Mechanisms of central neuropathic pain: a combined psychophysical and fMRI study in syringomyelia

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The pathophysiology of central pain syndromes is still poorly understood and their treatment remains a major challenge. It has long been suggested that lesions of the spinothalamic pathways are necessary for developing these pain syndromes. The recently proposed thermosensory disinhibition theory suggests that reduction of the inhibition of thermal sensory afferents that affect nociceptive systems may play a major pathophysiological role. Syringomyelia, which is frequently associated with central neuropathic pain, is characterized by a selective or preferential lesion of the spinothalamic tract resulting in thermosensory deficits of various extents and magnitudes. Thus, syringomyelia represents a unique ‘pathological model’ particularly suited to investigating the relationship between spinothalamic tract dysfunction, thermosensory deficits and pain. Here, we systematically compared the sensory loss (thermal and mechanical), using quantitative sensory testing, between 46 consecutive syringomyelia patients with or without neuropathic pain. We then further investigated the mechanisms of evoked pains in these patients, using functional MRI (fMRI) in a subgroup of patients with cold or brush-evoked alldynia, compared with patients without pain and healthy volunteers. We found no significant difference in the magnitude or extent of sensory deficits between patients with or without neuropathic pain, suggesting that lesions of the spinothalamic pathways are not sufficient for developing central pain. However, a different pattern of sensory deficits was observed between patients with spontaneous pain only (n = 11) and patients with both spontaneous pain and alldynia (n = 20), suggesting that the mechanisms of central pain are not univocal. In patients with spontaneous pain only, the thermal sensory loss was significantly more asymmetrical and there was a direct relationship between the extent of thermosensory deficits (i.e. deafferentation) and the intensity of burning pain. In contrast, patients with alldynia had reduced thermal deficits, in terms of both magnitude and extent. In addition, the sensory deficits were different between patients with cold or tactile alldynia, suggesting distinct pathophysiological mechanisms related to the sub-modalities of alldynia. Our fMRI study further confirmed this, showing that different sub-types of alldynia were associated with distinct patterns of brain activity, which do not necessarily correspond to the ‘pain matrix’ involved in acute physiological pain. The prefrontal cortex was the only area consistently activated by pathological evoked pains, suggesting that alteration of high-level pain modulatory mechanisms might play a major role in alldynia due to central lesion.

Keywords: alldynia; hyperalgesia; central pain; neuropathic pain; pathophysiology

Abbreviations: ACC = anterior cingulate cortex; BA = Brodmann area; fMRI = functional MRI; NPSI = Neuropathic Pain Symptom Inventory; PFC = prefrontal cortex; S1 = primary somatosensory cortex; S2 = secondary somatosensory cortex; VAS = visual analogue scale

Introduction

The control of central neuropathic pain remains a major therapeutic challenge, and the exact mechanisms of pain are largely unknown. Since the early 20th century description of the ‘thalamic syndrome’ (Head and Holmes, 1911; Garcin, 1937; Riddoch, 1938), two broad concepts of the pathophysiology of central pain have emerged: central disinhibition and/or central sensitization. Both these lead to neuronal hyperactivity/hyperexcitability of spinal/supraspinal nociceptive neurons (Pagni, 1989; Casey, 1991; Schott, 1996; Boivie 1999; Craig, 2000; Finnerup and Jensen, 2004; Attal and Bouhassira, 2004). Patients suffering from central neuropathic pain almost always have thermal sensory deficits within the painful area, consistent with the disinhibition theory of central pain (e.g. Boivie et al., 1989; Vestergaard et al., 1995; Bowsher, 1996; Bowsher et al., 1998). Thus, it has been suggested that lesions of the spinothalamo-cortical pathway may be necessary for developing such pain. However, it is not clear whether lesions of the spinothalamic pathways are sufficient, as few studies have directly compared patients presenting similar central lesions associated with or without neuropathic pain (Bouhassira et al., 2000; Defrin et al., 2001; Finnerup et al., 2003). Recently, Craig et al. (Craig et al., 1996, Craig, 1998, 2000, 2003) proposed a variation to the disinhibition theory. According to their thermosensory disinhibition theory, central pain is more specifically a result of disruption of the normal inhibition of the pathways mediating thermal sensation in nociceptive systems. In essence, this theory posits that central pain is an interoceptive thermoregulatory dysfunction due to alteration of the brain integration of pain and temperature (Craig, 1998, 2000, 2003).

Various painful symptoms (i.e. headache, musculoskeletal, visceral pains) have been observed in up to 90% of patients with syringomyelia. However, the most disabling are neuropathic pains, which are present in up to 40% of these patients (Milhorat et al., 1996; Boivie, 1999). Like other central pain syndromes due to spinal or brain injuries, these neuropathic pains are among the most difficult to treat (Finnerup and Jensen, 2004; Attal and Bouhassira, 2004). Syringomyelia is a lesion of the spinal cord characterized by an intra-spinal cavity that predominantly, or even selectively, affects the spinothalamic tract. Consequently, a major clinical finding in these patients is a predominant deficit of heat and/or cold sensations. Thus, syringomyelia is a unique ‘pathological model’ that appears particularly suited to investigating the relationship between spinothalamic tract dysfunction, thermosensory deficits and central pain.

In this present study of patients with syringomyelia, we compared the magnitude and extent of thermal sensory deficits in patients with or without pain, using quantitative sensory testing. We also analysed in these patients potential relationships between the topography, quality or intensity of the different painful symptoms (i.e. spontaneous ongoing pain, paroxysmal pain, allodynia, hyperalgesia) and the topography and/or magnitude of the sensory deficits. On the basis of the results of our psychophysical study showing differential pattern of sensory deficits between patients with or without allodynia, we performed a complementary study with functional MRI (fMRI). This study was performed in a selected subgroup of patients with cold or tactile allodynia (i.e. pain evoked by brushing or normally non-painful cold stimuli), which are the most frequently observed evoked pains in these patients. In particular, we aimed to determine whether different forms of allodynia associated with different sensory deficits involved distinct brain mechanisms and whether such pathological pain shares a common cerebral network with physiological pain (Bushnell et al., 1999; Casey, 1999; Treede et al., 1999; Davis, 2000; Peyron et al., 2000; Porro, 2003).

Material and methods

We included consecutive patients from the pain clinic (Ambroise Paré University Hospital) or department of neurosurgery (Kremlin-Bicêtre University Hospital) with a clinical history and symptomatology of syringomyelia, confirmed by spinal MRI. Exclusion criteria were major depression according to DSM-IV criteria, history of major psychiatric disease, head trauma, dementia or epilepsy. All the patients had a complete clinical sensory examination and pain assessment, including a psychophysical evaluation (i.e. quantitative sensory testing). We then recruited a subgroup of patients with cold and/or tactile allodynia, a subgroup of patients without pain and six healthy volunteers for a complementary fMRI study, carried out within a maximum of 3 days after the sensory examination. The study was approved by the Local Ethical Committee and all the patients and volunteers gave informed written consent.

Sensory evaluation

Clinical sensory examination

The mechanical sensitivity examination included assessment of gross tactile deficits (using a cotton swab), proprioceptive deficits (joint position, stereognosis), pinprick hypoalgesia by means of a pinwheel, graphesthesia and identification of movement direction using a cotton swab moved slowly in a proximal-distal direction.

