Sensory function in spinal cord injury patients with and without central pain

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Summary
Spinal cord injury (SCI) frequently results in neuropathic pain. However, the pathophysiology underlying this pain is unclear. In this study, we compared clinical examination, quantitative sensory testing (QST) and somatosensory evoked potentials (SEPs) in SCI patients with and without pain below spinal lesion level, with a control group of 20 subjects without injury. All patients had a traumatic SCI with a lesion above T10; 20 patients presented with spontaneous central neuropathic pain below lesion level, and 20 patients had no neuropathic pain or dysaesthesia. Patients with and without pain had a similar reduction of mechanical and thermal detection and pain thresholds, and SEPs. SCI patients with central pain more frequently had sensory hypersensitivity (brush- or cold-evoked pain, dysesthesia or pinprick hyperalgesia) in dermatomes corresponding to lesion level than SCI patients without pain. There was no difference in intensity of pain evoked by repetitive pinprick at lesion level between patient groups. There was a significant correlation between intensity of brush-evoked dysesthesia at lesion level and spontaneous pain below lesion level of SCI. These data suggest that lesion of the spinothalamic pathway alone cannot account for central pain in SCI patients, and that neuronal hyperexcitability at injury or higher level may be an important mechanism for pain below injury level.

Keywords: central pain; allodynia; neuronal hyperexcitability; spinothalamic function; dorsal column function

Abbreviations: ASIA = American Spinal Injury Association; NRS = numeric rating scales; QST = quantitative sensory testing; SCI = spinal cord injury; SEP = sensory evoked potential; VAS = visual analogue scales

Introduction
Neuropathic pain is a significant problem following spinal cord injury (SCI). Recent studies suggest that chronic neuropathic pain occurs in ~50% of SCI patients and that such pain represent a major burden to the patients (Anke et al., 1995; Siddall et al., 1999; Finnerup et al., 2001). Despite its severity, studies on SCI pain and its underlying mechanisms have been relatively few.

According to the SCI Pain Task Force of the IASP (International Association for the Study of Pain), there are two categories of neuropathic pain resulting from SCI: at level pain (= pain in segments corresponding to the level of cord injury) and below level pain (= pain in body parts corresponding to segments below the injury) (Siddall et al., 2000). While below level neuropathic pain is considered to be a central pain condition caused by spinal cord damage, at level pain may have peripheral and central components that are difficult to separate (Siddall et al., 1997). The mechanisms underlying neuropathic SCI pain are still hypothetical.

In particular, it is unclear why some patients develop pain in body parts that have lost their afferent input while others with the same degree of deafferentation do not develop such pain. A dominating clinical feature of central pain conditions is an abnormal spinothalamic function with altered sensitivity to temperature and pinprick (Boivie et al., 1989; Vestergaard et al., 1995; Bowsher, 1996). In post-stroke pain, for example, it has been suggested that pain only develops in those patients with partial or complete loss of spinothalamic functions and signs of increased response to certain stimuli in the deafferented body parts (Andersen et al., 1995; Vestergaard et al., 1995).

In spinal cord-damaged patients with at level and below level pain, some previous studies have determined sensory function and recorded pain (Eide et al., 1996; Bouhassira et al., 2000; Defrin et al., 2001). Eide et al. (1996) compared somatosensory abnormalities in painful and non-painful denervated areas at or below injury level in 16 SCI pain...
patients. They found that allodynia and wind up-like pain were more common in painful than in non-painful areas, and suggested hyperexcitability in spinothalamic tract neurons to be involved in the pathogenesis of pain. Bouhassira et al. (2000) studied 10 patients with painful and 11 patients with painless syringomyelia, and observed no significant difference in thermal or mechanical sensory function between patients with or without pain or between areas of spontaneous pain and adjacent non-painful areas. Pain was confined, however, to areas with maximal thermal deficit. In incomplete SCI patients with lesions restricted to the T4–L3 segments, Defrin et al. (2001) found no differences between thermal and tactile sensations in patients with or without chronic pain. In the pain patients, however, thermal thresholds were impaired more in body areas with pain than in areas without pain, which had almost normal thermal sensibility. Allodynia was only elicited in pain patients. Taken together, these observations, in SCI patients with at level and below level pain, suggest that abnormal spinothalamic activity and signs of hyperexcitability, originating either in the cord itself or from damaged afferent fibres at the segmental level, may play a role in their pain. From the above studies, it is difficult to determine the role of the peripheral and central components of the pain. As recently pointed out by Wall (2001), we need to know how much of spinal injury pain is caused by peripheral as opposed to central lesions. In order to determine the mechanisms underlying proper central pain after SCI, we looked only at patients with pain in areas below spinal injury level, where damaged root or nerve lesions causing pain are unlikely. To study the underlying mechanisms we (i) characterized the degree of disconnection of ascending sensory pathways by using quantitative sensory testing (QST) and somatosensory evoked potentials (SEPs); and (ii) studied the degree of sensory hypersensitivity at and below the level of injury. A group of SCI patients with central neuropathic pain were compared with a group of SCI patients without neuropathic pain and also with a control group without SCI. Parts of the study have been presented in abstract form previously (Finnerup et al., 2002b).

