Illness Behavior in Patients With Chronic Low Back Pain and Activation of the Affective Circuity of the Brain

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Objective: Patients with chronic low back pain (cLBP) show a range of behavioral patterns that do not correlate with degree of spinal abnormality found in clinical, radiological, neurophysiological, or laboratory investigations. This may indicate an augmented central pain response, consistent with factors that mediate and maintain psychological distress in this group. Methods: Twenty-four cLBP patients were scanned with functional magnetic resonance imaging while receiving noxious thermal stimulation to the right hand. Patients were clinically assessed into those with significant pain-related illness behavior (Waddell signs [WS]-H) or without (WS-L) based on WS. Results: Our findings revealed a significant increase in brain activity in WS-H versus WS-L patients in response to noxious heat in the right amygdala/parahippocampal gyrus and ventrolateral prefrontal and insular cortex (at a VoxelPThresh = 0.01). We found no difference between groups for heat pain thresholds ($t(22) = -1.17, p = .28$) or sensory-discriminative pain regions.

Conclusions: Patients with cLBP displaying major pain behavior have increased activity in the emotional circuitry of the brain. This study is the first to suggest an association between a specific clinical test in cLBP and neurobiology of the brain. Functional magnetic resonance imaging may provide a tool capable of enhancing diagnostic accuracy and affecting treatment decisions in cases where no structural cause can be identified. Key words: chronic low back pain, functional magnetic resonance imaging, illness behavior, limbic structures, noxious heat, Waddell signs.

cLBP = chronic low back pain; MRI = magnetic resonance imaging; fMRI = functional magnetic resonance imaging; VAS = visual analog scale; NSLBP = nonspecific low back pain; HPTol = heat pain tolerance; BOLD = blood oxygenation level dependent; WS = Waddell signs.

INTRODUCTION

M ost patients with chronic low back pain (cLBP) do not develop significant disability and largely continue to work and live despite their pain. A significant minority, however, develop a disability that prevents work and disrupts normal social activities. It is not clear what separates those that develop disability from those that do not, but neither difference in physical disease nor psychological factors adequately separate persons with disability from those without disability (1). Brain imaging studies are starting to reveal potential functional alterations in the cortical and subcortical processing of pain in patients with idiopathic nonspecific low back pain (NSLBP), which may contribute to the chronicity of pain and its associated behavioral attributes (2–5). However, only one study to date has investigated the relationship between cerebral pathophysiology and clinically important behavioral correlates in a low back pain population (6). Waddell signs (WS) are a series of validated and reproducible behavioral responses to clinical examination frequently found in patients with cLBP (7,8). The signs can be listed under five general categories: tenderness (superficial skin tender to light touch or nonanatomic deep tenderness not localized to one area), simulation (axial loading pressure on the skull of a standing patient induces lower back pain or rotation where the shoulders and pelvis rotated in the same plane induces pain), distraction (difference in straight leg raising in supine and sitting positions), regional (weakness in many muscle groups, i.e., “giveaway 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., nondermatomal), and overreaction (disproportionate facial or verbal expression, i.e., pain behavior). It was originally proposed that WS should draw attention to the possibility of exaggerated illness behaviors, defined by Waddell as “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” (9) and can be equated with pain behavior (10). A systematic review of the evidence on WS (11) suggested that patients with signs in three or more of these categories have greater pain perception and poorer treatment outcomes than do patients without such signs. Treatment options for these patients may be better informed by understanding the neural correlates of pain and its relationship to pain behavior.

Previous studies have suggested a link between psychological distress and pain perception in other chronic pain conditions, such as fibromyalgia. In a human brain imaging study, pain catastrophizing (independent of the influence of depression) was significantly associated with increased activity in areas related to pain anticipation (medial frontal cortex and cerebellum), attention (dorsal anterior cingulate and dorsolateral prefrontal cortices), emotional aspects of pain (claustrum), and motor control (12). These findings support theories suggesting that catastrophizing influences pain perception through altering attention and anticipation and through heightening emotional responses to pain (for review, see Ref. (13)). However, despite evidence of augmented central pain processing in patients with idiopathic or nonspecific cLBP (2,5), such a link between psychological factors and putative neurophysiological correlates of increased pain perception has not been demonstrated.