Thermal sensitivity was first examined using two thermo-rollers (Somedic, Sweden) at constant temperatures of 40°C (warm) and 25°C (cold). This allowed us to estimate the extent of the thermal deficits. We defined a metamer score, which was the sum of affected right and left dermatomes (for example, a T5T6 left and T5 right warm deficit was given the score 3). In order to evaluate the laterality of the sensory loss, we also defined an index of asymmetry of the thermal deficit, which was the difference between the metameric extension (i.e. number of dermatomes) of warm or cold deficits on the side with the maximal thermal impairment versus the contralateral side (for example, a T5T6 left and T5 right warm deficit was given the score 1, and a score 0 was given when the extent of the deficits was strictly symmetrical). We then evaluated the detection thresholds to warm and cold stimuli using a thermodiagnostic.
Quantitative sensory testing

Mechanical and thermal sensitivities were further evaluated using quantitative sensory tests (QSTs) carried out in a quiet room at a constant temperature (22°C) by the same experienced investigator. Measurements were taken in the area of maximal thermal deficit (i.e. the hand in 28 patients, the shoulder in 10 patients and the thoracic dermatomes in 8 patients) and in a normal area (i.e. the cervical C2/C3 dermatomes in 40 patients and the foot in 6 patients). For patients with pain, additional measurements were taken in the area of maximal pain and in an adjacent lesioned, but non-painful area. In patients with cold or heat allodynia, measurements of thermal detection thresholds were also taken in the lesioned but non-painful area adjacent to the site of allodynia, because the presence of severe thermal allodynia can mask a thermal deficit.

We assessed the detection and pain thresholds for mechanical static (punctate) stimuli using calibrated von Frey hairs (0.057–140 g). Care was taken to avoid stroking the skin with the hair and to apply only pressure. The patients were told to close their eyes during the procedure. The von Frey filaments were applied (at least twice) in ascending and descending order of stiffness. We defined the detection threshold as the lowest pressure perceived (at least twice) in ascending and descending order of stiffness. We defined the pain threshold as the lowest pressure that was considered painful by the patient. The force required to bend the filaments was converted to a threshold as the lowest pressure that was considered painful by the patient. We assessed the detection and pain thresholds for mechanical static (punctate) stimuli using calibrated von Frey hairs (0.057–140 g). Care was taken to avoid stroking the skin with the hair and to apply only pressure. The patients were told to close their eyes during the procedure. The von Frey filaments were applied (at least twice) in ascending and descending order of stiffness. We defined the detection threshold as the lowest pressure perceived by the subject within 3 s of the stimulus. We defined the pain threshold as the lowest pressure that was considered painful by the patient. The force required to bend the filaments was converted into log units.

We assessed thermal sensations using a Somedic thermostest (Somedic AB, Stockholm, Sweden). A contact thermode of Peltier elements measuring 25 × 50 mm was applied to the skin. The baseline temperature of the thermode was adjusted to the patient’s skin temperature. Thresholds were measured according to the method of limits: stimuli of increasing or decreasing intensities were applied, and for each stimulus the patient pressed a button that reversed the thermal stimulation as soon as they detected a sensation of cold or warmth (indicating the detection thresholds) or as soon as the stimulation became painful (indicating the pain thresholds). Inter-stimulus intervals were 6–8 s for detection thresholds, 15–20 s for heat pain thresholds and 20–30 s for cold pain thresholds. The maximum and minimum temperatures were set at 50°C for heat and 4°C for cold. The thermal rate of change was 1°C/s for detection thresholds and 2°C/s for pain thresholds. Thresholds were calculated as the average of five successive detection tests and three successive pain tests, and were expressed as absolute thresholds (°C).

We then induced pain by suprathreshold mechanical, hot and cold stimuli applied in a pseudo-random order, which were rated on a visual analogue scale (VAS) according to a method used in previous studies (Attal et al., 2000, 2004). We used selected von Frey hairs (between 6.2 and 140 g) for mechanical stimuli. The duration of thermal stimuli was 2 s with increasing steps of 4°C for hot stimuli (between 40 and 48°C) and 5°C for cold stimuli (between 5 and 20°C) and a thermal rate of change of 2°C/s. The patients were told that they could stop the sequence of stimuli at any time. If a VAS score of 80 or more was reported with one of the intensities, no higher stimuli were applied.

Assessment of neuropathic pain symptoms

In this study, central neuropathic pain, defined as pain associated with a lesion or dysfunction of the CNS, was considered to be present if pain was located in an area of sensory deficit directly related to the injury of the spinal cord, could not be attributed to any other condition and had specific characteristic descriptors (Bouhassira et al., 2005a). Patients with pain reported spontaneous ongoing pain, i.e. pain at rest and in the absence of any stimulation, which was frequently associated with pain paroxysms (electric shocks, stabbing). In some patients, spontaneous pain was associated with pain evoked by normally non-painful mechanical or thermal stimuli (i.e. allodynia). Patients with neuropathic pain filled out the Neuropathic Pain Symptom Inventory (NPSI) (Bouhassira et al., 2004) to assess the magnitude of the different neuropathic symptoms (i.e. ongoing pain, paroxysmal pain, evoked pain, paraesthesia/dysesthesia).

We investigated tactile allodynia (dynamic) using a paintbrush (three movements). We considered tactile alldynia to be present if stroking the skin evoked a clear sensation of pain. The intensity of allodynia was marked on a VAS (as the mean of two consecutive VAS scores at least 30 s apart).

We considered allodynia or hyperalgesia to static (punctate) mechanical, hot or cold stimuli to be present if pain could be evoked with a stimulus intensity that did not produce pain in the control area. Such clinically detectable allodynia corresponded to a decrease in pain thresholds of at least 1 SD from the mean pain thresholds measured in the control area. In patients with alldynia located in the hand (i.e. n = 12), we verified also that the pain thresholds were reduced by at least 1 SD from the mean pain thresholds measured in a group of healthy volunteers who participated in a previous psychophysical study (Bouhassira et al., 1999). This allowed us to rule out possible diagnostic bias due to the fact that the alldynia and control areas were not homologous in our patients. These clinical and psychophysical criteria were also compared with the patients’ self report of evoked pains by means of the NPSI.

Statistical analysis of clinical and psychophysical data

Results were expressed as means ± 1 SD. We used Wilcoxon’s signed rank test for comparison of paired data. Relationships between two variables were tested using the Kendall rank correlation (tau). We used ANOVA (analysis of variance), with Fisher’s post hoc least significant difference test, for inter-group comparisons. In all cases, P < 0.05 was regarded as significant.

Functional MRI study

Functional MRI was carried out in patients with cold alldynia (n = 6) or dynamic mechanical alldynia (n = 6), patients without pain (n = 6) and in six matched healthy volunteers (four women, two men, mean age: 48.3 ± 10.5 years, range: 37–67 years).

Imaging sequences

MRI was carried out using a 1.5 T GE High-Speed scanner (General Electric Medical Systems, Milwaukee, USA) with a standard head coil. Anatomical scans were collected using a high-resolution T1-weighted 3D Fast SPGR anatomical protocol (TE = 5 ms, TR = 140, matrix 256 × 256, FOV 240 × 240 mm, 124 slices of 1.5 mm thickness) after a sagittal T1-weighted fast scan view. The functional scans were collected using a blood oxygen level dependent contrast (BOLD) protocol with a T2*-weighted gradient echo-planar imaging sequence (TR = 3000, TE = 60 ms, Flip angle: 90°). Each functional scan consisted of 42 volume acquisitions (24 slices, 5 mm thickness, 240 × 240 mm FOV yielding a 70 mm3 isotropic voxel) for a total sequence time of 2 min 6 s. The scanning planes were oriented parallel to the anterior...
commissure-posterior commissure line and covered the top of the cortex down to the medulla. Subjects were placed supine on the MRI table and made comfortable in this position. They were told to relax, keep their eyes closed and not to move. A Velcro band held the head inside the antenna and limited macro-motion artefacts. The lights were dimmed and a support was placed under the knees if desired. Images were acquired over less than 45 min.