Material and methods

Subjects

Three groups each of 20 subjects participated. Inclusion criteria for the SCI pain group were: central neuropathic pain (≥ pain below level of spinal cord injury) after a traumatic SCI. Other reasons for the pain below lesion level (nociceptive, peripheral neuropathic, and psychogenic pain) should be excluded or considered highly unlikely. To ensure that pain patients had below level pain, the area of pain should be at least two dermatome segments below the lesion level, and only patients with an injury above the conus medullaris (with a skeletal level above T10) were included. MRI performed in 14 pain and nine pain-free patients confirmed that the lower border of the spinal cord lesion was above the 10th thoracic vertebra (N. B. Finnerup et al., unpublished results). Spasm-related pain below level, and at level or above level neuropathic pain were allowed in addition to the central pain. For the SCI pain-free group, the inclusion criteria were: a traumatic SCI above T10 with no neuropathic pain and no spontaneous dysaesthesias (unpleasant abnormal sensations). Non-unpleasant sensations (paraesthesias) and spasm-related pain were allowed. The control group comprised gender- and age-matched healthy persons with no pain history. Patients were excluded if they had known or clinical signs of concomitant cerebral damage including epilepsy or dementia (total score on the Mini-Mental State Examination [Folstein et al., 1975] on inclusion below 26). Patients were recruited from the Viborg rehabilitation centre for spinal cord injury, and controls were enrolled after advertisement at the hospital and the local blood bank. No analgesics were allowed, and patients were asked to refrain from spasmyltics on the day of examination.

Methods

All subjects were examined by the same examiner (N.B.F.). Examinations were done on three occasions. Patients and controls were first examined with QST including evaluation of evoked pain below level; SEPs were determined on a second, and examination of evoked pain at lesion level on a third occasion. Informed consent was obtained according to the Declaration of Helsinki. The study was approved by the local ethical committee (no. 1999/4492) and the Danish Data Protection Agency (no. 2000-41-0099).

History

A medical history was obtained. The Functional Independence Measure was used to estimate disability and dependence (Fuhrer, 1987). Pain patients filled out the Danish version of the McGill Pain Questionnaire (Melzack, 1975; Drewes et al., 1993) and localized their pain on a body chart in two dimensions (anterior and posterior). Numeric rating scales (NRS; 0–10) and visual analogue scales (VAS; 0–10) were used for assessing pain intensity. SCI patients reported spasms (considering both intensity and frequency) on an NRS 0–10.

Clinical examination

A neurological and physical examination was obtained. Spinal lesions were classified according to the American Spinal Injury Association’s (ASIA) standards for classification of SCI (Maynard et al., 1997). Spasticity was assessed by the investigator as a combined score of muscle tone using the Ashworth scale (Ashworth, 1964) and a clinical grading of tendon reflexes (Nielsen et al., 1996).
SEPs
SEPs were determined in 14 pain and 12 pain-free patients with the subject in a comfortable supine position. The posterior tibial nerve was stimulated at the ankle with rectangular stimuli of 0.2 ms duration at a stimulus rate of 3 Hz. The stimulus intensity was increased until a definite motor response was seen. Chlorided silver cup recording electrodes were placed over Cz (2 cm behind Cz) referenced to Fz, and over C3 (2 cm behind C3) referenced to C4 (2 cm behind C4) for left tibial nerve stimulation, and C4 referenced to C3 for right side stimulation (International 10–20 system). Electrodes were placed over the twelfth thoracic vertebral spinous process (T12) referenced to a site over the iliac crest. Lower and upper frequency limits were 10 and 3000 Hz. SEP outcome was scored based on changes in latency and amplitude and disappearance of SEP waveform components: normal [compared with a national reference material with a regression line based on height and age (Andersen et al., personal communication)], decreased (abnormal waveform or decreased latency or amplitude) and absent SEP (no response clearly distinguishable from noise).

