

Differences in Low Back Pain Behavior Are Reflected in the Cerebral Response to Tactile Stimulation of the Lower Back

Donna Lloyd, DPhil (Oxon),*† Gordon Findlay, BSc, MBChB, FRCS,‡ Neil Roberts, PhD,* and Turo Nurmikko, MD, PhD†

Study Design. Two groups of patients with chronic low back pain (cLBP) were scanned with functional magnetic resonance imaging during stimulation of the lower back; those showing 4 or 5 positive Waddell signs (WS-H) and those showing 1 or none (WS-L) as an index of pain-related illness behavior.

Objective. We hypothesized that patients showing good *versus* poor adjustment to cLBP mobilize cortical affective-cognitive functions differently in response to sensory stimulation and show increased reorganization of somatosensory cortex corresponding to the back.

Summary of Background Data. Some patients with cLBP go on to develop significant disability while the majority do not, and physical disease or psychosocial factors alone do not account for the difference. Neuroimaging studies have suggested abnormalities in cortical pain modulation systems can lead to variable pain and behavioral responses, which may account for these differences.

Methods. Fifteen WS-L and 13 WS-H patients were scanned with functional magnetic resonance imaging while receiving intense tactile stimulation to the lower back. Questionnaire measures of psychosocial function were also collected.

Results. There were no significant differences in cLBP duration or lumbar stimulation tolerance threshold between the 2 groups. Significantly more activation was seen in the WS-L *versus* WS-H group in regions previously associated with normal affective-cognitive processing of sensory input including posterior cingulate and parietal cortices; the magnitude of this activation negatively correlated with catastrophizing scores. WS-H patients showed a modest medial shift in primary somatosensory cortex activation relative to the WS-L group.

Conclusion. Successful adjustment to cLBP is associated with a patient's ability to effectively engage a sensory modulation system. In patients in whom such activation does not occur, subjective lack of control may predispose to altered affective and behavioral responses with poor adjustment to pain. Pain experience

may be further modified by reorganization of somatosensory cortex, contributing to maintenance of the chronic pain state.

Key words: chronic low back pain, fMRI, illness behavior, sensory modulation. **Spine 2008;33:1372–1377**

There are significant variations in how patients cope with chronic low back pain (cLBP); some patients seemingly manage normal lives whereas others develop considerable disability. Similarly, behavior in relation to pain (often referred to as “pain behavior” or “illness behavior”) varies greatly across the cLBP population and excessive amounts of pain behavior may represent a major lack of adjustment by the patient to their pain. Most cases are idiopathic with structural or psychosocial determinants explaining only a small part of the variance of pain intensity or disability.¹ By contrast, brain imaging studies have revealed pathophysiological mechanisms present in patients with cLBP.^{2–6} While these studies do not address pain behavior as such, they highlight the potential of functional alterations in the brains of cLBP patients contributing to both the chronicity of pain and associated behavioral attributes. In a magnetoencephalography study, stimulation of the lower back revealed a medial displacement of peak activation in the somatosensory cortex of patients with pain of the longest duration.³ In another study, activation of the “emotional brain” in response to thermal stimulation of the lower back was seen.⁶ Other groups have shown loss of gray matter in the prefrontal and somatosensory cortex.^{7,8}

While all these studies provide convergent evidence of the presence of cerebral pathophysiology, none of them were designed to look for clinically important behavioral correlates in the cLBP population. It is widely acknowledged that patients show highly variable pain behavior in the clinic. The significance of such behavior was recognized over 2 decades ago by Waddell *et al*⁹ who developed an instrument to clinically assess this aspect in patients with cLBP. The aim of the present study was to seek an answer to the question of whether this behavior is linked to differences in the cerebral processing of sensory signals coming from the lower back.