Thermal and tactile stimulation
For the six patients with cold allodynia, a static thermal stimulation at 22°C was applied in the area of maximal allodynia (i.e. the dorsum of the hand). This temperature was chosen on the basis of psychophysical tests carried out before the fMRI session. This stimulation induced a clear (although tolerable) sensation of pain when it was applied to the hand in patients with cold allodynia. In contrast, the same stimulus applied to the patients’ control area or to the hand in healthy volunteers evoked a sensation of coolness that was never described as painful or unpleasant.

For the six patients with allodynia to brush, tactile stimuli consisting of repetitive stroking with a soft brush (about once a second) were applied manually in the area of maximal allodynia (i.e. the dorsum of the hand).

The same cold (i.e. 22°C) and tactile stimuli were applied to the dorsal surface of the right hand of the six syringomyelic patients without pain and the six healthy volunteers. In addition, a painful cold stimulation (4°C) was applied to the dorsal surface of the right hand of the six volunteers. This stimulus was systematically tested before fMRI to ensure that it evoked a tolerable painful sensation.

Experimental design
For the patients with allodynia, each session consisted of one anatomical and one functional scan for tactile or cold stimulation of the allodynic hand. The functional scans consisted of four acquisition epochs without stimulation alternating with three epochs with cold or tactile stimulation, making a total of seven epochs of 18 s, for a total scan time of 2 min 6 s. After each scan, the patients were asked to describe their sensation and to rate the maximal pain intensity on a 100 mm VAS (0 = no pain; 100 = worst imaginable pain).

For the control healthy subjects and the patients without pain, each session consisted of one anatomical scan and three functional scans for tactile, non-noxious (22°C) and noxious (4°C) cold stimulation of the right hand applied in a random order. The stimulation model was similar to that described earlier. Each functional scan alternated seven epochs (four epochs without stimulation and three epochs with stimulation) lasting 18 s each. After each scan, the participants rated the pain intensity on a VAS. Non-painful tactile and cold sensations were assessed using a categorical scale (absent, mild, moderate, intense sensation).

Image processing and analyses
All data were processed using Statistical Parametric Mapping (SPM 99, Wellcome Department of Cognitive Neurology, London, UK) (Friston et al., 1995). For each subject, anatomical images were transformed stereotactically to Talairach coordinates (Talairach and Tournoux, 1988) using the standard template of the Montreal Neurological Institute (Ashburner and Friston, 1999). After correcting for motion of the patient, the functional scans were normalized with the same transformation and smoothed to a final smoothness of 6 mm using a Gaussian spatial filter. We discarded the first four volumes of each BOLD session to allow signal equilibrium.

We analysed the data on an individual (subject per subject) basis and across subjects (group analysis) using a cross-subjects variance (random effect analysis). For individual analysis, data from each run were modelled using the general linear model, with separate functions modelling the haemodynamic response to each experimental epoch of the patient. Covariates were used to model long-term signal variations (temporal cut-off: 110 s) and overall differences between runs. We computed different contrasts: (i) 22°C cold stimulation versus rest; (ii) tactile stimulation versus rest; (iii) 4°C cold stimulation versus rest; (iv) 22°C cold stimulation versus 4°C cold stimulation; (v) 4°C cold stimulation versus 22°C cold stimulation. Data from each stimulation were pooled for group statistical comparisons. We flipped the data from patients with left-sided allodynia to correspond with the data from patients with right-sided allodynia. We calculated statistical parametric maps for each contrast. The threshold for the Z maps was 3.09 (P < 0.001) for individual subject analysis. In these threshold-treated maps, activated clusters were considered significant if their spatial extent was greater than 3 voxels (or 210 mm³), corresponding to a type I error of P < 0.05. For group analysis, parametric maps were constructed using the same contrast and spatial extent but we used a corrected threshold of P < 0.05.

Results
Description of the patients
The syrinx was mostly due to type I Chiari malformation or trauma and was located at the cervical or cervicodorsal level. All patients had mild to severe thermal (warm and/or cold) deficit and/or hypoalgesia to pinprick most commonly confined to cervicodorsal dermatomes. The thermalgesic deficit was bilateral and symmetric in 19 patients and asymmetrical in 27 patients. It was strictly unilateral in 12 cases, consistent with the paramedian right or left extension of the syrinx on MRI. Some patients also had tactile sensibility deficits as assessed with vibration, von Frey hairs, graphesthesia, movement direction, joint position or stereognosis. The main clinical and demographic characteristics of the 46 patients (20 women, 26 men) who completed the study are summarized in Table 1.

Comparison of patients with or without neuropathic pain
Central neuropathic pain was present in 31 patients (Table 2). Pain was most commonly located in the superior limb (27 patients) including the neck (n = 7) or the thoracic segments (n = 5) or was located in the thoracic segments and lower limb (n = 4). Pain extended over 2–10 dermatomes (mean: 5.8 dermatomes) and was unilateral in most cases (n = 24). Spontaneous ongoing pain (without evoked pain) was present in 11 patients. Twenty patients also reported evoked pain (i.e. allodynia/hyperalgesia), mostly due to light tactile or cold stimuli (Table 2). A majority of painful patients (n = 24) had been previously treated with antidepressants or antiepileptics but most of them had stopped their
symptoms (neuropathic pain or paraesthesia). The duration of symptoms refers to first symptoms of syringomyelia, i.e. subjective loss of sensation or positive sensory symptoms (neuropathic pain or paraesthesia).

### Table 1: Demographic and clinical characteristics of the 46 patients included in the study

<table>
<thead>
<tr>
<th></th>
<th>Patients without neuropathic pain</th>
<th>Patients with neuropathic pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± standard deviation)</td>
<td>47.9 ± 13.7</td>
<td>44.7 ± 13.9</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>26/20</td>
<td>11/19</td>
</tr>
<tr>
<td>Duration of symptoms in years (mean ± standard deviation)</td>
<td>11 ± 8.5</td>
<td>14 ± 8.5</td>
</tr>
<tr>
<td>Aetiology of the syrinx</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chiari type I</td>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td>Spinal cord trauma</td>
<td>15</td>
<td>18</td>
</tr>
<tr>
<td>Primitive</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Localization of the thermal deficits</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper limbs, thorax</td>
<td>22</td>
<td>24</td>
</tr>
<tr>
<td>(cervical syrinx)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper limbs (cervical syrinx)</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Upper limbs, thorax</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>(cervicodorsal syrinx)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thorax, lower limbs</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>(dorsolateral syrinx)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deficits of other modalities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vibration</td>
<td>24</td>
<td>21</td>
</tr>
<tr>
<td>Tactile (von Frey hairs)</td>
<td>17</td>
<td>18</td>
</tr>
<tr>
<td>Graphaesthesia</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>Movement direction</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Joint position</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Stereognosis</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

The duration of symptoms refers to first symptoms of syringomyelia, i.e. subjective loss of sensation or positive sensory symptoms (neuropathic pain or paraesthesia).