QST
QST was carried out 10 cm below the dominant knee on the anterior-lateral part, except for vibration (tested on the anterior surface of the tibia) and skinfold pinch (tested above the knee). Measurements were obtained in a quiet room at 20–22°C with all patients lying on a couch in a supine relaxed position. However, five patients were examined in their wheelchair with the chair in the supine position. In cases of severe sensory loss, failure to respond to cut-off limits resulted in assignment of the cut-off limits as the threshold value. A threshold was considered normal if there was a modality-specific response within the range among the 20 healthy controls.

Tactile sensitivity to single stimuli
This parameter was assessed using von Frey hairs (Semmes–Weinstein monofilaments, Stoolting, IL, USA). The tactile detection threshold and pain detection threshold were determined as the force required to bend the filament using the up–down paradigm described by Chaplan et al. (1994). Detection of a single hair was defined as detection within 3 s.

Touch localization
This parameter was assessed by touching the skin with cotton wool for 2 s.

Identification of a slowly moving stimulus
Cotton was moved slowly 10 cm in a proximal-distal or transverse direction (Wall and Noordenbos, 1977; Danziger et al., 1996), and the ability to determine whether the stimulus was moving and the direction of movement was tested.

The sensation of vibration
Vibration sensation was tested using an electronic vibrometer (Somedic AB, Sweden) (Goldberg and Lindblom, 1979). The vibration frequency was 120 Hz, the application pressure was kept at ~650 g, and the amplitude was given as peak to peak amplitude. The average of the vibration perception threshold (the lowest amplitude at which the vibration was perceived) and the vibration disappearance threshold (the amplitude at which the vibration disappeared) was taken as the vibration threshold; the average of three consecutive measurements was used as the final threshold.

Thermal sensation
Thermal thresholds were determined by the Medoc Thermotest (TSA 2001, Israel) with a thermode of Peltier elements measuring 32 × 32 mm. From a baseline temperature of 30°C, temperatures changed at a rate of 1°C/s (cut-off limits at 50.5 and 0°C). Warm and cold detection thresholds, heat pain thresholds, heat pain tolerance thresholds and cold pain thresholds (in that order) were recorded using the method of limits. Thresholds were calculated as the average of five successive measurements with a random interstimulus interval of 3–6 s (two measurements for heat tolerance thresholds).

Pressure pain
Pressure pain threshold and pressure pain tolerance threshold were assessed over the anterior tibial muscle using a hand-held electronic pressure algometer (Somedic AB, Sweden), as described previously (Brennum et al., 1989), with a circular probe (1 cm²) and a pressure rate of 30 kPa/s. The thresholds were calculated as the mean value of three (two for tolerance threshold) consecutive determinations with an interstimulus interval of 60 s and expressed in kPa. The cut-off limit was 1200 kPa.

Skinfold pinch pain
Pain and pain tolerance thresholds were estimated by the use of a forceps coupled to the electronic algometer, and the thresholds (median of three and two determinations, respectively, as above) were expressed in kPa, with a cut-off of 1200 kPa.

Evoked pain
Evoked pain was studied below the level of injury on the dominant leg (in pain patients also in the area of maximal pain) and at injury level. At injury level, the border zone was mapped for three types of stimuli (brush, pinprick and cold)
based on methods used for mapping secondary hyperalgesic areas in experimental pain (LaMotte et al., 1991).

Brush-evoked pain and dysaesthesia. This was assessed by stroking the skin twice with a small brush at a rate of 1–2 cm/s. Allodynia was considered to be present if pain was evoked by the stimulus; the evoked pain was then measured on a VAS (0 = no pain; 10 = unbearable pain); in the absence of pain, brush-evoked dysaesthesia was recorded on a VAS (0 = no unpleasantness; 10 = unbearable unpleasantness).

Cold allodynia. Cold allodynia below the lesion level was assessed by running a thermo roll (20–22°C) twice across the skin. At lesion level, it was assessed by applying an acetone drop to the skin.

Pinprick hyperalgesia. This was considered to be present if bending a von Frey hair (no. 5.88, bending force 75.9 g/745 mN) evoked more pain than above injury level, and pain was assessed on a VAS.