In aberrant pain behavior, 3 main components can be identified: first, nonpainful sensory signals are experienced and reported as painful. Second, exaggerated behavior is manifested in response to painful stimuli compared with what is commonly seen in people subjected to

From the *Magnetic Resonance and Image Analysis Research Centre (MARIARC), University of Liverpool, Liverpool, UK; †Pain Research Institute, Clinical Sciences Centre, University Hospital Aintree, Liverpool, UK; and ‡Walton Centre for Neurology and Neurosurgery, Liverpool, UK.

Acknowledgment date: August 2, 2007. Revision date: October 15, 2007. Acceptance date: December 21, 2007.

The manuscript submitted does not contain information about medical device(s)/drug(s).

Foundation funds were received in support of this work. No benefits in any form have been or will be received from a commercial party related directly or indirectly to the subject of this manuscript. Funds were received for the Pain Relief Foundation, UK, in support of this work. Address correspondence and reprint requests to Turo Nurmikko, Pain Research Institute, Clinical Sciences Centre, University Hospital Aintree, Lower Lane, Liverpool, L9 7AL, UK; E-mail: tjn@liverpool.ac.uk

similar levels of pain. Third, there is an inability to tolerate activity, which may produce pain, leading to minimization of any activity judged as potentially inducing pain. In this study we explored 3 options in 2 groups of cLBP patients and healthy controls: that nonpainful sensory signals from the lower back are received or processed differently with excessive activation of the “pain matrix” in patients displaying major pain behavior, that the emotional circuitry of the brain is activated more in the same group, and that those not showing pain behavior and coping well despite their back pain show increased activation in regions that direct pain modulation. In addition, we explored the possibility that the groups differed in the extent to which their somatosensory cortex shows neuronal reorganization, as seen previously in low back pain.³

In this study, clinical judgment on pain behavior was made on the basis of Waddell signs (WS). Although WS do not imply a nonorganic *versus* organic pathology they form a yardstick to clinically assess behavioral features in a patient that can help therapeutic decision-making. These clinical signs have been validated and shown to be reproducible.¹⁰ Waddell and others originally proposed that WS could draw attention to the possibility of exaggerated illness behavior (defined as “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”¹¹). Subsequent studies have shown that high scores of WS are associated with poor physical performance, increased catastrophizing and poor treatment outcome.¹² Low scorers are no different from healthy subjects, indicating that they have developed techniques enabling them to cope in everyday situations without overt pain behavior.

■ Materials and Methods

Participants

Thirty cLBP patients [16 men; 14 women, aged between 21 and 67 years with a mean age of 45 years (SD = 12.2)] and 17 healthy controls [8 men; 9 women, aged between 25 and 53 years, mean age 31 years (SD = 8.1)] were recruited for the study. (Because of problems with the stimulation equipment, data were successfully acquired for 28 patients). Patients with a history of major neurological or psychiatric disease, head trauma, current drug or alcohol abuse or evidence of cognitive decline were excluded. The study had ethics committee approval and all participants gave informed written consent. Patients were examined independently by a spinal surgeon (G.F.) and a pain specialist (T.N.) for Waddell signs. Those with a low positive score (0–1 out of the 5 categories), were considered to show no pain behavior (WS-L), while patients with a high score (4–5 out of 5), were considered to represent a group with major pain behavior (WS-H). No patient with an intermediate score (*i.e.*, 2–3/5) was entered into the study. Inclusion criteria were: pain over 6 months; mechanical axial back pain without sciatica (referred pain to posterior thigh allowed if less intense than lower back pain); no previous operations for back pain (including facet denervation); magnetic resonance imaging (MRI) showing no structural spinal abnormality other than degener-

ative change in no more than three lumbar discs and straight leg raise associated with back pain (not leg pain). Patients were allowed to continue on stable medication, including opioids with an arbitrarily set highest accepted dose of 60mg of morphine per day (or an equivalent dose of an alternative opioid). Paracetamol (acetaminophen) was allowed within recommended doses (up to 4000 mg/day) as were low doses of antidepressants and antiepileptic drugs (*e.g.*, amitriptyline 35 mg/day, gabapentin 1200 mg/day).