### Table 2: General description of pain in the 31 patients with neuropathic pain

<table>
<thead>
<tr>
<th></th>
<th>Patients without neuropathic pain</th>
<th>Patients with neuropathic pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of pain in years (mean ± standard deviation)</td>
<td>10.4 ± 8.3</td>
<td>10.1 ± 8.3</td>
</tr>
<tr>
<td>Mean pain intensity (mean VAS score ± standard deviation)</td>
<td>56 ± 76</td>
<td>59 ± 74</td>
</tr>
<tr>
<td>Maximal pain intensity (mean VAS score ± standard deviation)</td>
<td>76 ± 20</td>
<td>74 ± 20</td>
</tr>
<tr>
<td>Dermatomal extension of the pain (mean ± standard deviation)</td>
<td>5.8 ± 2.7</td>
<td>5.6 ± 2.7</td>
</tr>
<tr>
<td>Quality of neuropathic pain (NPSI)</td>
<td>n (%)</td>
<td>Intensity (mean ± standard deviation)</td>
</tr>
<tr>
<td>Burning</td>
<td>23 (74)</td>
<td>2.3 ± 0.6</td>
</tr>
<tr>
<td>Deep pain (pressure/squeezing)</td>
<td>14 (45)</td>
<td>2.1 ± 0.7</td>
</tr>
<tr>
<td>Paroxysmal pain</td>
<td>19 (63)</td>
<td>2.8 ± 0.7</td>
</tr>
<tr>
<td>(electric shocks, stabbing)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paraesthesia/dysaesthesia (tingling, pins and needles)</td>
<td>24 (77)</td>
<td>3.7 ± 0.9</td>
</tr>
<tr>
<td>Allodynia (brush, pressure, cold)</td>
<td>20 (64)</td>
<td>4.7 ± 2.3</td>
</tr>
<tr>
<td>Allodynia to brush</td>
<td>12 (39)</td>
<td>5.1 ± 3.7</td>
</tr>
<tr>
<td>Allodynia to cold</td>
<td>11 (35)</td>
<td>5.8 ± 3.7</td>
</tr>
<tr>
<td>Allodynia to pressure</td>
<td>7 (22)</td>
<td>3.3 ± 3.5</td>
</tr>
</tbody>
</table>

Assessment of global pain intensity was performed with (0–100 mm) visual analogue scale (VAS). The intensity of the different components of neuropathic pain was assessed with the Neuropathic Pain Symptom Inventory (NPSI) including numerical scales (0–10) for each symptom. Pain intensity was assessed over the last 24 h.

### Table 3: Comparison of the socio-demographic and clinical characteristics between patients with or without neuropathic pain

<table>
<thead>
<tr>
<th></th>
<th>Patients without neuropathic pain</th>
<th>Patients with neuropathic pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± standard deviation)</td>
<td>43 ± 12</td>
<td>50 ± 14</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>11/4</td>
<td>15/16</td>
</tr>
<tr>
<td>Duration of symptoms in years (mean ± standard deviation)</td>
<td>9.3 ± 7</td>
<td>11.7 ± 9.2</td>
</tr>
<tr>
<td>Thresholds (mean ± standard deviation)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warm detection (°C)</td>
<td>46.5 ± 5</td>
<td>46 ± 5.6</td>
</tr>
<tr>
<td>Cold detection (°C)</td>
<td>13.7 ± 6.5</td>
<td>14.2 ± 6.7</td>
</tr>
<tr>
<td>Mechanical detection [log(mg)]</td>
<td>2.9 ± 0.9</td>
<td>2.7 ± 0.7</td>
</tr>
<tr>
<td>Vibration thresholds (Hz)</td>
<td>5.5 ± 1.2</td>
<td>5.8 ± 9.2</td>
</tr>
<tr>
<td>Heat pain (°C)</td>
<td>48.7 ± 2</td>
<td>47.1 ± 4.3</td>
</tr>
<tr>
<td>Cold pain (°C)</td>
<td>4.6 ± 1.5</td>
<td>8.2 ± 7.6</td>
</tr>
<tr>
<td>Mechanical pain [log(mg)]</td>
<td>5.1 ± 0.2</td>
<td>4.9 ± 0.5</td>
</tr>
<tr>
<td>Dermatomas (mean ± standard deviation)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warm</td>
<td>13.1 ± 11.2</td>
<td>13.7 ± 9.1</td>
</tr>
<tr>
<td>Cold</td>
<td>17.8 ± 13.2</td>
<td>13.2 ± 9.3</td>
</tr>
<tr>
<td>Pinprick</td>
<td>16.4 ± 12.2</td>
<td>12.9 ± 9.2</td>
</tr>
<tr>
<td>Tactile/propiocceptive impairment (n, %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Graphaesthesia</td>
<td>4 (27)</td>
<td>7 (27)</td>
</tr>
<tr>
<td>Movement direction</td>
<td>4 (27)</td>
<td>6 (23)</td>
</tr>
</tbody>
</table>

The duration of symptoms refers to first symptoms of syringomyelia, i.e. subjective loss of sensation or positive sensory symptoms (neuropathic pain or paraesthesia). Detection and pain thresholds were measured in the area of maximal thermal deficit.

The patients with or without pain were similar in terms of age, duration of symptoms and aetiology (Table 3). The thermal and mechanical detection thresholds measured in the area of maximal deficit, which reflects the magnitude of sensory deficit, and the extent of sensory deficits (i.e. the number of dermatomes) were similar between patients with or without neuropathic pain (Table 3). The same proportion of patients in both groups had an impairment of graphaesthesia and movement direction, indicating impairment of the dorsal column.

### Relationship between pain and sensory deficits

The painful area was always located within the area of maximal thermal deficit, but was only confined to a restricted part of this area. We detected no significant difference between the area of maximal spontaneous pain and an adjacent lesioned, but non-painful, area with respect to...
thermal and mechanical deficits (Fig. 1). Graphesthesia and/or detection of movement direction impairment were also similar between the two areas. We found no relationship between pain characteristics—intensity, duration and quality (i.e. burning, squeezing, electric shocks, etc.)—and magnitude (i.e. warm and cold detection threshold) or extent (i.e. number of dermatomes) of thermal deficits (data not shown).

However, the patients with neuropathic pain were heterogeneous and the pattern of sensory deficits was dramatically different between patients with spontaneous pain only and patients with both spontaneous pain and evoked pain.

Overall the patients with evoked pain ($n = 20$) had a less severe deficit in comparison with patients with spontaneous pain only or painless patients. As illustrated in Fig. 2, both the warm and cold detection thresholds measured in the area of maximal deficit, which concerned the hand, the shoulder or the thoracic segments in the same proportions (i.e. 60–63%, 18–20% and 15–17%) in the different groups of patients, were significantly less altered in patients with evoked pain. Also, the extent of the thermal deficit was significantly lower in these patients (6.2 ± 6 dermatomes) compared with patients with spontaneous pain only (13.0 ± 5.4 dermatomes, $P < 0.05$) and with patients without pain (14.7 ± 6.8 dermatomes, $P < 0.01$). This suggested that both the magnitude and the extent of thermal deficits were less severe in patients with allodynia.

The two groups of patients with pain also differed as regards the laterality of their thermal deficits. Thus, in 82% of patients with spontaneous pain only, the thermal deficit was unilateral or asymmetrical versus 55% of patients with allodynia and 27% of the patients without pain ($P < 0.01$). Consequently, in patients with spontaneous pain only, the metameric extension of warm or cold deficits on the side with the maximal thermal impairment and pain was larger.