Pain evoked by repetitive pinprick. This was evaluated by repetitively tapping the skin with a stiff von Frey hair driven by a computer-controlled solenoid at a rate of 2 Hz for 1 min or until pain became unbearable, as described previously (Eide et al., 1994; Gottrup et al., 1998). From a starting point where the hair is just touching the skin accurately, the hair is moved 3 mm forward and 3 mm back, contacting the skin for 300 ms. At lesion level, the tapping was performed manually. Patients quantified evoked pain on a VAS.

Statistics
For each patient, the thresholds for temperature, skinfold pinch and pressure were considered to be distributed normally, and mean values were used as final thresholds. Statistical differences between groups were calculated using one-way ANOVA (analysis of variance) or the non-parametric Kruskal–Wallis test; and between two sets of unpaired data using the unpaired t test or the Mann–Whitney U test. Correlations between non-parametric data were assessed using Spearman’s rank correlation. Fisher’s exact test was used to compare dichotomized data.

<table>
<thead>
<tr>
<th>Table 1 Subject characteristics</th>
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<tr>
<td>SCI pain patients</td>
</tr>
<tr>
<td>Number</td>
</tr>
<tr>
<td>Age (years), mean (SD)</td>
</tr>
<tr>
<td>Gender, males/females</td>
</tr>
<tr>
<td>Height (cm), mean (SD)</td>
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<td>Weight (kg), mean (SD)</td>
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</table>

*One-way ANOVA; †Fisher’s exact test; ‡Kruskal–Wallis test.

Results

Subject characteristics
The three groups were similar in terms of age, gender, height and weight (Table 1). Eleven SCI pain patients had a complete SCI (ASIA classification) while 13 SCI patients without pain had complete lesions. There were no significant differences in the two patient groups with respect to ASIA impairment scale, neurological level, Functional Independence Measure, mechanism of trauma and time since spinal injury (Table 2). Only four patients used analgesics (paracetamol, non-steroidal anti-inflammatory drug, and one also a weak opiate). On the last examination, two additional pain patients were receiving treatment with lamotrigine. SCI pain patients reported significantly more spasms than SCI pain-free patients (P = 0.00, Mann–Whitney U test), but there was no difference in spasticity measured on the Ashworth scale and grading of tendon reflexes (Table 2).

Spontaneous pain and sensory abnormalities
All patients in the SCI pain group had spontaneous pain below lesion level (Fig. 1), and all except one also described dysaesthesia: five patients had spontaneous pain at lesion level, and six patients complained of visceral pain. Onset of pain after SCI occurred within the first 6 months in 13 patients, and later in seven patients. The mean duration of pain was 14.1 years. The median pain intensity was scored as 5 (NRS 0–10). At the last examination, which was done ~1 year after the two first sessions, three patients had a decrease in pain intensity, one spontaneously and two probably attributable to lamotrigine treatment.

In general, the area of pain represented only a fraction of the body area with sensory abnormality. In 19 patients, pain was restricted to an area with altered or absent somatic sensation to pinprick or touch. One patient (no. 5, Fig. 1) had pain outside the area, with altered sensation to pinprick and touch examined by bedside tests (ASIA classification). The most frequent words used spontaneously by the patients to describe their pain and dysaesthesias were ‘pricking’ and ‘tingling’, ‘burning’ or ‘scalding’, ‘freezing’ and ‘taut’. None in the pain-free group had pain or dysaesthesia at or below SCI level, but 17 had constant or intermittent non-painful sensations described as ‘pricking’, ‘tingling’, ‘taut’, ‘warm’ or ‘throbbing’.

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Spinothalamic versus dorsal column function

Most SCI patients had impairment in all sensory modalities, mainly affecting sensibility for temperature and noxious stimuli, with no differences between the two SCI groups. Tables 3, 4 and 5 show thresholds for SCI patients compared with controls. There were no differences in any of the thresholds between pain and pain-free patients (Table 3). Three pain patients did not report pain in the area tested (nos 2, 6 and 9). We therefore compared the 17 patients with pain in the area tested with six patients with paraesthesias and 17 with no abnormal sensations in the area. There were no differences in any of the thresholds between these groups, or between the 17 patients with pain compared with 23 patients without pain in that area (Kruskal–Wallis and Mann–Whitney U test).

