetic Resonance Imaging of the Brain – FMRIB - University of Oxford), part of the FMRIB software library[55] (FSL 5.0.4). The following pre-processing steps were applied; Motion correction using MCFLIRT;[25] spatial smoothing using a Gaussian kernel of FWHM 5mm; mean-based intensity normalisation of all volumes by the same factor and non-linear highpass temporal filtering (σ = 120s Gaussian-weighted LSF straight line fitting). A general linear model (GLM) was applied on a voxel by voxel basis to these data using FILM (FMRIB's Improved Linear Model) with local autocorrelation correction of the data[73] to model BOLD signal intensity changes in response to the visual cues. Three regressors were constructed by convolving a boxcar function (the stimulus input function: Green/Yellow/Red visual cue = 1; baseline = 0) with a gamma haemodynamic response function (lag, 6s; SD, 3s). Voxel-wise parameter estimates (PEs) were derived for each regressor using the appropriate contrast. To determine the cerebral response to a visual cue indicating the certain expectation the leg would be raised, the uncertain expectation of the leg being raised and the certain expectation that the leg would not be raised we specified the contrasts Green vs. Rest [C1], Yellow vs. Rest [C2] and Red vs. Rest [C3] for the 10 secs period when only the visual cue was presented (the activation in response to the 5 secs period when the leg was moved was modelled as an event of no interest). We then specified additional contrasts of directionality to determine where the response to the visual cue signifying certain pain was greater than the response to the visual cue signifying no pain (i.e., Green > Red; [C4]); where the response to the visual cue signifying certain pain was greater than the response to the visual cue signifying uncertain pain (i.e., Green > Yellow; [C5]); where the response to the visual cue signifying uncertain pain was greater than the response to the visual cue signifying certain pain (i.e., Yellow > Green; [C6]) and where the visual cue signifying uncertain pain was greater than the response signifying no pain (i.e., Yellow > Red; [C7]). The subject level

statistical images were registered to MNI (Montreal Neurological Institute) standard space using FLIRT (FMRIB's Linear Image Registration Tool[25]).

Higher-level analysis was carried out using FLAME[8,71,72] (FMRIB's Local Analysis of Mixed Effects). Z (Gaussianised T/F) statistic images were thresholded using clusters determined by $Z > 2.3$ and a cluster significance threshold of $P = 0.05$ (mixed effects; corrected for multiple spatial comparisons according to Gaussian Random Field theory[74]). Group-wise independent t-test comparisons were applied within the GLM to determine the difference in activation between WS groups (i.e., WS-H vs. WS-L). In addition, the following questionnaire and pain scores were also added to the group General Linear Model (GLM) analysis of fMRI data as covariates of interest: $VAS_{now,}$ $VAS_{5Day,}$ catastrophizing (rumination, magnification and helplessness), fear-avoidance beliefs, anxiety and depression. These scores were used as regressors within the GLM to confirm a positive covariance with the BOLD signal, allowing identification, voxel-by-voxel, of those areas of the brain where there was a difference in activation between groups relating to a difference in scores. A positive interaction indicated that the group difference between WS-H and WS-L varied as a function of the covariate. Coordinates are given in MNI space[16] and anatomical regions identified using the Harvard-Oxford Cortical and Subcortical Structural Atlas and the Jülich histological (cyto- and myelo-architectonic) atlas in FSLView (fsl.fmrib.ox.ac.uk/fsl/fslview/).