In a positron emission tomography study by Derbyshire et al. (3), patients with cLBP and healthy controls were given noxious thermal stimulation to the hand to highlight abnormalities in the...
central nervous system processing of pain, which may implicate mechanisms that mediate/modulate pain in this patient group. Both groups showed similar consistent and reliable activation of central pain areas, with the only difference between groups seen in posterior cingulate gyrus (BA23). One factor that may have contributed to this underwhelming group difference was the lack of significant pain-related illness behavior or distress in the patients tested. On average, they had WS in only two of the five possible categories, no significant depression, and self-reported clinical pain levels in the mild-moderate range. This profile does not typify a significant number of cLBP patients who present with high levels of pain-related anxiety, depression, and self-reported pain and exhibit prominent illness behaviors (for a review, see Ref. (14)). Patients exhibiting signs in four or more categories and elevated clinical pain levels are therefore predicted to have an augmented central pain response, which may be consistent with factors that mediate and maintain psychological distress in this group (15).

To test this hypothesis, two groups of cLBP patients were scanned with functional magnetic resonance imaging (MRI) while receiving noxious thermal stimulation to the right hand. Our aims were to a) confirm that patients assessed clinically as having illness behavior (defined by WS) also scored higher on self-report measures of pain-related fear, catastrophizing, anxiety, and depression when compared with patients without illness behavior; b) investigate whether patients with illness behavior also have lowered pain tolerance to noxious thermal stimuli applied to the hand; and c) investigate whether the cortical and subcortical response to noxious heat stimuli differed significantly between these patient groups.

METHODS

Participants

Thirty patients with cLBP (16 men and 14 women) aged between 21 and 67 years (with a mean [M; standard deviation [SD] age of 45 [12.4] years) were recruited to the study. Because of technical problems with the stimulus delivery system, 6 patients were unable to complete the scanning part of the study, and so data are presented from the remaining 24. The study protocol was approved by the local NHS ethics committee and the University of Liverpool ethical review board and was conducted in accordance with the Helsinki Declaration (1989). Data collection took place between 2003 and 2005. Participants gave fully informed written consent of their willingness to participate. The inclusion criteria were as follows: pain for 6 months, mechanical back pain without sciatica, no previous operations for back pain (including facet denervation), and MRI showing no structural spinal abnormality other than degenerative change in excess of recommended doses.

To clinically differentiate patients with cLBP based on whether they demonstrated significant pain-related illness behavior, the presence of WS was assessed independently by two clinical specialists. To secure two distinct patient populations for this study, it was deemed that patients must show 4/5 or 5/5 positive WS to be eligible for the high levels of illness behavior cohort (WS-H), whereas to be eligible for the low levels of illness behavior group, patients must show 0/5 or 1/5 positive WS (WS-L). Eleven patients (6 women) with either WS-H patients and 13 patients (6 women) who had one or no positive WS formed the WS-L group.

The age difference between patient groups (i.e., WS-H versus WS-L) was nonsignificant (WS-H: M [SD] = 44 [12.8] years, WS-L: M [SD] = 49 [19.9] years; p = .55, independent t test comparison), as was the difference in mean duration of low back pain (WS-H: mean = 107 months, WS-L: mean = 112 months; p = .91). All patients were on stable medication at the time of scanning1. Ongoing medication (where known) did not differ substantially between groups, with most patients taking nonsteroidal anti-inflammatory drugs (9 WS-H patients and 4 WS-L patients) and paracetamol (acetaminophen up to 4000 mg/d; 7 WS-H patients and 5 WS-L patients). Eight patients in each group were on low doses of opioids (up to 60 mg/d; one patient in the WS-H group was on stable modified release morphine sulfate at 60 mg/d); three patients in the WS-H group were on low doses of antidepressants (25 mg/d; one patient in the WS-H group was on citalopram at 40 mg/d), and no one reported taking medication in excess of recommended doses.

Apparatus and Materials

To deliver painful hot thermal stimulation to the right hand of both patient groups during functional MRI (fMRI) scanning, a Peltier thermode was used as part of the Thermal Sensory Analyzer system (TSA-II; Medoc, Haifa, Israel), an MRI compatible device capable of delivering temperatures throughout the thermosensory range (from painful cold to painful hot) in seconds. The timings for the stimuli were controlled via custom software installed on a Dell laptop.

Design and Procedure

Immediately before fMRI scanning, participants were tested for their individual heat pain tolerance (HPTol) thresholds to noxious thermal stimulation. While inside the scanner room, the Peltier thermode was attached to the participant’s right hand and incremental steps in temperature were applied, starting at a resting room temperature of 32°C, then rising over 2 seconds to a minimum experimental temperature of 44°C (duration, 6 seconds), with a subsequent 2°C increase every 6 seconds to a maximum temperature of 50°C. Participants were instructed to numerically rate the painfulness of the heat stimulus until it reached a level of 7/10. It was explained to participants that this value should indicate that they are experiencing moderate to severe pain and do not wish the thermal temperature to rise any further. After a short delay, this procedure was repeated and the highest value was then taken as the participant’s HPTol for the fMRI scan.