Methods

To deliver intense tactile stimulation to the participants' lower back a custom-made contact plate was designed that was safe to use in the MR environment and did not result in degradation of the quality of the MR image. This was controlled by a Thandor TG503 5 MHz Pulse/Function Generator with a Digi-timer Constant Current Stimulator (model D57A) to deliver the same frequency of stimulation (0.25 Hz) at a tolerance threshold determined for each subject. All patients had normal cutaneous sensation in the lower back as determined by the examining specialists.

Immediately before functional MRI (fMRI) scanning participants were tested for their individual lumbar stimulation tolerance threshold (LSTT). While inside the scanner room the contact plate was placed on the participant's lower back after which they lay horizontally on the scanner bed securing the plate in place. The intensity of stimulation (measured in mA) was increased manually by the experimenter starting at 0 mA (reaching a maximum of 14.5 mA). The stimulus was perceived to be an intense and unpleasant but nonpainful slow wave vibration.* Intensity was rated numerically by participants from 0 (no stimulation) until it reached a level of 7 of 10 (the point at which the participant did not wish the intensity of the stimulus to increase any further). This procedure was repeated and the final value was then taken as the participant's LSTT for the fMRI scan.

Participants were also asked to complete several questionnaires. This included the visual analogue scale (VAS¹³), scoring how much low back pain they were currently experiencing (VAS_{now}) or the average pain experienced in the last 5 days (VAS_{5Day}); the Pain Coping Strategies Questionnaire¹⁴; the activities subscale of the Fear Avoidance Beliefs Questionnaire¹⁵ and the Hospital Anxiety and Depression Scale.¹⁶ Healthy controls were only required to complete the VAS and Hospital Anxiety and Depression Scale to confirm they did not have significant levels of pain, anxiety or depression. As predicted, scores on these measures were normal for the population and are not considered further.

During the fMRI scan stimulation was alternated with periods of rest (no stimulation) in an ABAB blocked design where A = rest (duration 15 seconds) and B = stimulation (duration 15 seconds). The total scan time was 5 minutes 15 seconds. Participants were instructed to focus on the sensation occurring on the lower back throughout the scan.

Whole brain fMRI was carried out on a 1.5T General Electric Signa LX/Nvi scanner using the blood oxygenation level-dependent contrast technique. Data were analyzed within the

*We purposefully chose an intense, inherently unpleasant stimulus deemed sufficient to activate the common nociception processing circuitry at subliminal levels (revealing excessive pain-related activation in either group) and invoke attentional and cognitive circuitries responsible for modulation of painful and non-painful sensation without causing undue discomfort and subsequent movement.

general linear model as implemented in FEAT5 software, part of the FMRIB Software Library.¹⁷ Preprocessing steps included motion correction, spatial smoothing, mean-based intensity normalization, and nonlinear high-pass temporal filtering. Contrast images for each subject were computed and transformed into MNI standard space.¹⁸ Group-wise independent *t* tests were performed to determine the difference in activation to stimulation of the lower back between patient groups and between patients and healthy controls in a mixed effects model. Z statistical images were thresholded at $Z > 2.3$ and cluster corrected for multiple comparisons at $P = 0.05$ (details of data acquisition and analysis are available online through Article Plus).

■ Results

General

Fifteen patients met the criteria for WS-L and 13 for WS-H. The mean difference in age (1 SD) between patient groups was nonsignificant (WS-H mean = 44 (11.7) years; WS-L mean = 46 (13.3) years; $P = 0.586$) as was the difference in mean chronicity of low back pain (WS-H mean = 112 (86.7) months; WS-L mean = 123 (115) months; $P = 0.801$). However, the difference in age between both patient groups and healthy controls was significant (control mean = 31 (2.0) years; $P < 0.01$). Ongoing stable medication did not differ substantially between groups with most patients taking NSAIDs (9 WS-H, and 4 WS-L patients) and paracetamol (7 WS-H and 5 WS-L patients). Eight patients in each group were on low doses of opioids; 1 patient in the WS-H group was on stable modified release morphine sulfate at 60 mg/day. None reported taking medication in excess of recommended doses.