RESULTS

Questionnaire Data

WS-H participants rated both their anxiety (Mean score = 11.4; $t(27) = 2.914$, $p = .007$) and depression (Mean score = 10.3; $t(27) = 3.365$, $p = .002$) levels higher than WS-L participants (Mean score = 8.5 and 6.8 respectively). There was no significant difference between WS groups on the FABQ activities subscale (Mean score for WS-H = 19.2; Mean

score for WS-L = 14.9; t(27) = 1.762, p = .089) but there was on the work subscale (Mean score for WS-H = 35.5; Mean score for WS-L = 19.4; t(27) = 2.857, p = .008). Those in the WS-H group rated their own pain level greater than the WS-L group on the VAS_{now} (Mean WS-H score = 5.9; Mean WS-L score = 4.2; t(27) = 2.649, p = .013) but there was no difference over the 5-day average (Mean WS-H score = 5.3; Mean WS-L score = 5.1; t(27) = .155, p = .878). Finally, on the PCS, WS-H participants scored higher on both the rumination (Mean score = 10.7; t(27) = 2.761, p = .010) and magnification (Mean score = 4.4; t(24) = 3.137, p = .004) subscales than WS-L participants (Mean score = 7.1 and 2.6 respectively) but there was no difference in scores on the helplessness subscale (Mean score = 12.6 vs. 9.0; t(27) = 1.905, p = .067).

Within-group fMRI analysis of certain painful movement of the leg (Green cue), uncertain painful movement of the leg (Yellow cue) and certain expectation of no painful movement of the leg (Red cue) in participants with high levels of pain behaviour (WS-H)

For the WS-H group significant supra-threshold activity was seen only in response to the Red visual cue (vs. rest) across two separate clusters: left anterior intraparietal sulcus (x,y,z = -42, -50, 50mm; Z = 3.16) extending into posterior supramarginal gyrus (x,y,z = -52, -44, 42mm; Z = 3.12), superior parietal lobe (BA7a; x,y,z = -38, -56, 50mm; Z = 3.0) and left superior lateral occipital cortex (x,y,z = -28, -64, 38mm; Z = 2.88) and left sensorimotor cortex (BA4a/BA3b; x,y,z = -22, -30, 58mm; Z = 3.0) extending into posterior cingulate gyrus (BA23; x,y,z = -4, -22, 28mm; Z = 2.89) and supplementary motor area (x,y,z = -12, -20, 50mm; Z = 2.85). No other comparisons were significant.

Within-group fMRI analysis of the response to visual cues in participants with the lowest levels of pain behaviour (WS-L)

For the WS-L group significant supra-threshold activity was observed only in response to the contrast of Yellow vs. Red visual cues in a single cluster of activity centred on the right posterior supramarginal gyrus (x,y,z = 56, -44, 18mm; Z = 3.99) extending into the angular gyrus (x,y,z = 50, -52, 16mm; Z = 3.64), with additional peaks in the superior and inferior lateral occipital cortex (x,y,z = 44, -62, 4mm; Z = 3.85) and temporo-occipital junction (x,y,z = 42, -60, 6mm; Z = 3.53). No other comparisons were significant.

Between-group comparisons of main effects (WS-H vs. WS-L)

WS-H participants showed significantly more activity than WS-L participants in response to the Red visual cue in a cluster comprising left precentral (BA4/6) and posterior cingulate gyrus (x,y,z = -4, -24, 48mm; Z = 2.97) with an adjacent peak in left primary somatosensory cortex (BA3a; x,y,z = -22, -32, 48mm; Z = 2.69). A second cluster was seen in right superior parietal lobe (5m; x,y,z = 8, -46, 62mm; Z = 3.1) extending into primary somatosensory cortex (BA3b; x,y,z = 22, -38, 64mm; Z = 2.65) and occipital pole (x,y,z = 6, -98, 14mm; Z = 2.9; Figure 1. Note: This difference was seen at the slightly lower cluster-corrected Z threshold of Z > 2.1, P = .05). No other comparisons were significant and there were no areas more active in the WS-L group.