Spinothalamic function

This was defined as temperature or pinprick sensation. Three patients in the pain group and one in the pain-free group had detectable spinothalamic function (non-significant difference) (Tables 4 and 5). Two patients had preserved function for both warm and cold; both were in the pain group. One of these could not feel warm in the normal range but suddenly felt a strong burning painful heat at the level of tolerance; the other had warm thresholds within the range of controls, and heat pain and pain tolerance thresholds below controls (heat alldynia and heat hyperalgesia); both had decreased cold thresholds. One patient (pain free) had detectable cold but no warm sensation within the temperature range. Pinprick sensation was preserved in four patients (Tables 4 and 5). All three patients in the pain group with signs of preserved spinothalamic function had pain in the area tested.

Vibration sense

Vibration sense as a proper dorsal column function has been questioned (Cook and Browder, 1965; Calne and Pallis, 1966). Seven pain and six pain-free patients had a detectable vibration threshold. If the vibration sense was included in dorsal column function, seven pain and seven pain-free
patients had some degree of preserved dorsal column function (Tables 4 and 5).

**Sensory hypersensitivity**

**History**

Eight pain and no pain-free patients reported allodynia (pain evoked by normally non-painful stimuli) ($P = 0.003$, Fisher's exact test) (Table 2). All eight patients had alldynia to touch, and one also reported cold allodynia. Only one patient described alldynia in the area of central pain, while seven described alldynia in dermatomes at lesion level. Additionally, one patient described more widespread alldynia in periods with severe pain, e.g. in these periods his face is so sensitive that he cannot shave.
Furthermore, several patients reported that light touch provoked spasms, some of which were painful. Patients with allodynia (n = 8) had a significantly higher intensity of spontaneous pain (median 7, range 3–8) than patients who did not report allodynia (median 4, range 3–7) (P = 0.031, Mann–Whitney U test).

Fig. 1 (A) Area of absent or impaired sensation to pinprick or light touch. The examination was done in two key points in each of 28 dermatomes according to the ASIA classification (Maynard et al., 1997). (B) Area of spontaneous pain in 20 SCI pain patients.
Evoked pain or dysaesthesia below level

In the areas tested, four pain patients had evoked pain (three had cold allodynia when examined with the thermo roll, three had pinprick hyperalgesia and three had pain evoked by repetitive pinprick) (Table 4). No pain-free patients had evoked pain below injury (Table 5).

Evoked pain or dysaesthesia at injury level

Hyperaesthesia. When screening the border zone, significantly more pain patients than pain-free patients (14 versus six) reported hyperaesthesia to one of the stimulations applied (brush, pinprick or cold) \( (P = 0.026, \text{Fisher’s exact test}). \)

Brush-evoked allodynia or dysaesthesia. Nine pain and no pain-free patients had brush-evoked pain or dysaesthesia \( (P = 0.001, \text{Fisher’s exact test}). \) The intensity of brush-evoked pain or dysaesthesia at lesion level was significantly higher in SCI patients with pain than in patients without pain \( (P = 0.001, \text{Mann–Whitney} U \text{test}) \) (Fig. 2).

Cold-evoked dysaesthesia. Dysaesthesia to an acetone droplet was seen in two pain and no pain-free patients (non-significant difference).

Pinprick hyperalgesia. Nine pain versus three pain-free patients had pinprick hyperalgesia (non-significant difference). The intensity of pinprick hyperalgesia at lesion level was significantly higher in SCI patients with pain than patients without pain \( (P = 0.028, \text{Mann–Whitney} U \text{test}) \) (Fig. 2).

Pain to repetitive pinprick. Seven patients in each group had pain evoked by repetitive pinprick (Tables 4 and 5), and no difference was found in intensity of pain evoked by repetitive pinprick between the two patient groups (Fig. 2). The evoked pain was clearly different from several segments above the border zone. One patient had pain evoked by repetitive pinprick that did not differ from above injury (face), and he was not included as having pain evoked by repetitive pinprick at level. Pain evoked by repetitive pinprick was present typically at and just above the border zone, and the sensation of pain started within the first seconds.