During the fMRI scan noxious thermal stimulation (in the range of 44°C–50°C and a measured HPTol of 7/10) of the thenar, eminence of the right hand was alternated with periods of innocuous warm (40°C) stimulation in an ABAC blocked design, where A = rest (room temperature of 32°C; duration, 15 seconds), B = hot painful stimulation (duration, 9 seconds), and C = warm stimulation (duration, 9 seconds). This order was counterbalanced between participants. The total scan time was 5 minutes 51 seconds. Participants were instructed to focus on the thermal stimulation on their hand throughout and not to move the hand or head.

Before the fMRI scanning session, each participant in the study was also asked to complete several questionnaires. This included the visual analog scale (VAS (16)), a 10-cm horizontal line on which the patients made a vertical mark to indicate how much back pain they were currently experiencing (VASmax) and the average pain they had had in the last 5 days (VASmin), the Pain Coping Strategies Questionnaire (17); the activities only subscale of the Fear Avoidance Beliefs Questionnaire (18), as many of the WS-H patients were not and had not been working for a number of years; and the Hospital Anxiety and Depression Scale (19).

Scanning Procedure

Magnetic resonance data were acquired using a 1.5-T Sigma LX/Nvi neuro-optimized system (General Electric, Milwaukee, WI). fMRI was performed with a blood oxygenation level–dependent (BOLD) sensitive T2*-weighted multislice gradient echo planar imaging sequence (echo time = 40 milliseconds, repetition time = 3 seconds, flip angle = 90°, field of view = 19 cm, 64 x 64 matrix). Twenty-four contiguous 5-mm-thick axial slices were prescribed

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1This is more ethical than asking patients to stop their pain relief and would have made them more comfortable (and therefore less likely to move) during the scanning procedure. There is no evidence to support the idea that pain medication, at the low doses our patients were taking, has any effect on the BOLD signal (15), and there was no empirical evidence that heat pain tolerance thresholds were markedly different between the two groups. Therefore, we do not feel that pain medication compromised our results.
ILLNESS BEHAVIOR AND LOW BACK PAIN

parallel to the anterior commissure–posterior commissure line and covered the whole brain. One hundred seventeen echo planar imaging volumes were collected in total (after saturation scans). For the purpose of anatomical referencing and visualization of brain activation, a high-resolution $T_1$-weighted three-dimensional inversion recovery–prepared gradient echo (IRp-GRASS) sequence was also acquired (echo time = 5.4 milliseconds, repetition time = 12.3 milliseconds, $T_1$ = 450 milliseconds, 1.6-mm-slice thickness, field of view = 20 cm, 256 $\times$ 192 matrix), with 124 axial slices covering the whole brain.

Data Analysis

Questionnaire data and noxious HPTol thresholds collected from participants before fMRI scanning were entered into SPSS v20 (SPSS Inc, Chicago, IL) to calculate group mean differences (independent $t$ tests) and Pearson $r$ bivariate correlations.

All fMRI image processing and statistical analyses were 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 (FSL 5.0.4 [20]). The following preprocessing steps were applied: motion correction using MCFLIRT [21], spatial smoothing using a Gaussian kernel of FWHM 5 mm, mean-based intensity normalization of all volumes by the same factor; and nonlinear highpass temporal filtering ($\sigma = 48$ seconds, Gaussian-weighted LSF straight-line fitting).

A general linear model 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 (22) to model BOLD signal intensity changes in response to thermal stimulation. Two regressors were constructed by convolving a boxcar function (the stimulus input function: noxious/innocuous thermal stimulation = 1; baseline = 0) with a gamma hemodynamic response function (lag, 6 seconds; SD, 3 seconds). Voxel-wise parameter estimates were derived for each regressor using the appropriate contrast. To determine the cerebral response to noxious and innocuous thermal stimulation of the hand, the contrasts noxious heat versus rest (C1) and innocuous warm versus rest (C2) were analyzed. A contrast of these main effects (i.e., [C1–C2]) revealed those areas more responsive to noxious heat (versus innocuous warm) stimulation of the hand (i.e., those areas showing a nociceptive rather than a thermoreceptive response). The inverse contrast revealed those areas where the response to the warm stimulus was greater than that to noxious heat.

The subject-level statistical images were then registered into Montreal Neurological Institute standard space using FLIRT (FMRIB’s Linear Image Registration Tool) [21].