INSERT FIGURE 1 ABOUT HERE

Correlations of between-group fMRI data with questionnaire scores

Scores on the questionnaire items were then added into the GLM as covariates of interest for those scales where there were significant differences between the two WS groups. A positive covariance with the BOLD signal indicates that any difference between the WS-H and WS-L groups varies as a function of the covariate. Such a relationship was seen in response to the Green vs. Yellow visual cue and scores on the anxiety subscale of the HADS

in right insula (extending into the putamen; x,y,z = 3, 12, 0mm; Z = 3.45), right frontal pole (x,y,z = 42, 40, 8mm; Z = 3.35), pregenual ACC (x,y,z = 0, 40, 4mm; Z = 3.19) and paracingulate gyrus (x,y,z = -12, 52, 8mm; Z = 3.15; Figure 2). The only other questionnaire to show significant interactions with the fMRI data was the PCS again in response to the Green vs. Yellow visual cue and scores on the rumination subscale in left superior parietal lobe/precuneus (BA7; x,y,z = -4, -80, 46mm; Z = 3.19) extending into the superior division of the lateral occipital cortex bilaterally (x,y,z = -12, -82, 44mm and x,y,z = 14, -68, 48mm; Z = 2.81) and intracalcarine cortex (BA17/18; x,y,z = 6, -78, 10mm; Z = 2.83). Scores on the rumination subscale of the PCS also positively covaried with the group difference in response to the Green visual cue in right premotor cortex (BA6; x,y,z = 62, 6, 36mm; Z = 3.21), superior parietal lobe/precuneus (x,y,z = 10, -82, 54mm; Z = 3.08), left inferior parietal lobe at the level of the secondary somatosensory cortex/parietal operculum (x,y,z = -66, -22, 28mm; Z = 3.08) and left hippocampus (x,y,z = -12, -16, -18mm; Z = 3.06) and in the contrast of Green vs. Red in right premotor cortex (x,y,z = 60, 6, 36mm; Z = 3.23), right sensorimotor cortex (BA1/BA4a; x,y,z = (x,y,z = 64, -6, 36mm; Z = 3.43), posterior division of the right supramarginal gyrus (x,y,z = 50, -40, 12mm; Z = 3.08) and cuneal cortex (BA18; (x,y,z = 10, -82, 32mm; Z = 3.06). No other comparisons with questionnaire measures were significant.

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DISCUSSION

This study has confirmed that regions involved in encoding nociceptive signals and the subsequent response are also activated in the anticipation of pain and that the psychological perspective of the individual can modulate the perceived characteristics of the noxious stimulus, changing neural patterns of activity and overt behaviour. Based on the literature, we predicted that participants with the highest levels of pain behaviour (WS-H)

should have significantly higher self-reported pain-related distress and disability and show increased cortical activity in response to certain pain in rostral-cingulate cortex, anterior insula and cerebellum and uncertain pain in vmPFC, mid-cingulate cortex and hippocampus. We found that those participants with 4/5 or 5/5 WS did indeed score significantly higher on self-reported anxiety, depression, catastrophizing and fear-avoidance beliefs related to work than those participants with 0 or 1 positive signs. Furthermore, when these scores were used as regressors within the GLM a positive covariance with the BOLD signal was found in response to certain (vs. uncertain) pain with the anxiety subscale of the HADS in anterior insula, pregenual ACC and the frontal pole and with the rumination subscale of the PCS in prefrontal and parietal cortex and hippocampus. Our findings suggest that pain behaviour related to chronic states of LBP are maintained by brain regions implicated in emotional processing (insula, pregenual ACC) and cognitive control and attention (fronto-parietal cortex) during the expectation of certain pain in those with high levels of pain-related anxiety and distress.

The insula and ACC are part of the medial pain system involved in processing the motivational-affective features of noxious stimuli as well as the motor system pathways needed for generating behaviour.[58,64] The ACC contains both nociceptive neurons and neurons involved in pain anticipation.[24,30] Foltz and White[17] were the first to demonstrate that anxious patients who 'augmented' their pain were most likely to benefit from cingulotomy. Therefore, the interaction between anxiety and increased activity in these regions in response to a visual cue signalling an upcoming expected vs. unexpected pain is not only in accordance with previous studies in healthy controls[46,47] but might reasonably be expected in clinical populations with the highest levels of pain-related distress and behaviour. The pregenual ACC in particular is thought to be related to the affective or "suffering" component of pain.[64] Peyron et al[45] in their meta-analysis further suggested that activation in this brain region may