Questionnaire Data

WS-H patients rated their own pain levels as significantly greater than WS-L patients on the VAS_{now} (WS-H Mean = 6.0 (1.6); WS-L Mean = 3.7 (1.9); $P = 0.004$) but not on the 5-day average (WS-H Mean = 5.4 (2.9); WS-L Mean = 5.1 (2.2); $P = 0.77$). They also scored significantly higher on the catastrophizing subscale of the CSQ (WS-H Mean = 19.2 (7.6); WS-L Mean = 9.3 (7.0); $P = 0.006$) but not on any other measure (all P 's $> .05$). WS-H patients rated their depression levels significantly higher than WS-L patients (WS-H Mean = 10.3 (3.2); WS-L Mean = 7.0 (4.0); $P = 0.038$) but not their anxiety levels (WS-H Mean = 11.0 (3.7); WS-L Mean = 9.5 (4.2); $P = 0.380$) and showed only a nonsignificant trend towards an increased score on the Fear Avoidance Beliefs Questionnaire activities subscale (WS-H Mean = 19.6 (8.2); WS-L Mean = 14.0 (6.4); $P = 0.078$).

Lumbar Stimulation Tolerance Threshold

Independent *t* tests revealed no significant difference in mean LSTT between the 3 groups (WS-H = 7.3 (2.2) mA; WS-L = 8.4 (3.5) mA; Controls = 8.6 (3.4) mA; all comparisons $P > 0.05$). *Post hoc* comparisons found no evidence of a significant difference in mean LSTT between males and females in our cohort of healthy controls (Males = 9.5 (3.4) mA; Females = 7.9 (3.3) mA;

$P = 0.346$) or in the WS-H patient group (WS-H males = 7.1 (2.4) mA; WS-H females = 7.5 (2.2) mA; $P = 0.754$) with a just significant difference in the WS-L group (WS-L males = 9.8 (3.4) mA; WS-L females = 6.3 (1.5) mA; $P = 0.041$).

Within Group fMRI Data

Inclusive masking revealed activation common to all 3 groups in right anterior insula and right ventrolateral prefrontal cortex only. This was due to the fact that the WS-H group showed entirely right-lateralized activity in and around anterior insula and ventrolateral prefrontal cortex (BA44/45) to tactile stimulation of the lower back with no significant response in SI, SII or subcortical sites evident at this threshold (Table 1).

In response to the same stimulus healthy controls showed additional activation of right SII (BA42) extending into parietal operculum and inferior parietal lobe (BA40) and SI (BA2) and in sites across insula cortex extending into sylvian fissure and anterior temporal pole (Table 1). Subcortical activation was seen in brain stem including periaqueductal gray. In the WS-L group, in addition to activity in right ventrolateral prefrontal and insula cortices, bilateral activation was also seen in SI and SII and inferior parietal lobe (BA40; including supra-marginal gyrus and ventral bank of sylvian fissure) and superior and medial frontal gyrus (BA8/9) extending into rostral anterior cingulate cortex (BA32). No subcortical activation was seen (Table 1).

Between-Group fMRI Data

Compared with healthy controls, the WS-L group demonstrated significantly more activation in left superior parietal lobe (BA7; $x, y, z = -30, -72, 42$ mm; $Z = 3.45$) and left extrastriate visual cortex (BA18/19; $x, y, z = -40, -80, -16$ mm; $Z = 3.08$) including fusiform gyrus (BA37/18; $x, y, z = -40, -60, -10$ mm; $Z = 3.45$). There were no areas of increased activation in healthy controls *versus* WS-L patients and no significant differences in activation between healthy controls and the WS-H patients.