Higher-level random-effect analysis was carried out using FLAME (FMRIB’s Local Analysis of Mixed Effects [23,24]). $Z$ (Gaussianized T/F) statistic images were thresholded using clusters determined by $Z > 2.3$ (corresponding to a VoxelPThreshold $= 0.0107$) and a cluster significance threshold of $p = .05$ (corrected for multiple spatial comparisons according to Gaussian random field theory [25]). To identify brain activation where the response to noxious thermal stimulation was greater than innocuous (warm) stimulation, a group statistical map of the contrast of main effects (C3) was calculated across all individual group members, creating the group map “noxious heat–warm.” Group-wise independent $t$ test comparisons within the general linear model were then applied to determine the difference in activation to noxious heat (versus innocuous warm) between patient groups (i.e., WS-H versus WS-L). Coordinates are given in Montreal Neurological Institute space (26) and identified using the Harvard-Oxford Cortical and Subcortical Structural Atlas inside FSLView (fsl.fmrib.ox.ac.uk/fsl/fslview/).

RESULTS

Questionnaire Data

WS-H patients rated both their anxiety (mean score = 11.7; $t(22) = 2.34, p = .029$) and depression (mean score = 10.9; $t(22) = 3.21, p = .004$) levels significantly higher than did WS-L patients (mean score = 8.1 and 6.6, respectively). They also scored significantly higher on the catastrophizing subscale of the Pain Coping Strategies Questionnaire (mean score for WS-H patients = 19.5; mean score for WS-L patients = 9.3; $t(22) = 3.47, p = .002$) but not on any other measure (all $p$ values > .004, corrected for multiple comparisons; see Table 1). There was no significant difference between patient groups on the Fear Avoidance Beliefs Questionnaire activities subscale (mean score for WS-H patients = 19.6; mean score for WS-L patients = 15.8; $t(22) = 1.41, p = .17$). WS-H patients rated their own pain levels greater than did WS-L patients on the VAS$_{now}$ (mean WS-H score = 5.8; mean WS-L score = 3.9; $t(22) = 2.45, p = .023$), but this did not survive correction for multiple comparisons and there was also no difference over the 5-day average (mean WS-H score = 6.6; mean WS-L score = 5.0; $t(20) = 1.94, p = .067$).

TABLE 1. Mean (SD) for Questionnaire Measures Completed by cLBP Patients With (WS-H) or Without (WS-L) Significant Illness Behavior

<table>
<thead>
<tr>
<th>Measure</th>
<th>WS-H Group (n = 11)</th>
<th>WS-L Group (n = 13)</th>
<th>Mean Difference</th>
<th>$t$</th>
<th>$df$</th>
<th>$p$</th>
<th>$r_{partial}^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS$_{Day}$</td>
<td>5.8 (1.7)</td>
<td>3.9 (2.1)</td>
<td>1.9</td>
<td>2.45</td>
<td>22</td>
<td>.023</td>
<td>.215</td>
</tr>
<tr>
<td>VAS$_{Day}$</td>
<td>6.6 (1.3)</td>
<td>5.0 (2.2)</td>
<td>1.6</td>
<td>1.94</td>
<td>20</td>
<td>.067</td>
<td>.158</td>
</tr>
<tr>
<td>HADS$_{Anxiety}$</td>
<td>11.7 (4.8)</td>
<td>8.1 (2.7)</td>
<td>3.6</td>
<td>2.34</td>
<td>22</td>
<td>.029</td>
<td>.199</td>
</tr>
<tr>
<td>HADS$_{Depression}$</td>
<td>10.9 (3.4)</td>
<td>6.6 (3.2)</td>
<td>4.3</td>
<td>3.21</td>
<td>22</td>
<td>.004</td>
<td>.319</td>
</tr>
<tr>
<td>FABQ$_{Activity}$</td>
<td>19.6 (8.2)</td>
<td>15.8 (4.8)</td>
<td>3.8</td>
<td>1.41</td>
<td>22</td>
<td>.172</td>
<td>.083</td>
</tr>
<tr>
<td>CSQ</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diverting</td>
<td>13.7 (9.0)</td>
<td>7.8 (6.4)</td>
<td>5.9</td>
<td>1.87</td>
<td>22</td>
<td>.075</td>
<td>.137</td>
</tr>
<tr>
<td>Reinterpreting</td>
<td>8.3 (7.1)</td>
<td>6.3 (6.5)</td>
<td>2.0</td>
<td>0.706</td>
<td>22</td>
<td>.487</td>
<td>.022</td>
</tr>
<tr>
<td>Catastrophizing</td>
<td>19.5 (7.8)</td>
<td>9.3 (6.6)</td>
<td>10.2</td>
<td>3.47</td>
<td>22</td>
<td>.002</td>
<td>.353</td>
</tr>
<tr>
<td>Ignoring</td>
<td>12.1 (6.5)</td>
<td>14.8 (6.3)</td>
<td>-2.7</td>
<td>-1.02</td>
<td>22</td>
<td>.317</td>
<td>.045</td>
</tr>
<tr>
<td>Praying</td>
<td>17.3 (10.9)</td>
<td>10.5 (6.2)</td>
<td>6.8</td>
<td>1.81</td>
<td>22</td>
<td>.090</td>
<td>.140</td>
</tr>
<tr>
<td>Coping</td>
<td>20.7 (5.2)</td>
<td>23.4 (7.1)</td>
<td>-2.7</td>
<td>-1.03</td>
<td>22</td>
<td>.314</td>
<td>.046</td>
</tr>
<tr>
<td>Increasing</td>
<td>15.4 (3.5)</td>
<td>13.3 (7.9)</td>
<td>2.1</td>
<td>0.844</td>
<td>22</td>
<td>.410</td>
<td>.028</td>
</tr>
</tbody>
</table>