be related to stress and anxiety and this may maintain the chronic pain state as it has been shown to modify its activity prior to the arrival of a noxious stimulus in populations with post-traumatic stress disorder.[50] Although joint activation of the ACC, insula and prefrontal cortex is common in chronic pain syndromes (as a product of shared expression of opioid receptors[13]) due to the limited interconnections between anterior insula and the pregenual cingulate it is more likely they are engaged simultaneously in a parallel distributed network that is involved in affective responses to noxious stimuli.[64] Previous studies using pain-related visual cues have also shown activation of the medial pain pathway. For example, Shimo et al[54] used pictures of a man carrying luggage in a half-crouching posture to trigger activation of pain affect regions in people with cLBP. These authors found activation in regions similar to the present study including insula cortex, premotor and posterior cingulate cortices, hippocampus, fusiform gyrus and cerebellum. The authors suggest that visual stimuli can cause memory retrieval of unpleasant experiences and prolong the chronic pain condition. This interpretation is further supported by a recent study in healthy controls showing that neutral images that had previously been paired with nociceptive information elicited a reactivation of pain-related brain responses in insula and putamen.[19] We observed a similar activation of insula (extending into the putamen) during visual cues signalling pain, suggesting a possible mechanism by which pain is augmented through a pain-related reactivation from visual cues associated with leg-movement evoked pain resulting in high levels of pain behaviour in our patients.

Catastrophizing, like anxiety, can also augment pain perception through increased attention to painful stimuli (assessed by the rumination subscale) or through increased emotional responses to pain (assessed by the magnification subscale). A difference in activation between groups relating to a difference in rumination scores was observed in response to the contrast of Green vs. Yellow visual cues in superior parietal lobe (BA7) and lateral occipital cortex. There were also interactions with the rumination subscale in response

to the Green visual cue only in the superior parietal and premotor cortex, secondary somatosensory cortex and hippocampus and also in the Green vs. Red contrast in premotor and sensorimotor cortex and supramarginal gyrus. Right premotor cortex has previously been associated with anticipation of experimental pain and higher catastrophising levels in a group with fibromyalgia.[22] The posterior parietal/operculum regions, as well as containing nociceptive neurons[52] are implicated in memory recall[27] and are also involved in the higher-order analysis of noxious events such as aversion learning, spatial processing and attention.[14,34,48] The hippocampus, similarly, has been implicated in anticipation of experimental pain in healthy controls[24,5,46,47,48] and in a recent study by Mutso et al (2014)[41] populations of patients with sub-acute (1-4 months) and chronic back pain (>10 years) showed extensive hippocampal reorganisation and those with persistent pain had decreased connectivity between hippocampus and medial prefrontal cortex. The hippocampus may underlie learning and emotional abnormalities associated with chronic pain as the hippocampus is a key component of the mesocorticolimbic circuit involved in aversive learning[26] and chronic pain can be thought of as a state of continual learning coupled with an inability to extinguish aversive associations.[2] This proposal has received recent support from an experimental study in healthy controls using visual objects presented either alone or paired with painful heat stimuli.[18] Forkmann et al[18] showed that pain catastrophizing can amplify the interruptive effect of pain and that this pain-related disruption of visual encoding was associated with activity in the same region of the hippocampus during encoding. This augmentation of the interruptive function of pain on memory by pain catastrophizing agrees with other findings[60,57] and may reflect particular problems in disengaging from pain in NSLBP populations with high levels of pain behaviour.[33,59,60]