Correlation between at level evoked sensations and below level spontaneous pain

Within the pain group, 10 patients had brush- and/or cold-evoked dysaesthesia and/or pinprick hyperalgesia (two patients with wind up-like pain only not included) compared with three patients without pain \( (P = 0.041, \text{Fisher’s exact test}) \) (Tables 4 and 5). The 10 pain patients with evoked pain or dysaesthesia at lesion level had significantly higher intensities of spontaneous pain and higher intensities of spasms than the 10 patients without evoked pain at level \( (P = 0.03 \text{ and } 0.004, \text{respectively, Mann–Whitney} U \text{test}) \), and more patients with evoked pain reported paroxysms (seven versus one, \( P = 0.044, \text{Fisher’s exact test} \)). The intensity of evoked sensations to brush at lesion level was significantly correlated to the intensity of spontaneous central pain below lesion level (Spearman’s \( r = 0.60, P = 0.005, n = 20 \)), and to intensity of spasms (Spearman’s \( r = 0.65, P = 0.002, n = 20 \)).

The intensity of pinprick hyperalgesia was correlated to the intensity of spasms (Spearman’s \( r = 0.61, P = 0.004, n = 20 \)) but not to the intensity of spontaneous pain \( (P = 0.08) \). The intensity of wind up was not correlated to the intensity of spontaneous pain or to spasms \( (P = 0.78 \text{ and } 0.75, \text{respectively}) \).

Five patients (nos 1, 5, 10, 12 and 16, Fig. 1) had at level spontaneous ongoing pain (defined as pain within two dermatomes below the neurological level) in addition to the below level pain. However, in all of these patients, the most severe pain was the below level pain. Four of these five patients had evoked pain at level compared with six of 15 without at level spontaneous pain (non-significant difference). To study if the co-existence of at level ongoing pain had any influence on the results, we performed the calculations without these five patients. The six pain patients with only evoked pain or dysaesthesia at lesion level still had significantly higher intensities of spontaneous pain and higher intensities of spasms than the nine patients without evoked or spontaneous pain at level \( (P = 0.03 \text{ and } 0.04) \), and now intensity of evoked sensations to both brush and pinprick were positively correlated to spontaneous pain and spasms \( (P = 0.009 \text{ and } 0.02, \text{respectively, for brush, and } P = 0.04 \text{ and } 0.04, \text{respectively, for pinprick}) \).

Discussion

This study analysed pain, quantitative sensory measures and somatosensory evoked responses in SCI patients with and without pain below injury level and compared these with findings in a gender- and age-matched control group without injury. The main finding is a higher intensity of brush-evoked dysaesthesia and pinprick hyperalgesia at the lesion level in SCI patients with central pain as opposed to SCI patients without pain below injury level, despite a similar degree of lost somatosensory function in the two groups. These findings suggest that neuronal hyperexcitability expressed as hypersensitivity at the segmental lesion level is an important mechanism underlying pain below injury level. This notion is supported further by the demonstration of a significant correlation between brush-evoked pain intensity at lesion level and spontaneous pain below lesion level of SCI. Previous studies (Eide et al., 1996; Defrin et al., 2001), including SCI patients with pain at and below lesion level, have also suggested that neuronal hyperexcitability could play a role in pain in SCI patients. However, since these studies have included at level pain and lumbar lesions, a clear distinction between central and peripheral components of the pain is difficult (Siddall et al., 1997).
Neuronal hyperexcitability

Brush-evoked pain or dysesthesia in the border zone at the lesion level was only seen in pain patients, and in most patients it was seen in areas with no spontaneous pain present. The severity of brush-evoked allodynia in the area of spontaneous pain has been correlated previously to intensity of ongoing pain in neuropathic pain conditions, e.g. in postherpetic neuralgia (Rowbotham and Fields, 1996). However, this is the first study, to our knowledge, to show a correlation between the intensity of evoked symptoms along the edge of the damaged dermatome at the level of lesion, and intensity of spontaneous below level pain and intensity of spasms. Evoked pain and dysesthesia in pain areas below lesion level were only present in a few patients, all with incomplete SCI. However, at level evoked pain and dysesthesia were present in both complete and incomplete SCI, which may indicate that hyperexcitability is also present in complete SCI. These findings suggest that mechanisms sustaining spontaneous pain and evoked dysesthesia and motor excitability share common mechanism(s), and we believe that a neuronal hyperexcitability due to loss of input to certain populations of neurons and/or a lack of inhibition could be responsible for this effect.