SD = standard deviation; cLBP = chronic low back pain; WS-H = group with high levels of illness behavior; WS-L = group with low levels of illness behavior; VAS = visual analog scale; HADS = Hospital Anxiety and Depression Scale; FABQ = Fear Avoidance Beliefs Questionnaire; CSQ = Coping Strategies Questionnaire. *Significant difference at the $p \leq .004$ level (Bonferroni corrected for multiple comparisons).

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TABLE 2. Regions Showing a Significant Increase in BOLD Response to a Noxious (Versus Innocuous) Thermal Stimulus on the Right Hand in WS-H and WS-L Patients

<table>
<thead>
<tr>
<th>Region</th>
<th>MNI Coordinates (x, y, z), mm</th>
<th>Maximum Z Score</th>
<th>R/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>WS-H</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temporal pole</td>
<td>52  14  −12</td>
<td>3.80</td>
<td>R</td>
</tr>
<tr>
<td>−54  10  −20</td>
<td>3.54</td>
<td>L</td>
<td></td>
</tr>
<tr>
<td>Inferior frontal gyrus (BA47)</td>
<td>44  22  −16</td>
<td>3.59</td>
<td>R</td>
</tr>
<tr>
<td>−44  22  −8</td>
<td>3.60</td>
<td>L</td>
<td></td>
</tr>
<tr>
<td>Anterior insular cortex</td>
<td>40  16  −12</td>
<td>3.54</td>
<td>R</td>
</tr>
<tr>
<td>Amygdala/Parahippocampal gyrus</td>
<td>10  −2  −18</td>
<td>3.47</td>
<td>R</td>
</tr>
<tr>
<td>Putamen</td>
<td>30  −2  −8</td>
<td>3.46</td>
<td>R</td>
</tr>
<tr>
<td>Superior temporal gyrus</td>
<td>−52  0  −2</td>
<td>3.67</td>
<td>L</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>−4  −56  −18</td>
<td>4.12</td>
<td>L</td>
</tr>
<tr>
<td>Secondary somatosensory cortex</td>
<td>−54  −20  28</td>
<td>2.82</td>
<td>L</td>
</tr>
<tr>
<td>WS-L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inferior frontal gyrus (BA47)</td>
<td>48  14  0</td>
<td>4.26</td>
<td>R</td>
</tr>
<tr>
<td>−48  30  8</td>
<td>3.60</td>
<td>L</td>
<td></td>
</tr>
<tr>
<td>Anterior insular cortex</td>
<td>36  22  −4</td>
<td>3.48</td>
<td>R</td>
</tr>
<tr>
<td>−38  4  2</td>
<td>3.45</td>
<td>L</td>
<td></td>
</tr>
<tr>
<td>Temporal pole</td>
<td>50  14  −6</td>
<td>3.81</td>
<td>R</td>
</tr>
<tr>
<td>Inferior frontal gyrus (BA44/45)</td>
<td>−46  18  22</td>
<td>4.48</td>
<td>L</td>
</tr>
<tr>
<td>Putamen</td>
<td>−14  8  0</td>
<td>3.79</td>
<td>L</td>
</tr>
<tr>
<td>−30  6  −2</td>
<td>3.48</td>
<td>R</td>
<td></td>
</tr>
</tbody>
</table>

BOLD = blood oxygenation level dependent; MNI = Montreal Neurological Institute; WS-H = group with high levels of illness behavior; WS-L = group with low levels of illness behavior; R/L = right/left.