![Fig. 1](https://example.com/fig1.png) Comparison of the thermal (warm and cold) detection thresholds (expressed in °C) between the area of maximal pain (black columns) and an adjacent lesioned but not painful area (hatched columns) in patients with neuropathic pain. Warm and cold detection thresholds were similar in the two areas.

![Fig. 2](https://example.com/fig2.png) Comparison of the thermal (warm and cold) detection thresholds (expressed in °C) measured in the area of maximal deficit, between patients with spontaneous pain only (black columns), patients with both spontaneous pain and evoked pain (grey columns) and patients without pain (white column). Thermal detection thresholds, reflecting the magnitude of warm and cold sensory deficits, were significantly less altered in patients with evoked pain in comparison with the two other groups of patients. **$p < 0.01$.**
compared with the contralateral side (Fig. 3). In addition, in patients with spontaneous pain only, we evidenced a direct correlation between burning pain intensity (assessed with the NPSI) and the extent of thermal deficits (Rho = 0.63; P < 0.01 and Rho = 0.59, P < 0.01 for warm and cold deficits, respectively). No such correlation was observed in patients with spontaneous and evoked pain.

Allodynia was located in the area of spontaneous pain, but was restricted to only a small area. It could be induced by brush (n = 12), cold (n = 11), pressure (n = 7) and heat (n = 5), and the results of quantitative sensory testing were consistent with the self report of evoked pain by means of the NPSI. Allodynia to cold, pressure or heat was always associated with hyperalgesia to these stimuli. The pattern of sensory deficits depended on the sub-modality of allodynia. Thus, the thermal deficit was less severe in the patients with cold allodynia compared with those with brush-evoked allodynia, suggesting different pathophysiological mechanisms between the sub-types of allodynia. Both the cold detection threshold (25.0 ± 5.7 versus 18.6 ± 8.2°C) and warm detection threshold (36.0 ± 3.7 versus 43.4 ± 5) measured in the area of maximal deficit were significantly less impaired (P < 0.01) in patients with cold allodynia compared with patients with tactile allodynia.

**fMRI study**

**Cold-related fMRI activation in healthy volunteers**

The normal subjects reported a moderate, but never painful, cold sensation with the 22°C stimulus. The BOLD signal during the non-painful cold stimulation showed a significant increase (i.e. ‘activation’) bilaterally in the insula and contralaterally in the secondary somatosensory and inferior parietal cortices compared with the signal at rest (Fig. 4A and Table 4).

All volunteers described the 4°C cold stimulus as painful, with a mean pain intensity of 56 ± 18. Like the 22°C stimulus, the painful cold stimulus induced activation bilaterally in the insular, inferior parietal and secondary somatosensory cortices compared with rest (Fig. 4B). We also observed a significant increase in the signal in the anterior cingulate cortex (ACC) [Brodmann area (BA) 24], with five out of six subjects showing prominent activation in this area. We also observed significant activation in other areas, including the lateral prefrontal areas [ipsilateral dorsolateral prefrontal cortex (DLPFC) corresponding to BA 9/46], the inferior and medial frontal gyrus and contralateral supplementary motor cortex. In two to three of the six subjects, we also saw significant activation in the lenticular nuclei, the hippocampus and the cerebellar lobes.

**Cold allodynia**

Patients with cold allodynia described the 22°C cold stimulation as painful in all cases, with a mean intensity of 59 ± 24, which was similar to that evoked by the painful 4°C cold stimulus in healthy volunteers. The pain sensation was mostly described as deep and freezing, and sometimes burning with a tingling sensation. Cold allodynia induced a pattern of brain activation similar to that induced by painful cold in healthy volunteers. Activated areas included the middle/posterior insula, ACC, secondary somatosensory cortex and inferior parietal areas (Fig. 4C and Table 4). We also observed significant activation in other areas, including the lateral prefrontal areas [ipsilateral dorsolateral prefrontal cortex (DLPFC) corresponding to BA 9/46], the inferior and medial frontal gyrus and contralateral supplementary motor cortex. In two to three of the six subjects, we also saw significant activation in the lenticular areas and cerebellar lobes.

**Cold-related activation in painless syringomyelic patients**

Syringomyelic patients without pain (n = 6) had anaesthesia or severe thermal hypoaesthesia. They could not perceive
the 22°C stimulation, and the 4°C cold stimulation was felt as very weak or absent, and never painful. Consistent with the sensory experience of the patients, we observed very little significant brain activation induced by the cold stimuli (data not illustrated). In only two and three of the six subjects, respectively, the 22°C stimulation and the 4°C stimulation induced an activation of the contralateral inferior parietal cortex (BA 40), S2 and ipsilateral inferior frontal gyrus (BA 44, 47).

**Tactile-related fMRI activation in volunteers and patients**

*Tactile stimulation in normal subjects and patients without pain*

In the six healthy volunteers, tactile stimulation of the right hand resulted in significant contralateral activation of the post-central gyrus (primary somatosensory cortex (S1)), the inferior and superior parietal areas, and to a lesser extent, the contralateral secondary somatosensory cortex (S2) (Table 5 and Fig. 5A). We observed a similar pattern of activation (not illustrated) in the six pain-free patients with syringomyelia, who all felt the tactile stimuli normally (Table 5).

*Brush-induced allodynia*

Patients with brush-induced allodynia (n = 6) found the brush-induced stimulation of the hand painful in all cases (mean pain intensity: 61 ± 21). The pain sensation was described mostly as burning in four patients and as electric shocks in two patients.

In these six patients, tactile stimulation of the hand caused significant activation of the ipsilateral and contralateral posterior parietal areas (S1, S2, inferior and superior parietal cortex), the ipsilateral and contralateral middle frontal gyrus, and also the contralateral thalamus, caudate nucleus, and supplementary motor area (Table 5 and Fig. 5B). In contrast, we observed no activation in the anterior cingulate area (BA 24, 32). Thus, the allodynic patients had a unique activation pattern in the contralateral thalamus and bilaterally in the frontal gyrus, corresponding to the DLPFC, including area BA 45/46.

**Discussion**

The present study used psychophysical testing and fMRI to investigate the relationships between spinothalamic tract dysfunction, thermosensory deficits and central pain in patients with syringomyelia. We found no simple direct relationship between the magnitude or extent of sensory loss and the presence, quality or intensity of neuropathic pain. However, in patients with pain, the pattern of sensory deficits was related to the presence of allodynia and hyperalgesia (i.e. evoked pains). Moreover, the sub-modalities of allodynia (i.e. cold or tactile) were also associated with different sensory abnormalities, suggesting that these neuropathic
Table 4 Average Z-scores and activation in normal subjects submitted to non-painful and painful cold stimulation of the right hand (n = 6), in patients submitted to normally non-painful cold stimulation to the alldynic hand (n = 6)