Contrary to our predictions, we found greater activity in the WS-H vs. WS-L group in response to the Red visual cue when psychological variables were not included in the model

in left precentral and posterior cingulate gyrus, superior parietal and occipital lobe and primary somatosensory cortex. This response to the Red visual cue was also seen in the WS-H within-group analysis in left pre- and postcentral gyrus extending into posterior cingulate gyrus. The posterior cingulate cortex (PCC; incorporating the posterior middle cingulate cortex – pMCC - using the nomenclature described by[63]) is involved in visuospatial orientation that is mediated through its extensive parietal lobe connections (for a review see[65]) and very early orienting responses to noxious stimuli through caudal cingulate motor areas[9,38,76] and spinal cord and motor cortex projections.[15] The dorsal part of PCC (dPCC) may share some functions with pMCC and be involved in orienting the body towards innocuous and noxious somatosensory stimuli and assessment of self-relevant sensation.[66] It is therefore likely that dorsal parts of the posterior cingulate and superior parietal lobes are involved in visually-guided nocifensive responses.[14,34] The posterior cingulate gyrus also forms mnemonic associations to sensory inputs to guide future behaviour.[65] As activation of these regions was seen in our study in those with the highest levels of pain behaviour, even in response to cues that signalled no painful movement of the leg, it may suggest an inability to effectively discriminate the threat value of sensory/environmental pain triggers in this population or disengage from the threat value of leg movement in this experiment, an idea that warrants further investigation.

In Figure 3 we propose a preliminary potential model of how visual cues may modify expectation of impending pain via a pathway involving the decoding of visual cues anticipating pain by visual cortex and hippocampus and decoding of context by prefrontal cortex. Here, the two systems of cue-based expectancies map onto subscales of rumination (fronto-parietal network, implicated in cognitive control and attention[10]) and anxiety (limbic network, implicated in emotional processing[44]). The fronto-parietal network in particular may play an important role in expectancy-induced modulation of pain.[5,28]

INSERT FIGURE 3 ABOUT HERE

Limitations of the current study

A possible weakness of our study was the use of a 1.5T vs. 3T scanner as this may have affected the sensitivity of our results. Previous studies have shown that in other motor tasks, such as finger tapping, there is a large amount of overlap in activation between 1.5T and 3T, particularly at more liberal thresholds.[42] However, the extent of activations at 3T is greater than at 1.5T and we therefore may not have seen activation in key areas because of the lower field strength. Future studies should aim to replicate these findings at 3T. Another possible limitation is the fact that it is known that individuals with high trait-anxiety may be more likely to respond to psychological stress with exaggerated respiration,[23] which may produce significant decreases in cerebral blood flow (CBF) that are unrelated to task-evoked activation.[21] However, several studies have found that the increase in signal associated with stimulus-induced regional activation is independent of that associated with CO_2 inhalation-induced increases in CBF[51] and that the BOLD response to photic stimulation under hypercapnic (using breath holding) conditions does not differ from normocapnic response conditions.[32] Also, Corfield et al[11] reported no significant interaction between the effects of visual stimulation and PCO_2 levels on the intensity of BOLD signal response in occipital cortex. Therefore, it is unlikely that our results can be explained by increased respiration in the more anxious WS-H group but future studies should integrate the measurement of real-time PCO_2 with the BOLD response to control for this possibility. Finally, it is possible that WS are, at least in part, reflections of central sensitization, and the fMRI differences between the WS-H and WS-L groups are a manifestation of neurological changes associated with central sensitization. We have shown previously that there is some cortical re-organisation in response to differences in WS[35]. However, it is impossible to demonstrate ‘cause and effect’ with our current cross-sectional design. We also cannot argue that there is more ‘nociceptive

input' in the WS-H cohort, which leads to more central sensitisation as both groups have similar levels of NSLBP and don't differ over their 5-day average of self-reported pain. Future investigations of whether WS change as the result of central sensitisation[6,36] should use a longitudinal study design in which some participants may go on to develop chronic LBP from the sub-acute stage.