Activations were determined by clusters of Z > 2.3, p = .05 (corrected for multiple comparisons). MNI coordinate and peak Z score of the maximum activating voxel in each cluster are shown with the laterality of response (R/L).

**Noxious HPTol Thresholds**

Independent t tests (two-tailed) revealed no significant difference in the amount of heat pain tolerated by the patient groups (HPTol WS-H mean [SD] = 46.9°C (1.9°C); WS-L mean [SD] = 46.0°C (2.1°C); t(22) = −1.17, p = .28). Furthermore, there was no significant group × sex interaction (F(1,20) = 1.344, p = .26, η\_partial^2 = 0.063), indicating that there was no difference in mean HPTol levels between men and women in either of the patient groups (WS-H men = 47.2°C, WS-H women = 46.7°C; t(9) = −0.45, p = .66; WS-L men = 45.4°C, WS-L women = 46.8°C; t(11) = 1.20, p = .26).

**Within-Group fMRI Data Reveal Patterns of Activation in Response to Painful Hot (Versus Innocuous Warm) Stimulation of the Hand in Patients With NSLBP**

Inclusive masking revealed activation common to both groups in response to noxious hot (versus innocuous warm) thermal stimulation of the hand in bilateral ventrolateral prefrontal cortex (BA47; x, y, z = 42, 42, 4 mm), right anterior insular (x, y, z = 40, 18, −8 mm), and right putamen (x, y, z = 30, −2, 4 mm). Table 2 lists the regions showing significant activation in response to noxious hot (versus innocuous warm) thermal stimulation of the hand in each patient group. WS-H patients showed further right lateralized activation of amygdala/parahippocampal gyrus and bilateral activation of temporal pole and cerebellum (Fig. 1). In response to the same stimulation, far less widespread activation was observed in WS-L patients occurring predominantly in bilateral inferior frontal gyrus (BA47/44/45), anterior insular, and putamen (Fig. 2).

**Between-Group fMRI Analyses Reveal a Significant Increase in Response to Noxious Thermal Stimulation of the Hand in WS-H Versus WS-L Patients**

A comparison of the activity between the two patient groups revealed significantly more activation in WS-H versus WS-L patients in response to noxious (versus innocuous) heat entirely in the right hemisphere in the amygdala (x, y, z = 26, −4, −14 mm; Z = 3.85), inferior frontal gyrus (BA47; x, y, z = 46, 20, −18 mm; Z = 3.62), extending into insular cortex (x, y, z = 42, 14, −16 mm; Z = 3.53), and superior mid–temporal gyrus (x, y, z = 52, 4, −14 mm; Z = 3.47; see Fig. 2). There were no areas more responsive to noxious thermal stimulation in WS-L versus WS-H patients or areas of significant deactivation in response to a noxious thermal stimulus.

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2This difference was significant using a fixed-effects model by forcing the random-effects variance to zero in FLAME. Because fixed effect ignores cross session/subject variance, reported activation is with respect to the subjects present and not necessarily representative of the wider population.

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D. M. LLOYD et al.
Post Hoc Correlations Between % BOLD Signal Change and Questionnaire Scores

To investigate the relationship between heat activation scores and psychometric measures (specifically anxiety, catastrophizing, fear, and pain), we created an inclusive mask based on the regions identified as being more responsive to noxious hot (versus innocuous warm) thermal stimulation to the hand common to both groups (i.e., ventrolateral prefrontal cortex, insular, and...
putamen), extracted the % BOLD signal change across these regions (using FEATQuery; fsl.fmrib.ox.ac.uk/fsl/fsl-4.1.9/feat5/featquery), and correlated these values with the questionnaire measures (using Pearson r). The minimum p value accepted for significance was divided by the number of correlations performed and a significance level of p ≤ .01 was accepted. Furthermore, because of the known link between depression and catastrophizing in chronic pain populations (see Ref. (12)), depression was partialled out from the analysis.

The correlation showed that pain scores for the 5-day average positively correlated with % BOLD signal change in these areas, although not enough to survive correction for multiple comparisons (r = 0.448, p = .05). Analyzing the groups separately revealed further correlations between % BOLD signal change and Hospital Anxiety and Depression Scale anxiety scores (r = −0.708, p = .049) and catastrophizing (r = −0.677, p = .065), in addition to the VAS 5-day average for the WS-H group (r = 0.665, p = .072), but nothing approaching significance for the WS-L group and nothing that survived correction for multiple comparisons.