Compared with the WS-H patients the WS-L group also showed significantly more activation in midline retrosplenial cingulate cortex (BA23/31; peak of activation at $x, y, z = 4, -54, 18$ mm; $Z = 3.23$) extending on the right into striate (BA17; peak of activation at $x, y, z = 22, -66, 10$ mm; $Z = 3.54$) and extrastriate cortex (BA18; peak of activation at $x, y, z = 14, -76, 24$ mm; $Z = 3.14$; Figure 1). Left-lateralized activity was seen across inferior parietal cortex (BA40; $x, y, z = -46, -50, 42$ mm; $Z = 3.36$) extending into superior parietal lobe (BA7; $x, y, z = -38, -66, 38$ mm; $Z = 3.08$). A significant negative correlation between the magnitude of the blood oxygenation level-dependent response in these areas and scores on the catastrophizing subscale of the CSQ was identified ($r = -0.431$, $P = 0.023$). No other psychometric measures were related and there were no areas of increased activity in the WS-H patient group.

Table 1. Regions of Significant Activity in Response to Intense Stimulation of the Lower Back in Healthy Controls, WS-L and WS-H Chronic Low Back Pain Patients

Region	MNI Co-ordinates (x,y,z mm)			Max Z Score	R/L
Healthy controls					
Inferior parietal lobe (BA40)	62	-32	38	4.09	R
Mid-insula	34	6	4	3.97	R
Sylvian fissure	44	10	-6	3.67	R
Superior temporal gyrus	54	2	2	3.66	R
Secondary somatosensory cortex (SII; BA42)	62	-20	18	3.58	R
Posterior insula	40	-16	-10	3.57	R
Primary somatosensory cortex (SI; BA2)	62	-18	24	3.44	R
Brainstem	12	-20	-24	2.87	R
Periaqueductal grey	4	-34	-30	2.47	R
WS-L					
Ventrolateral prefrontal cortex (BA44/45)	52	8	10	4.08	R
Inferior parietal lobe (BA40)	60	-30	36	3.66	R
	-42	-48	40	3.50	L
Dorsolateral prefrontal cortex (BA9/46)	48	30	26	3.60	R
Superior temporal gyrus	46	-34	16	3.43	R
Intraparietal sulcus (BA40/7)	-40	-42	38	3.41	L
Supramarginal gyrus (BA40)	-50	-58	42	3.41	L
Mid-insula	34	6	-2	3.39	R
Putamen	-24	-2	4	3.36	L
Sup-med frontal gyrus (BA8/9)	-6	38	42	3.28	L
	4	28	50	3.13	R
Secondary somatosensory cortex (SII; BA42)	±62	-20	18	3.24 (2.46)	BI
Posterior insula	40	-2	-2	3.16	R
Anterior cingulate gyrus (BA32)	-12	24	34	3.13	L
Anterior insula	30	22	-2	3.01	R
Primary somatosensory cortex (SI; BA2)	±62	-18	24	2.46	BI
WS-H					
Ventrolateral prefrontal cortex (BA44/45)	50	10	6	3.66	R
Anterior insula	46	12	2	3.50	R
Superior temporal gyrus	58	4	4	3.38	R

Regions showing significant activation in response to intense tactile stimulation of the lower back (vs. rest) in healthy controls, WS-L and WS-H chronic low back pain patients. Activations are determined by clusters greater than $Z > 2.3$, $P = 0.05$. MNI co-ordinate and peak Z score of the maximum activating voxel in each cluster are shown with the laterality of response.

R indicates right; L, left; BI, bilateral; Med., medial; Sup., superior; Mid., middle.

Evidence for Reorganization of Primary Somatosensory Cortex in cLBP

By reducing the group cluster-based threshold level to $P < 0.05$ (uncorrected) activation of SI was seen across