<table>
<thead>
<tr>
<th>BA</th>
<th>Side</th>
<th>Coordinates</th>
<th>Normal subjects cold 22°C</th>
<th>Normal subjects cold 4°C</th>
<th>Alldynic patients cold 22°C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Z  x  y  z</td>
<td>Z  x  y  z</td>
<td>Z  x  y  z</td>
<td></td>
</tr>
<tr>
<td>Insula</td>
<td>47, 48</td>
<td>Contra</td>
<td>4.05 -39 +4 -11</td>
<td>6.20 -36 -6 +12</td>
<td>6.04 -36 -18 +4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ipsi</td>
<td>5.26 +38 +22 -11</td>
<td>5.04 +40 +14 -2</td>
<td>6.35 +38 +15 -4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Contra</td>
<td>4.89 -38 +20 -10</td>
<td>4.82 -30 +20 -2</td>
<td>6.62 -37 +22 -4</td>
</tr>
<tr>
<td>Posterior parietal</td>
<td>40</td>
<td>Ipsi</td>
<td>6.04 -46 -48 +42</td>
<td>7.83 +50 -46 +58</td>
<td>5.36 +48 -44 +52</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Contra</td>
<td>7.25 -48 -44 +60</td>
<td>7.25 -48 -44 +60</td>
<td>5.37 -48 -34 +42</td>
</tr>
<tr>
<td>7</td>
<td>Ipsi</td>
<td>5.36 +8 -78 +54</td>
<td>6.10 +32 -58 +62</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Contra</td>
<td>7.25 -38 -52 +62</td>
<td>4.79 -21 -63 +40</td>
<td></td>
</tr>
<tr>
<td>ACC</td>
<td>24</td>
<td>Ipsi</td>
<td>6.05 +2 +28 +28</td>
<td>5.02 -2 +30 +18</td>
<td>4.99 -1 +26 +34</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Contra</td>
<td>5.51 +6 +28 +46</td>
<td>5.80 +8 +28 +40</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Contra</td>
<td>4.82 -2 +24 +44</td>
<td>6.11 -4 -4 +34</td>
<td></td>
</tr>
<tr>
<td>S2</td>
<td>–</td>
<td>Ipsi</td>
<td>5.81 +52 -18 +4</td>
<td>5.54 +40 -20 +2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Contra</td>
<td>7.68 -48 -22 +10</td>
<td>6.91 -48 -28 +16</td>
<td></td>
</tr>
<tr>
<td>Frontal</td>
<td>44, 45</td>
<td>Ipsi</td>
<td>5.44 -56 -28 +16</td>
<td>5.64 +46 +36 +12</td>
<td>4.98 +52 +24 +22</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Contra</td>
<td>5.38 +56 +32 +18</td>
<td>5.37 -44 -48 +10</td>
<td>5.65 -48 +44 +2</td>
</tr>
<tr>
<td>46</td>
<td>Ipsi</td>
<td>5.27 +30 +44 +25</td>
<td>4.83 +48 +35 +30</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Contra</td>
<td>4.81 +20 +54 +36</td>
<td>4.15 +14 +14 +58</td>
<td></td>
</tr>
<tr>
<td>Thalamus</td>
<td>–</td>
<td>Ipsi</td>
<td>4.92 +4 -8 +4</td>
<td>4.84 -8 -26 +4</td>
<td>5.26 -15 -16 +18</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Contra</td>
<td>5.86 +14 0 +16</td>
<td>4.99 +16 +8 -2</td>
<td></td>
</tr>
<tr>
<td>Caudate</td>
<td>–</td>
<td>Ipsi</td>
<td>5.31 -14 -8 +18</td>
<td>5.15 -12 +18 -2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Contra</td>
<td>5.08 -16 +8 +8</td>
<td>5.07 -32 -2 -2</td>
<td></td>
</tr>
<tr>
<td>Putamen</td>
<td>–</td>
<td>Contra</td>
<td>4.83 -4 -11 +53</td>
<td>5.13 -8 -4 +52</td>
<td></td>
</tr>
<tr>
<td>SMA</td>
<td>6</td>
<td>Contra</td>
<td>5.50 +48 +6 +42</td>
<td>4.88 -43 -18 +10</td>
<td>4.99 -9 -26 -10</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>20</td>
<td>Contra</td>
<td>7.58 +26 -74 -28</td>
<td>4.86 -30 -56 -20</td>
<td></td>
</tr>
<tr>
<td>Cerebellar lobes</td>
<td>–</td>
<td>Ipsi</td>
<td>5.08 +48 +6 +42</td>
<td>4.88 -43 -18 +10</td>
<td>4.99 -9 -26 -10</td>
</tr>
</tbody>
</table>

Z-values > 3.09 represent significant activity (P < 0.05). The coordinates are expressed in millimetres according to the reference lines defined by Talairach and Tournoux (1988): x = medial-lateral; 0 midline, + right; y = anterior-posterior; 0 anterior commissure, + anterior; z = superior-inferior; 0 commissural line, + superior. Abbreviations: BA: Brodmann area; Ipsi: ipsilateral; contra: contralateral; assoc.: associative; SMA: supplementary motor cortex; S2: secondary somatosensory cortex; ACC: anterior cingulate cortex.

Pain symptoms are sustained by distinct pathophysiological mechanisms. This was further confirmed by our fMRI study showing that there is no unique network of brain structures associated with pathological pain. The different sub-types of allodynia were associated with distinct patterns of brain activation, which do not necessarily correspond to the ‘pain matrix’ involved in acute physiological pain.

Previous investigations using QSTs in patients with central pain due to stroke or spinal cord injury have generally concluded that although these patients have thermal deficits, their fine tactile and vibratory sensations are preserved (Beric et al., 1988; Boivie et al., 1989; Leijon et al., 1989; Vestergaard et al., 1995; Bowsher, 1996, 1998). Therefore, lesions of the spinoholamic system, regardless of level in the CNS, were considered as necessary for developing central neuropathic pain. These data provided some support for the ‘imbalance theory’, which suggests that the mechanisms of central pain are due to an imbalance in the sensory information conveyed by the residual dorsal column system and the impaired spinoholamic system (Beric et al., 1998). However, these studies were limited in that they did not include appropriate control groups of patients with similar central lesions but not suffering from pain.

In the present study, we used two complementary approaches to investigate the correlation between pain and sensory deficits. First, we compared the magnitude and extent of thermal and mechanical deficits between syringomyelia patients with or without pain, matched by age, and duration and aetiology of the syrinx. We did not observe an overall significant difference between these two groups of patients for the extent or magnitude of the sensory deficits. These results are consistent with those of two previous studies using a similar approach in patients with spinal cord injury (Defrin et al., 2001; Finnerup et al., 2003). We then compared the magnitude of thermal and mechanical deficits between an area of maximal spontaneous pain and an adjacent lesioned, but non-painful, area for each patient. We did not find a significant difference between these two body areas for the magnitude of thermal or mechanical deficits, which was consistent with previous studies.
Brain disorders evidenced in patients with spontaneous pain only
regulatory motivation. The asymmetry of the thermal sen-
or lesion in the thermosensory systems inducing a thermo-
physiological condition of the body. In this perspective, it
pain not only as a sensation but also as a 'homeostatic
ceptions, the main originality of this theory is that it views
condition hypothesis, which emphasizes the role of thermal deficit
of central pain, in particular, the thermosensory disinhib-
more asymmetrical and there was a correlation between
patients may be related to a profound sensory deafferentation
ous ongoing pain was located in an area of minimal sensory
deficit and was associated with allodynia and hyperalgesia.
Thus, in accordance with recent data in patients with
Wallenberg’s syndrome that central pain was less frequently observed when the thermal deficit was symmetrical (MacGowan et al., 1997).
In contrast, in the second subgroup of patients, spontan-
eous ongoing pain was located in an area of minimal sensory
deficit and was associated with allostodynia and hyperalgesia.
Thus, in accordance with recent data in patients with
central post-stroke pain (Greenspan et al., 2004), sensory
deafferentation does not seem to be involved in spontane-
ous pain when it is associated with evoked pain in patients
with syringomyelia. In this category of patients, central
neuropathic pain may involve other mechanisms such as
direct changes to the electrophysiological properties of
nociceptive neurons, resulting in hyperexcitability (i.e.
central sensitization), or more indirect changes in excitabi-
ity due to alterations of pain modulatory systems. The
symptomatology of these patients was reminiscent of the
behavioural changes observed in animal models of ischaem-
ic or excitotoxic spinal cord injury that showed hyper-
excitability of the nociceptive dorsal horn neurons
(Yezierski, 1996; Vierck et al., 2000). However, unlike in
animals, such a sensitization does not seem to be genera-
lized, as none of the patients had a hyperalgesia to any
type of stimuli. In contrast, the patients generally had
dissociated allodynia, suggesting that the different sub-
modalities of evoked pain involve distinct pathophysiological
mechanisms.