DISCUSSION

The motivation for the present study was the well-known clinical observation that patients with low back pain show a range of behavioral patterns that do not correlate with degree of spinal abnormality found in clinical, radiological, neurophysiological, or laboratory investigations. This observation was the basis for Waddell’s original development of tests to enable clinicians to recognize important behavioral aspects in their patients. The approach used in the present study was to compare two groups of patients who both had cLBP but who showed limited spinal abnormality and had not undergone any surgical procedures and who would show completely different behavioral patterns. Two distinct groups of patients were identified (i.e., WS-H and WS-L) who were categorized based on extremes in the range of WS but who, in other clinical features (e.g., duration of pain, disk degeneration, lack of surgery, medication, etc), were very similar. Noxious heat applied to the right hand was chosen as the inductor of pain that would not be compromised by differences in the pain-mediating pathways supplying the lower back. Indeed, similar HPTol thresholds across the groups provided evidence of this. Any BOLD signal change in response to the heat pain stimulus would therefore be primarily due to mechanisms underlying the generic processing of pain, which we predicted would be different in the two patient groups. Although WS served as a tool for assessment of behavior in a clinical context, levels of anxiety, catastrophizing, and fear were also expected to contribute to these brain processes because of the relationship between them and the experience of pain.

Using this rationale, increased right lateralized activity was observed in the WS-H group compared with the WS-L group in limbic structures including the amygdala and insular cortex, which have reciprocal functional connections to ventrolateral prefrontal cortex and temporal lobe. The similarity in peripheral HPTol thresholds among patients and the lack of increased activity in lateral somatosensory pathways serving the sensory-discriminative aspects of pain suggests that differences in cerebral activations between the two groups were not driven by somatosensory signals but by distinct functions of limbic structures involved in the affective response to pain. Conceivably, a similar engagement of affective circuitry during the clinical examination of WS may result in exaggerated perception of pain and the aberrant behavioral responses seen in the WS-H patient group, even if the mechanical provocation used is insufficient to activate the sensory-discriminative pain system.

Both patient groups showed increased activity in response to noxious thermal stimulation (compared with innocuous warm stimulation) in bilateral ventrolateral prefrontal cortex, right anterior insular, and right putamen, which likely reflects pain-specific responses, negative emotional responses, and/or activation of reward circuitry in response to pain (27). For example, increased activity in insular cortices in pain perception is well documented and activates transiently with pain in patients with chronic back pain (2) and may be involved in the extent to which pain becomes chronic (28). It has also been reported during the anticipation of pain in fibromyalgia (versus osteoarthritis patients and healthy controls; (29)), which further correlated with clinical pain scores and number of tender points but not psychological coping factors (catastrophizing and anxiety). Similarly, we found a positive correlation existed between clinical pain scores on the 5-day average but negative correlations with anxiety and catastrophizing in our WS-H patient group. However, because of the lack of significant correlations, further validation is needed to support the idea that neural activity related to pain behavior is mediated by clinical pain scores in this cohort.

A between-group comparison showed increased activity in WS-H versus WS-L patients in response to the same thermal stimulus within the right ventrolateral prefrontal cortex and anterior insular and unique activation in the right amygdala. A recent study by Hashmi et al. (27) demonstrated similar increases in emotion-related circuitry (amygdala and medial prefrontal cortex) when comparing chronic back pain to acute/subacute back pain. The authors suggested that this increase may underlie the transition from an acute to a chronic state. They also showed that emotion-related circuitry was not dependent on psychological comorbidities (such as anxiety and depression) but was related to the subjective salience of pain. The amygdala is frequently activated in human imaging studies of experimental heat pain (30–33). It is well positioned to integrate nociceptive-specific information from the spinal cord and brainstem with highly processed polymodal information from the thalamus and cortex, enabling it to attach emotional significance to painful events and modulate pain behavior and experience through the descending inhibitory control of pain (for a review, see Ref. (34)). The relationship between WS-H pain-related activity and the amygdala suggests that the pain percept has been transformed from a pain-oriented one to an emotional one, possibly centered on fear, anxiety, and catastrophizing (35). A neuroimaging study investigating pain sensitization through
daily application of noxious heat over a 12-day period showed increased affective pain ratings and increased hippocampal and amygdala activation (36). This suggests a role for these structures in the retrieval of contents relevant for affective pain processing and perception and may indicate a learning effect leading to pathological pain sensitivity in our chronic pain cohort. We also see increased amygdala/parahippocampal activity in our WS-H cohort, which may represent a sustained but faulty engagement of the normal antinociceptive system not dependent on peripheral input but maintained by central processing.