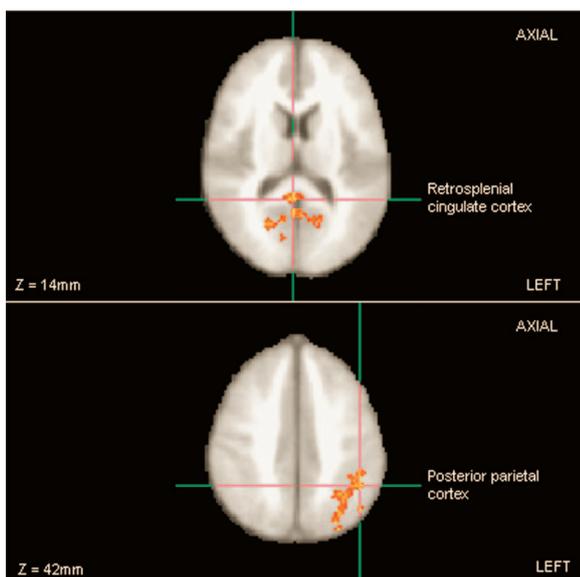


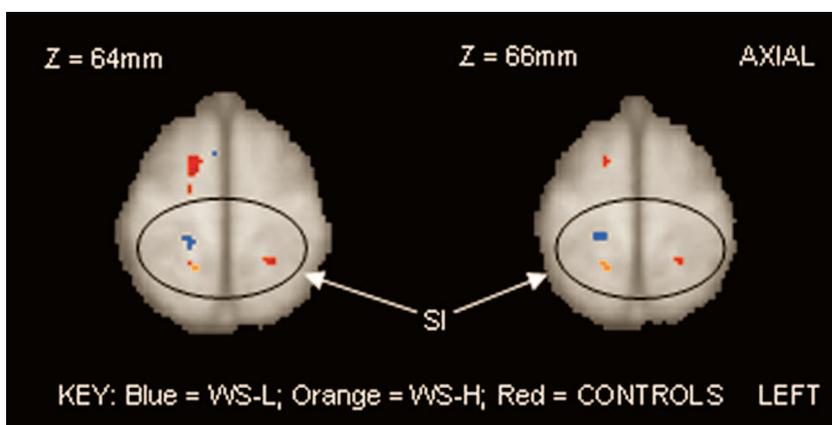
Figure 1. Regions showing significantly more activation in response to intense tactile stimulation of the lower back (vs. rest) in WS-L versus WS-H chronic patients with low back pain. Maps were cluster-based thresholded at $Z > 2.3$, $P = 0.05$ (corrected for multiple comparisons) and are shown axially and in radiologic convention.

all 3 groups corresponding to the expected somatotopic representation of the lower back (see Ref. ³). Figure 2 illustrates the position of this activation across 2 2-mm axial slices (starting at $z = 62$ mm). Healthy controls show bilateral activation of SI with a peak in the left hemisphere at $x,y,z = -20, 43, 64$ mm and in the right hemisphere at $x,y,z = 18, 44, 64$ mm. The WS-H group had a discrete cluster of activity occurring entirely in the right hemisphere (7 voxels), with a peak at $x,y,z = 15, 46, 65$ mm indicating a medial shift in the x direction of 3 mm and a posterior shift in the y direction of 2 mm. The WS-L patient group showed a much larger cluster of activity in the right hemisphere (23 voxels), with a peak at $x,y,z = 19, 35, 63$ mm. Compared to the WS-L group, the WS-H group had a significant medial shift in the x-direction of 4 mm ($P = 0.001$), a posterior shift in the y-direction of 9 mm ($P < 0.001$) and a dorsal shift in the z-direction of 2 mm ($P = 0.006$).

Discussion

Group comparisons revealed no major difference between WS-H and WS-L groups in common pain-activated cortical regions suggesting that pain behavior cannot be linked to excessive or reduced engagement of the pain matrix in either patient group. Similarly, we did not find preferential activation of the affective brain in

Figure 2. Activation of primary somatosensory cortex (SI) in all 3 groups corresponding to the somatotopic representation of the back across 2 2-mm axial slices (starting at $z = 64$ mm). Maps were cluster-based thresholded at $P < 0.05$ (uncorrected) and are shown in radiologic convention.



WS-H patients. Our results are different from those of Baliki *et al*,⁶ who showed increased activation in the medial prefrontal cortex and anterior cingulate cortex in a low back pain cohort compared with healthy volunteers. Methodologic factors, including the use in our study of a nonpainful stimulus, may account for this difference.