Table 5 Average Z-scores and activation in normal subjects submitted to non-painful tactile stimulation of the right hand (n = 6), in painless syringomyelic patients submitted to non-painful tactile stimulation of the right hand (n = 6) and in allodynic patients submitted to abnormally painful tactile stimulation of the right or left hand (n = 6)

<table>
<thead>
<tr>
<th>Brain areas</th>
<th>BA</th>
<th>Side</th>
<th>Normal subjects</th>
<th>Patients without pain</th>
<th>Allodynic patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Coordinates</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Z x y z</td>
<td>Z x y z</td>
<td>Z x y z</td>
</tr>
<tr>
<td>S1 1, 2</td>
<td>1  2</td>
<td>Contra</td>
<td>4.81 -52 -34 +56</td>
<td>6.04 -42 +42 +62</td>
<td>4.93 -22 -38 +58</td>
</tr>
<tr>
<td>S2 –</td>
<td>–</td>
<td>Ipsi</td>
<td>4.79 -52 -30 +18</td>
<td>6.51 -52 -18 +12</td>
<td>4.89 -66 -23 +16</td>
</tr>
<tr>
<td>Posterior parietal 40</td>
<td>Ipsi</td>
<td>Contra</td>
<td>5.42 +52 -38 +50</td>
<td>5.29 -40 +38 +48</td>
<td>6.31 -56 -36 +44</td>
</tr>
<tr>
<td>Frontal 45, 46</td>
<td>Ipsi</td>
<td>Contra</td>
<td>6.36 -46 -52 +56</td>
<td>5.29 -40 +38 +48</td>
<td>6.31 -56 -36 +44</td>
</tr>
<tr>
<td>Medial thalamus</td>
<td>–</td>
<td>Contra</td>
<td>5.36 -16 -6 +10</td>
<td>5.15 +18 +12 +10</td>
<td>5.32 -10 +6 +54</td>
</tr>
<tr>
<td>Caudate 6</td>
<td>–</td>
<td>Ipsi</td>
<td>5.15 +18 +12 +10</td>
<td>5.32 -10 +6 +54</td>
<td>5.32 -10 +6 +54</td>
</tr>
<tr>
<td>Angular 39</td>
<td>–</td>
<td>Ipsi</td>
<td>4.85 +50 -58 +44</td>
<td>4.85 +50 -58 +44</td>
<td>4.85 +43 -50 +32</td>
</tr>
</tbody>
</table>

Z-values ≥ 3.09 represent significant activity (P < 0.05). The coordinates are expressed in millimetres according to the reference lines defined by Talairach and Tournoux (1988): x = medial-lateral; y = right; y = anterior-posterior; 0: anterior commissure; + anterior; z = superior-inferior; 0: commissural line; + superior. Abbreviations: BA: Brodmann area; Ipsi: ipsilateral; contra; contralateral; assoc.: associative; SMA: supplementary motor cortex; S2: secondary somatosensory cortex; ACC: anterior cingulate cortex.

(Eide et al., 1996). Thus, our results primarily confirm that
lesions of the spinothalamic tract may be necessary, but are
not sufficient to account for central pain.

Although overall the thermal deficits were not different
between patients with or without pain, the patients with
pain were heterogeneous for both neuropathic pain symp-
toms and deficits. In particular, we could clearly distinguish
two subgroups of patients. Patients with ‘pure’ spontaneous
pain had a more severe deficit than patients with both sponta-
neous and evoked pains (i.e. allodynia and hyperalgesia). Patients in the first subgroup had strongly reduced responses
to thermal and mechanical stimuli in the area of spontaneous
pain, suggesting that spontaneous neuropathic pain in these
patients may be related to a profound sensory deafferentation
of supraspinal structures. In addition, in this specific sub-
group of patients, the thermal deficit was significantly
more asymmetrical and there was a correlation between
the intensity of burning pain and the extent of thermal defi-
cits. These data are compatible with the disinhibition theory
of central pain, in particular, the thermosensory disinhibi-
tion hypothesis, which emphasizes the role of thermal deficit
(Craig, 1998, 2000, 2003). In contrast with traditional con-
ceptions, the main originality of this theory is that it views
pain not only as a sensation but also as a ‘homeostatic emotion’ and an aspect of interoception, defined as the
physiological condition of the body. In this perspective, it
is proposed that central pain is the result of an imbalance
or lesion in the thermosensory systems inducing a thermo-
regulatory motivation. The asymmetry of the thermal sen-
sory loss evidenced in patients with spontaneous pain only
is compatible with this hypothesis since it could reflect an
imbalance in thermoregulation that involves bilateral brain
integration (Craig, 1998). Interestingly, it has been reported
in patients with Wallenberg’s syndrome that central pain
was less frequently observed when the thermal deficit was
symmetrical (MacGowan et al., 1997).

In contrast, in the second subgroup of patients, spontan-
eous ongoing pain was located in an area of minimal sensory
deficit and was associated with allostodynia and hyperalgesia.
Thus, in accordance with recent data in patients with
central post-stroke pain (Greenspan et al., 2004), sensory
deafferentation does not seem to be involved in spontane-
ous pain when it is associated with evoked pain in patients
with syringomyelia. In this category of patients, central
neuropathic pain may involve other mechanisms such as
direct changes to the electrophysiological properties of
nociceptive neurons, resulting in hyperexcitability (i.e.
central sensitization), or more indirect changes in excitabi-
lity due to alterations of pain modulatory systems. The
symptomatology of these patients was reminiscent of the
behavioural changes observed in animal models of ischaem-
ic or excitotoxic spinal cord injury that showed hyper-
excitability of the nociceptive dorsal horn neurons
(Yezierski, 1996; Vierck et al., 2000). However, unlike in
animals, such a sensitization does not seem to be genera-
lized, as none of the patients had a hyperalgesia to any
type of stimuli. In contrast, the patients generally had
dissociated allodynia, suggesting that the different sub-
modalities of evoked pain involve distinct pathophysiological
mechanisms.
Spinal cord injury and pain  

Fig. 5 Brain areas activated (in yellow) during brush stimuli of the right hand in the control healthy volunteers (A), and during application of the same stimuli in the patients with brush-evoked allodynia (B). The left side of the image corresponds to the left side of the brain. Abbreviations: S1: primary somatosensory cortex; S2: secondary somatosensory cortex; inf. parietal: inferior parietal cortex; Thal.: thalamus; DLPFC: dorsolateral prefrontal cortex.

Our complementary study using fMRI further illustrated the multiplicity of pathophysiological mechanisms involved in central pain. This study showed distinct patterns of brain activation during cold and tactile allodynia.