Brush-evoked pain (mechanical allodynia) is a classical feature of peripheral neuropathic pain and is considered to be a manifestation of central neuronal hyperexcitability driven from peripheral abnormal afferent fibres or from sensitized dorsal root ganglion cells (Jensen et al., 2001). The allodynia seen in patients with central pain is less clear. Previous studies in post-stroke pain indicate that the pain is linked to brush-evoked pain or dysesthesia and increased thermal and pinprick sensation in the painful denervated body parts (Andersen et al., 1995; Vestergaard et al., 1995). These observations have led to the proposal that post-stroke pain is caused by the development of neuronal hyperexcitability in neurons that have lost their normal patterned afferent input. A similar mechanism may also play a role in the occurrence of SCI pain in segmental body parts below the cord injury level.

The rostral level at which hyperexcitability responsible for evoked and spontaneous pain occurs is not known, and may include higher structures. In SCI pain patients, hyperexcitability in spinal (Loeser et al., 1968) and thalamic neurons (Lenz et al., 1994) has been found. In animal studies of SCI, spinal grey matter lesions and hyperexcitability of dorsal horn neurons adjacent to spinal injuries have been related to at level pain (Hao et al., 1992; Yezierski and Park, 1993; Christensen and Hulsebosch, 1997; Drew et al., 2001). The influence of abnormal activity in the dorsal horn on below level pain has been unclear. Animal studies point to a relationships between at level and below level neuropathic pain, and suggest below level neuropathic pain to be a result of a combination of long tract deafferentation and an activation of rostral targets by other sources of spinal activity (for a review see Vierck et al., 2000).

Pharmacological studies lend support to the importance of neuronal hyperexcitability for SCI pain. Lidocaine, which is thought to inhibit nerve membrane hyperexcitability by blocking voltage-sensitive sodium channels, and ketamine, which blocks NMDA (N-methyl-D-aspartate) receptors and thereby glutamatergic excitation, are effective in SCI at and below level pain (Loubser and Donovan, 1991; Eide et al., 1995; Attal et al., 2000). Increasing GABAergic inhibition

<table>
<thead>
<tr>
<th>Table 3 Threshold medians (ranges) at the dominant calf in controls, incomplete SCI pain patients and incomplete SCI pain-free patients</th>
<th>Controls (n = 20)</th>
<th>SCI pain patients (n = 9)</th>
<th>SCI pain-free patients (n = 7)</th>
<th>P*</th>
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<td>VT (μm)</td>
<td>2.27 (0.8–4.04)</td>
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<td>18.8 (3.1–150)</td>
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<td>PPT (kPa)</td>
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<td>1200 (233–1200)</td>
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<td>SFT (kPa)</td>
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<td>SFTT (kPa)</td>
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<td>(log 0.1 mg)</td>
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<td>CDT (°C)</td>
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<td>0 (0–21.7)</td>
<td>0 (0–23.8)</td>
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<td>CPT (°C)</td>
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<td>HPT (°C)</td>
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*SCI pain versus SCI pain-free group, Mann-Whitney U test. CDT = cold detection threshold; CPT = cold pain threshold; HPT = heat pain threshold; HPTT = heat pain tolerance threshold; PPT = pressure pain threshold; PPTT = pressure pain tolerance threshold; SFT = skinfold pinch pain threshold; SFTT = skinfold pinch pain tolerance threshold; TDT = tactile detection threshold to single stimuli; TPT = tactile pain detection threshold; VT = vibration threshold; WDT = warm detection threshold.
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<th>SCI patients with pain (n = 20)</th>
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<th>Pain intensity*</th>
<th>Localize touch</th>
<th>Direction sense</th>
<th>SEP Vibration</th>
<th>Von Frey 0.41–447 g</th>
<th>Pressure pain –1200 kPa</th>
<th>Pinch pain</th>
<th>Pinprick</th>
<th>Cold 30–0°C</th>
<th>Warm 30–50.5°C</th>
<th>Evoked pain below level¹</th>
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*Neurological level; *parentheses indicate pain intensity on the last examination (at level hypersensitivity) in patients with a decrease in pain from first to last examination; ³brush or cold allodynia, pinprick hyperalgesia and/or pain evoked by repetitive pinprick below the injury level; ²evoked dysaesthesia or pain to brush or cold and/or pinprick hyperalgesia in dermatomes at injury level; ¹pain evoked by repetitive pinprick at injury level. ASIA class: see footnotes to Table 2.