Conclusions

The capacity to modulate pain in response to expectancy varies substantially between individuals[77,70] and may reflect crucial differences in the ability to recruit endogenous analgesia to protect bodies from long-term exposure to pain. We have revealed key brain regions involved in the anticipation of a clinically-relevant pain in a population with NSLBP and the highest levels of pain behaviour. Furthermore, we have shown that activity of these regions is modulated by scores on psychometric tests of pain-related distress, namely anxiety and catastrophising. Our results concur with previous literature in suggesting that catastrophising appears to be associated with brain areas involved in attention to pain and that any effective intervention should take into account the perceived threat of pain, particularly for high catastrophizers. A correctly targeted treatment may induce enduring changes in relevant brain circuitry. For example, a recent study by Seminowicz et al[53] investigated grey matter changes after cognitive behavioural therapy (CBT) in patients with chronic pain. These authors found that, after treatment, decreased pain catastrophising was associated with treatment-related increases in grey matter in hippocampus, left DLPFC, venterolateral prefrontal cortex, right posterior parietal cortex, somatosensory regions and the ACC, which may reflect increased top-down control over pain and cognitive reappraisal of pain and/or increased attentional diversion abilities decreasing the fear and emotional impact of pain. The hippocampus in particular may in future become a therapeutic target for pain as this structure was recently shown to have altered neurogenesis and short-term plasticity in a mouse model

of neuropathic pain and decreased volume in chronic back pain and chronic regional pain syndrome patients.[40] Any changes in hippocampal structure after CBT may provide an important neuromarker of the normalisation of hippocampal function in pain learning, memory and emotion.

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FIGURE LEGENDS

Figure 1. Increased activation in WS-H vs. WS-L participants in response to the Red visual cue (signalling that the leg would not be moved). Maps were cluster-based thresholded at $Z > 2.1$, $P = 0.05$ (corrected for multiple comparisons) and are shown in the axial and coronal plane in radiological convention (right side of brain on left side of figure).

Figure 2. Activation maps showing those areas of the brain where there was a difference in BOLD response between groups relating to a difference in anxiety and rumination scores as measured by the A) PCS and B) HADS, respectively in the contrast of expected (Green) vs. unexpected (Yellow) pain. Maps were cluster-based thresholded at $Z > 2.3$, $P = 0.05$ (corrected for multiple comparisons) and are shown in the axial and sagittal plane in radiological convention (right side of brain on left side of figure).

Figure 3. A schematic model of a suggested brain organisation whereby visual cues may modify expectation of impending pain. We propose a pathway involving decoding of visual cues anticipating pain by visual cortex, through the hippocampus and posterior parietal cortex and decoding of context by prefrontal cortex. Here, two systems of cue-based expectancies map onto subscales of rumination (fronto-parietal, implicated in cognitive control and attention) and anxiety (insula-anterior cingulate cortex, implicated in emotional processing).

TABLE 1. Baseline demographic data for WS-L and WS-H groups showing mean scores ±1SD (HADS = Hospital Anxiety and Depression Scale[75]; FABQ = Fear-Avoidance Beliefs Questionnaire[69]; VAS = Visual Analogue Scale[49]; PCS = Pain Catastrophizing Scale[56]). Significant differences between groups are indicated by *.

	WS-L	WS-H
Gender	9 males; 7 females	7 males; 6 females
Mean age (years)	47(13.1)	45(10.2)
Duration of clinical pain (months)	112(113.3)	114(85.4)
HADS		
Anxiety	8.5(2.7)	11.4(2.6)**
Depression	6.8(3.1)	10.3(2.5)**
Total	15.3(4.1)	21.8(3.9)***
FABQ		
Work	19.4(14.3)	35.5(16.0)**
Activities	14.9(5.8)	19.2(7.4)
Total	34.2(16.9)	54.7(19.5)**
VAS		
Now	4.2(2.0)	5.9(1.4)*
5-day average	5.1(2.0)	5.3(2.6)
PCS		
Rumination	7.1(3.9)	10.7(3.2)**
Magnification	2.6(1.7)	4.4(1.4)**
Helplessness	9.0(5.3)	12.6(4.7)
Total	18.7(9.8)	27.8(7.9)*

*p < .05; **p < .01; ***p < .001