In addition to having a primary function in pain processing and pain unpleasantness, increased activity within a hippocampal network has also been associated with anxiety-induced hyperalgesia in healthy controls (37) and anticipatory anxiety and panic disorders including social phobia and generalized anxiety disorder in clinical populations (38,39). Similarly, right ventrolateral prefrontal cortex, in addition to the integration of sensory and visceral information with affective signals (40), has been reported in adolescents with generalized anxiety disorder (41). Somatic symptom disorder with predominant pain is described in *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)* as persistent and chronic pain at one or more sites that cannot be explained by physiological process or physical disorder and is associated with high affective descriptions of an individual’s pain and emotional dysregulation (42). A study by Gündel et al. (43) investigating the role of affect regulating brain structures such as prefrontal cortex in somatoform pain disorder found no difference in pain threshold or intensity ratings in response to experimentally induced thermal pain between patients and controls. They did, however, find increased parahippocampal, amygdala, and anterior insular responses in patients in response to thermal pain and decreased ventromedial prefrontal/orbitofrontal cortex activity indicative of dysfunctional pain processing in affect regulating regions. Activation of the brain’s “defense system” (including periaqueductal gray, amygdala, and parahippocampal gyrus (37,44)) in patients with somatoform pain disorder is observed in other idiopathic chronic pain syndromes including NSLBP (5), fibromyalgia syndrome (12,45), irritable bowel syndrome (46), headaches (47), and nondermatomal somatosensory deficits (i.e., conversion disorder (48)), suggesting that chronic pain cannot simply be discussed in terms of distinct diseases because much of the neural processing underlying it is common to superficially different conditions.

In addition to the amygdala, further unique activation in the WS-H group was seen in the cerebellum. Activation of the cerebellum in response to pain has been reported in previous studies investigating response to pressure pain in cLBP (5,49). Another recent study by Ung et al. (50) provided further structural evidence of the importance of the amygdala and cerebellum in cLBP. They used multivariate analyses to detect cLBP neuroanatomy based on gray-matter density changes from 47 patients and 47 healthy controls. The primary drivers for the differences between patients and controls included prefrontal cortices, but there were also differences in the temporal lobe, including the amygdala, and the cerebellum. Reviewing the evidence, Moulton et al. (51) have argued that the cerebellum is an important integrator of pain modulation, although the exact mechanisms are unknown. We speculate that its relationship to pain behavior might be mediated by the amygdala because this was also uniquely activated in our WS-H but not WS-L population.

It is worth underlining that the WS-L patients in the present study represent a select group who successfully cope with their pain, with little anxiety, depression, or catastrophizing, despite the fact that their spinal disorder did not differ by any feature from that in the WS-H group. The low levels of fear and anxiety in WS-L patients, despite reporting average pain scores similar to those in WS-H patients, presumably result from successful adjustment to the pain. The lack of activation to heat pain of the amygdala likely reflects this adjustment because in a previous study, we found that good adjustment to cLBP was associated with increased activity in regions associated with normal cognitive-affective processing of sensory input (tactile stimulation to the lower back) including posterior cingulate and parietal cortex, which also negatively correlated with catastrophizing scores (6). The ability of our WS-L group to effectively engage a sensory modulation system may protect against the subjective fear associated with daily activities related to altered affective and behavioral responses and the poor adjustment to pain seen in our WS-H cohort.

The representation of back pain is not a unitary construct and engages distinct brain circuitry as a function of the distress and suffering of back pain. In our study, patients with cLBP and severe levels of illness behavior recruited additional neural circuitry related to processing emotion in response to a painful stimulus more readily than patients without such behavior. This may indicate a brain signature underlying emotional distress and poor coping associated with cLBP. The effect of cognitive-behavioral treatment in improving coping skills and normalizing behavior of psychologically disabled patients with cLBP suggests that these abnormalities may be reversible (52). This theory has some support based on the results of a case study by Moseley (53) in which a patient with cLBP was given 2.5 hours of pain physiology education and underwent fMRI scans before and after the intervention. Despite the fact that the pain levels remained unchanged, the repeat fMRI scan showed a significant reduction in activation in frontal, parietal, and cingulate cortices without any apparent increase detected. Reversing abnormal activity levels in the amygdala might also lead to pain relief. Although the results of the current pilot study are promising, the sample size is modest, and future studies testing larger populations will be needed to investigate further the role of neurolimbic circuits and pain modulation in cLBP patients to clarify the relationship between emotional brain circuitry and pain behavior.
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D. M. LLOYD et al.

REFERENCES


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