However, our finding of increased activation in right posterior (retrosplenial) cingulate and extrastriate cortex and left posterior parietal lobe in the WS-L *versus* WS-H patients (Figure 2) suggests a fundamental difference between the 2 groups in their ability to process afferent sensory input from the lower back. These areas have previously been implicated in the top-down modulation of pain^{19,20} and may provide a mechanism of successful adjustment in those who cope well with the pain.

The posterior cingulate cortex is commonly activated during painful as well as emotional stimuli and, with the posterior parietal cortex, is likely involved in orienting towards innocuous and noxious somatosensory stimuli.^{19,20} Inputs from the dorsolateral prefrontal cortex (DLPFC) to posterior cingulate cortex may provide one mechanism by which WS-L patients effectively distract themselves from the signals arising from the lower back²¹ as only the WS-L patient group showed increased suprathreshold activation of right DLPFC, an area believed to represent a reciprocal system for active inhibition of salient sensory information through “top-down” cognitive control *via* ACC.²² The lack of DLPFC and ACC activation in the WS-H patients would therefore represent the inability to fully engage these cortical regions when needed and effectively control signals from the lower back leading to a more pronounced display of behavioral signs. The negative correlation with scores on the catastrophizing subscale of the CSQ in the WS-L group supports the view that successful activation of these regions may be associated with good coping and prevention of pain behavior.

The modest shift in the locus of primary somatosensory cortex activation seen in the WS-H patient group was expected and has been described before in both cLBP³ and complex regional pain syndrome,²³ suggesting cortical reorganization as a response by particular populations of

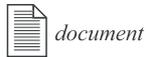
chronic patients to long-term nociceptive input. Unexpectedly, only healthy controls and WS-L patients activated SI bilaterally even though stimulation was bilateral and proximal structures (such as the trunk) have predominantly bilateral receptive fields.²⁴ It is possible that cortical dysfunction or even local atrophy has occurred in the WS-H patient group and this interpretation gains support from a recent study showing reduction in gray matter mass in somatosensory cortex in cLBP patients, which negatively correlated with the unpleasantness dimension of ongoing pain.⁷

The patient’s behavior in the clinic during testing for WS is the sum of 2 functions; quality and intensity of somatosensory signals arising from the lower back, and their cognitive-affective appraisal. In this study, we show increased processing in nonsensory specific cortex in WS-L compared with WS-H patients suggesting successful orientation to and top-down control of somatic information on the body. In clinical terms, the WS-L patients represent a well-adjusted group confirmed by normal responses to Waddell tests and low levels of depression and catastrophizing with a capacity for effective endogenous pain modulation. This, rather than excessive engagement of regions that encode intensity and unpleasantness of pain predominantly separated the 2 groups. It should be pointed out that the design of the present study allows us to discuss cerebral responses to sensory stimulation only and not to tasks designed to elicit emotional reactions. The latter may be an equally fruitful avenue to explore in future studies. Nevertheless, if the present results can be corroborated, the next obvious question is whether a cognitive, behavioral, or pharmacological manipulation can be developed to specifically target the brain structures identified in our patients.

■ Key Points

- Patients with chronic low back pain show variable degrees of pain behavior.
- Patients coping well with none or 1 WS activate cortical regions critical for top-down modulation of painful and nonpainful sensation in response to low back stimulation.

- Patients with high WS scores and elevated levels of catastrophizing lack this response but show more reorganization in primary somatosensory cortex.



document

Appendix available online through Article Plus.

Acknowledgments

The authors thank Niamh Redmond, Sioban Kelly, Heather Cameron, and Kate MacIver for technical assistance and the staff and radiographers at the Walton Centre for Neurology and Neurosurgery, Liverpool, UK.