Numerous studies using PET (e.g. Talbot et al., 1991; Jones et al., 1991; Coghill et al., 1994, 1999; Casey et al., 1996; Derbyshire et al., 1997; Derbyshire and Jones, 1998, Peyron et al., 1999; Tölle et al., 1999) or fMRI (e.g. Davis et al., 1995, 1998; Disbrow et al., 1998; Porro et al., 1998) have investigated changes in brain activity in response to experimental noxious stimuli. These studies suggested a network of cortical areas, a possible ‘pain matrix’, that are involved in the processing of nociceptive information. Most of these studies showed activation in S1, S2, the posterior and anterior parts of the insula, the ACC and the thalamus. In several studies, other brain areas, including the brainstem, the basal ganglia, the cerebellum and various structures within the PFC, were also activated although their role in pain processing is still unclear. These studies were carried out on healthy volunteers and generally used experimental thermal (mostly heat) stimuli. Thus, it is not clear whether the same ‘pain matrix’ is involved in pathological chronic pain conditions, notably neuropathic pain. A few studies have been carried out on patients with allodynia due to peripheral (Petrovic et al., 1999; Peyron et al., 2004) or central (Peyron et al., 1998) neurological lesions. Although these studies were not in agreement, the general consensus was that the pattern of brain activation for chronic pain is not the same as that observed in healthy volunteers. In particular, involvement in pathological pain of the ACC, one of the most commonly activated regions in studies on experimental pain, is controversial. Several factors may explain the discrepancies between the different studies. These include the heterogeneity of the clinical conditions and/or symptomatology and methodological differences such as variation in the mode of stimulation.

The present study is the first to investigate specifically different sub-types of allodynia in a homogeneous group of patients.

Non-noxious cool stimuli in healthy volunteers induced a predominant bilateral activation in the insular cortex to the detriment of S1. In accordance with previous studies (Craig and Bushnell, 1996; Craig et al., 2000; Hua et al., 2005) these data tend to confirm the prevailing role of the insula in the integration of thermosensation. In contrast, the application of the same cold stimulus in patients with cold allodynia induced a pattern of brain activation similar to that due to normal cold pain sensation in healthy volunteers. In both cases, we observed significant activation in the insula, the ACC, the thalamus, and the parietal and frontal cortices, consistent with previous studies using noxious cold stimuli (Davis et al., 1998; Craig et al., 2000; Kwan et al., 2000). Most of these structures are included in the ‘pain matrix’. These data are compatible with the idea that cold allodynia is due to a hyperexcitability of nociceptive pathways induced by central sensitization and/or disinhibition. However, our results do not necessarily imply that allodynia is simply the result of an amplification or ‘leftward shift’ of the stimulus–response function in the physiological cold pain systems. Although the spatial activation pattern seems similar, a difference in the temporal pattern, that is, the dynamic aspect of the activation of these structures, cannot be excluded.

Our results regarding cold allodynia apparently contradict the PET study of Peyron et al. (1998). This study, which looked at patients with cold allodynia due to Wallenberg syndrome, is the only other functional neuroimaging study of patients with central pain. The study found a significant increase in the signals in the thalamus, the S1, pre-central and inferior frontal gyri, and the bilateral parietal lobules, but not in the ACC. Thus, it was concluded that cold allodynia was associated with abnormal responses in the lateral (sensori-discriminative) pain pathways rather than in the medial (affective) pain pathways. However, the patients in this study had a combination of tactile and cold allodynia,
and the stimuli consisted of a mixture of cold and rubbing stimulation within the allodynic area. As the sub-modality of allodynia was ambiguous, it is not clear whether similar results would have been observed with static cold stimuli. Therefore, apparent discrepancies between their study and ours may be explained by differences in the selection of patients and stimulation mode. This is important because in our study dynamic mechanical (i.e. brushing) stimuli of the hands evoked a different brain activation to static cold stimuli.

Unlike cold allodynia, we found that brush-evoked allodynia did not induce significant activation of several structures of the ‘pain matrix’, particularly the insula and the ACC. The pattern of activation was similar to that induced by non-painful brushing in healthy volunteers and patients without pain. In all groups, innocuous cutaneous tactile stimuli induced contralateral activation of S1 and bilateral activation of S2. Similar results have been reported in numerous studies of brain activation evoked by tactile stimuli in healthy volunteers, although other areas, such as the frontal, posterior parietal or insular cortices were also activated in some studies (refs. in Burton and Sinclair, 2000; Poro et al., 2004). In our study, brush-evoked allodynia was characterized by a consistent activation of the thalamus and PFC.

The different patterns of activation between the two sub-types of allodynia, which were not due to differences in the intensity of pain, probably reflect distinct pathophysiological mechanisms. One major difference between the basic mechanisms of cold and tactile allodynia is that tactile allodynia is elicited by activation of the mechanoreceptors (large diameter fibres) that normally convey non-noxious tactile sensations (Koltzenburg et al., 1992, 1994; Ochoa and Yarnitzki, 1993). Therefore, we can infer that this pathological painful sensation results from profound abnormalities in the somatosensory processing in the CNS. In contrast, like physiological pain, cold allodynia is mediated by fine afferent fibres and may therefore depend on a less severe alteration of somatosensory processes. Consistent with this are studies, under both pathological and non-pathological conditions, that have shown interactions between the thermal and nociceptive systems (Defrin et al., 2002; Bouhassira et al., 2005b). Nevertheless, the large differences in the activation induced by tactile and cold allodynia indicate that there is neither a unique ‘pain matrix’ nor an ‘allodynia network’.

A series of functional imaging studies using the capsaicin model of pain in healthy volunteers came to the same conclusions (Iadarola et al., 1998; Baron et al., 1999; Witting et al., 2001; Lorenz et al., 2002, 2003). Although this experimental model cannot be considered as a true model of neuropathic pain, it has been shown repetitively that topical application or intra-dermal injection of capsaicin transiently reproduces certain pathological painful symptoms, such as heat or brush-evoked allodynia, in healthy volunteers. Despite differences in the experimental design, most of the fMRI or PET studies of experimental tactile or heat allodynia induced by capsaicin showed an alteration in the high-level pain modulatory mechanisms (Iadarola et al., 1998; Baron et al., 1999; Lorenz et al., 2002, 2003).

The PFC seems to be activated in most of the imaging studies carried out in patients or when using various acute experimental stimuli or the capsaicin model in healthy volunteers. Frontal lobe activity during pain was generally considered to be connected with cognitive and attentional processing of painful stimuli (Casey, 1999; Peyron et al., 1999). However, the frontal cortex may also be more directly involved in the perception of pain, notably through the modulation of diencephalon or brainstem structures participating in pain modulation (Lorenz et al., 2003). The modulatory function of the PFC on pain perception has also been illustrated by its key role in the placebo effect (Wager et al., 2004).

In conclusion, our study shows that central neuropathic pain due to syringomyelia cannot be considered as a simple amplification of normal pain. Both our psychophysical and functional neuroimaging data demonstrate that different central neuropathic pain symptoms are sustained by distinct mechanisms. From a clinical perspective, these data suggest that these symptoms should respond differently to treatment (Attal et al., 2000, 2002) and confirm the importance of a mechanism-based classification of patients with neuropathic pain, including central pain.

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References

Bouhassira D, Attal N, Parker F, Brasseur L. Quantitative sensory evaluation of painful and painless patients with syringomyelia. In: Devor M,


Finnerup NB, Johannesen IL, Fuglsang-Frederiksen A, Bach FW, Jensen TS. Sensory function in spinal cord injury patients with and without central pain. Brain 2003; 126: 57–70.