→ = normal, ↓ = decreased, ↑ = increased, − = absent, + = present, NA = not accessible (if patients did not volunteer for SEP, or if pressure and pinch were not possible because of evoked spasms or autonomic reactions).
Table 5  QST and SEPs below the level of injury and evoked sensations below and at the level of injury in SCI patients without pain

<table>
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<tr>
<th>SCI patients without pain (n = 20)</th>
<th>ASIA class</th>
<th>Level*</th>
<th>Localize touch</th>
<th>Direction sense</th>
<th>SEP</th>
<th>Vibration &lt;150 μm</th>
<th>Von Frey 0.41–447 g</th>
<th>Pressure pain –1200 kPa</th>
<th>Pinch pain –1200 kPa</th>
<th>Pinprick</th>
<th>Cold 30–0°C</th>
<th>Warm 30–50.5°C</th>
<th>Evoked pain below level²</th>
<th>Evoked sensations at level³</th>
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See footnotes to Table 4.
with either baclofen or propofol is also effective (Herman et al., 1992; Canavero et al., 1995). Lamotrigine, an antiepileptic drug affecting sodium channels and excitatory amino acids involved in neuronal hyperexcitability, is also suggested to be effective in SCI patients with spontaneous and evoked neuropathic pain (Finnerup et al., 2002a).

In the present study, not all patients exhibited signs of hyperexcitability. A similar lack of clinical hyperexcitability has also been noted in post-stroke pain (Andersen et al., 1995; Vestergaard et al., 1995), and in central neuropathic pain due to multiple sclerosis (Svendsen et al., personal communication). While this may indicate that other mechanisms are at play, another possibility is that the clinical measures are not sensitive enough to detect hyperexcitability. Alternatively, it is possible that hyperexcitability had been present at some earlier time point after injury, since allodynia seems to have an early onset (Siddall et al., 1999).

**The spinothalamic and dorsal column pathways and pain**

This study shows that pain is present in those areas with lost afferent input. This observation is similar to what is seen in post-stroke pain, another central pain condition (Vestergaard et al., 1995). The role of the spinothalamic tract in mediating pain is well known (Willis and Westlund, 1997). Clinical studies have also shown that lesioning of the spinothalamic tract or its cortical projection sites plays an important role in the development of central neuropathic pain (Boivie et al., 1989; Vestergaard et al., 1995). In agreement with other reports on SCI pain (Eide et al., 1996; Defrin et al., 2001), the present study found that spinothalamic tract damage may be a necessary but not sufficient condition for the development of SCI below level pain, since deficits of spinothalamic functions (pinprick and temperature sensation) were equally severely affected in SCI patients without pain. Interestingly, one previous study compared stroke patients with and without central pain and found that central post-stroke pain patients with supratentorial lesions had larger deficits of AΔ-fibre-mediated sharpness and cold than pain-free stroke patients, and infratentorial pain patients additionally had a deficit of C-fibre-mediated warmth and hot pain (Bowsher et al., 1998). Their study also showed that alldyic central post-stroke pain patients had greater deficits for warmth than patients without alldynia. A comparison between allodynia and small fibre function cannot be done in the present study where only three patients had any signs of preserved thermal sensibility.

The present study could not confirm the imbalance theory proposed by Beric et al. (1988), which suggests that dysfunction of the spinothalamic tract and preservation of the posterior columns are prerequisites for development of central pain. This may be related to different methodology used to access spinothalamic and dorsal column function or to the criteria used for classification. In this study, dorsal column function was defined as preserved knowledge of movement or position (Wall and Noordenbos, 1977; Nathan et al., 1986; Danziger et al., 1996) or preserved SEP (Halliday and Wakefield, 1963; Dimitrijevic et al., 1983). Vibration sense was not included in dorsal column functions since studies have suggested that combined lesions of dorsal and posterolateral columns are necessary to abolish sense of vibration (Cook and Browder, 1965; Calne and Pallis, 1966). Furthermore, vibration threshold was difficult to determine correctly because of projection of vibration to areas with preserved sensation, variability of threshold, persistence of sensation, and presence of spontaneous or evoked sensations that were difficult to separate from true vibration sense. Pinprick and temperature sensation were used as predictors of the spinothalamic tract function (Willis and Westlund, 1997). Further studies are needed to clarify the role and interaction of spinothalamic tract and dorsal column in pain.

**Conclusions**

The present study shows pain in body segments below a spinal cord lesion to be linked to the presence of abnormal evoked sensations in segments at the level of injury, suggesting that neuronal hyperexcitability in second or third order neurons, which have lost their normal afferent input, is an important mechanism for pain below spinal injury.

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