References

- Peters ML, Vlaeyen JW, Weber WE. The joint contribution of physical pathology, pain-related fear and catastrophizing to chronic back pain disability. *Pain* 2005;113:45–50.
- Derbyshire SW, Jones AK, Creed F, et al. Cerebral responses to noxious thermal stimulation in chronic low back pain patients and normal controls. *Neuroimage* 2002;16:158–68.
- Flor H, Braun C, Elbert T, et al. Extensive reorganization of primary somatosensory cortex in chronic back pain patients. *Neurosci Lett* 1997;224:5–8.
- Giesecke T, Gracely RH, Grant MA, et al. Evidence of augmented central pain processing in idiopathic chronic low back pain. *Arthritis Rheum* 2004;50:613–23.
- Gracely RH, Geisser ME, Giesecke T, et al. Pain catastrophizing and neural responses to pain among persons with fibromyalgia. *Brain* 2004;127:835–43.
- Baliki MN, Chialvo DR, Geha PY, et al. Chronic pain and the emotional brain: specific brain activity associated with spontaneous fluctuations of intensity of chronic back pain. *J Neurosci* 2006;26:12165–73.
- Schmidt-Wilcke T, Leinisch E, Ganssbauer S, et al. Affective components and intensity of pain correlate with structural differences in gray matter in chronic back pain patients. *Pain* 2006;125:89–97.
- Apkarian AV, Sosa Y, Sonty S, et al. Chronic back pain is associated with decreased prefrontal and thalamic gray matter density. *J Neurosci* 2004;24:10410–5.
- Waddell G, McCulloch JA, Kummel E, et al. Nonorganic physical signs in low-back pain. *Spine* 1980;5:117–25.
- Waddell G, Main CJ, Morris EW, et al. Normality and reliability in the clinical assessment of backache. *Br Med J (Clin Res Ed)* 1982;284:1519–23.
- Waddell G. Clinical assessment of lumbar impairment. *Clin Orthop* 1987;110–20.
- Fishbain DA, Cole B, Cutler RB, et al. A structured evidence-based review on the meaning of nonorganic physical signs: Waddell signs. *Pain Med* 2003;4:141–81.
- Price DD, McGrath PA, Rafii A, et al. The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. *Pain* 1983;17:45–56.
- Rosenstiel AK, Keefe FJ. The use of coping strategies in chronic low back pain patients: relationship to patient characteristics and current adjustment. *Pain* 1983;17:33–44.
- Waddell G, Newton M, Henderson I, et al. A Fear-Avoidance Beliefs Questionnaire (FABQ) and the role of fear-avoidance beliefs in chronic low back pain and disability. *Pain* 1993;52:157–68.
- Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;67:361–70.
- Smith SM, Jenkinson M, Woolrich MW, et al. Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage* 2004;23(suppl 1):S208–S219.
- Jenkinson M, Smith S. A global optimisation method for robust affine registration of brain images. *Med Image Anal* 2001;5:143–56.
- Maddock RJ. The retrosplenial cortex and emotion: new insights from functional neuroimaging of the human brain. *Trends Neurosci* 1999;22:310–6.
- Peyron R, Garcia-Larrea L, Gregoire MC, et al. Parietal and cingulate processes in central pain. A combined positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) study of an unusual case. *Pain* 2000;84:77–87.
- Valet M, Sprenger T, Boecker H, et al. Distraction modulates connectivity of the cingulo-frontal cortex and the midbrain during pain—an fMRI analysis. *Pain* 2004;109:399–408.
- Lorenz J, Minoshima S, Casey KL. Keeping pain out of mind: the role of the dorsolateral prefrontal cortex in pain modulation. *Brain* 2003;126:1079–91.
- Maihofner C, Handwerker HO, Neundorfer B, et al. Patterns of cortical reorganization in complex regional pain syndrome. *Neurology* 2003;61:1707–15.
- Robinson CJ, Burton H. Somatic submodality distribution within the second somatosensory (SII), 7b, retroinsular, postauditory, and granular insular cortical areas of M. fascicularis. *J Comp Neurol* 1980;192:93–108.