American Pain Society
RESEARCH
EDUCATION
TREATMENT
ADVOCACY
PUBLISHED BY ELSEVIER

The Journal of Pain, Vol 17, No 5 (May), 2016: pp 577-587
Available online at www.jpain.org and www.sciencedirect.com

Brain Areas Involved in Anticipation of Clinically Relevant Pain in Low Back Pain Populations With High Levels of Pain Behavior

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Abstract: **The purpose of this study was to identify neural correlates of pain anticipation in people with nonspecific low back pain (NSLBP) that correlated with pain-related distress and disability, thus providing evidence for mechanisms underlying pain behavior in this population. Thirty NSLBP sufferers, with either high levels of pain behavior or low levels on the basis of Waddell signs, were scanned with functional magnetic resonance imaging while a straight-leg raise (of the side deemed to cause moderate pain in the lower back) was performed. On each trial colored 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 versus unexpected pain the group difference in activation between patients with high levels of pain behavior and low levels of pain behavior covaried as a function of anxiety scores in the 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 behavior associated with some chronic pain states.**
Perspective: ***This article shows a likely neural network for exacerbating pain anticipation in NSLBP contributing to high levels of pain behavior in some people. This information could potentially help clinicians and patients to understand how anticipation of pain may contribute to patient pain and disability.***

Key words: *Anxiety, catastrophizing, nonspecific low back pain, pain behavior, Waddell Signs.*

Fear of pain, driven by anticipation (and not actual sensory experience), is suggested to be a strong negative reinforcer for persistent avoidance behavior 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 shown in several studies by 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 did not. The underlying neural mechanisms of such behavior are, however, unknown. The purpose of this study was to determine which neural structures mediate the anticipation of pain in patients with nonspecific low back pain (NSLBP) and furthermore, whether there is a different level of brain activation, detectable with functional magnetic resonance imaging (fMRI), in 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 control subjects including anterior cingulate cortex (ACC; Brodmann area [BA] 32/24),

Received August 19, 2015; Revised November 19, 2015; Accepted January 11, 2016.
This study was funded by the Health and Safety Executive, United Kingdom, and the Pain Relief Foundation, United Kingdom.
The authors have no conflicts of interest to declare.
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1526-5900/$36.00

http://dx.doi.org/10.1016/j.jpain.2016.01.470

cerebellum, ventral premotor, and ventromedial prefrontal cortex (vmPFC), periaqueductal gray, and hippocampus.[7,24,46-48] 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 the vmPFC, midcingulate cortex, and hippocampus, and knowledge that noxious stimulation is certain to occur involves activation of the rostral cingulate cortex, anterior insula, and cerebellum.[40,46,47]

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 (WS)[68] and used a series of questionnaires designed to measure these factors (see Methods for details). The 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 behavior 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 behavior, assessed using WS, and scores on psychometric measures of pain-related distress and disability (compared with a control group of NSLBP patients without such traits) in response to a certain (ie, predictable, occurring in 100% of all trials) or an uncertain (ie, unpredictable, occurring in 50% of all trials) painful event. Rather than use an experimental pain stimulus we adapted the 'straight-leg raise' (SLR), the common clinical test used in the diagnosis of sciatica, to exploit the common feature seen in cLBP patients whereby this simple maneuver 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 behavior (measured according to WS) would show increased activity in response to a certain painful event (in the rostral cingulate cortex, anterior insula, and cerebellum) and uncertain pain (in vmPFC, midcingulate cortex, and hippocampus), which furthermore correlates with psychometric measures of pain-related distress and disability compared with a control group of NSLBP patients without such traits.

Methods

Participants

Thirty participants with NSLBP (16 male and 14 female), aged between 21 and 67 years (with a mean age of 45 years; SD = 12.4) were recruited. Because of excessive head movement, 1 participant was removed from the final analysis and data are presented for the remaining 29 participants (the participant was removed on the basis of the criterion for acceptable head motion set by Kornelsen et al,[29] who performed fMRI in 11 failed back surgery syndrome patients and 14 healthy control subjects). We can confirm that head motion in our study did not exceeded 2 mm in any data set and there was no difference in head motion between groups (patients with high numbers of WS [WS-H] = .062 mm vs patients with low numbers of WS [WS-L] = .068 mm; P = .527). However, 1 participant still had a mean absolute displacement of >2 SDs 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 and the University of Liverpool ethical review board and was conducted in accordance with the Declaration of Helsinki (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 surgeries for back pain (including facet denervation), magnetic resonance imaging showing no structural spinal abnormality other than degenerative change in no more than 3 lumbar discs, and SLR associated with back pain (not leg pain).

To differentiate participants with NSLBP on the basis of their pain-related behavior, each patient underwent a clinical examination by 2 specialists (spinal surgeon [G.F.], pain physician [T.N.]) independently, which included the assessment of WS. The aim was to identify WS-H participants versus WS-L participants. 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 nonanatomic deep tenderness not localized to 1 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; ie, 'give-away weakness' or when the patient does not give full effort on minor muscle testing or sensory loss in a stocking or glove distribution; ie, nondermatomal), and over-reaction (disproportionate facial or verbal expression; ie, pain behavior).

WS have been shown to have good construct validity[3] and are suggested to be a reliable basis for identifying patients with cLBP.[2] Unfortunately, a "validated" cutoff and data on the sensitivity/specificity of WS are lacking. However, Waddell et al[68] originally suggested that the presence of $\geq$3 signs represents a positive nonorganic test and this definition has been used in most previous studies.[20] In the present study, we chose to use a more conservative definition to secure 2 distinct NSLBP populations, namely the presence of $\geq$4 positive symptoms as the cutoff for the WS-H group and the presence of 1 or 0 positive signs as the cutoff for WS-L group. Thirteen participants (6 female) formed the WS-H group and the