

# Sensory determinants of thermal pain

Ruth Defrin,<sup>1</sup> Avi Ohry,<sup>3</sup> Nava Blumen<sup>3</sup> and Gideon Urca<sup>2</sup>

Departments of <sup>1</sup>Physiotherapy and <sup>2</sup>Physiology and Pharmacology, Sackler School of Medicine, Tel-Aviv University, Ramat Aviv and <sup>3</sup>Department of Neurorehabilitation, Sheba Medical Center, Tel-Hashomer, Israel

Correspondence to: Gideon Urca, Department of Physiology and Pharmacology, Sackler School of Medicine, Tel-Aviv University, Ramat Aviv, Israel 69978  
E-mail: gurca@post.tau.ac.il

## Summary

It is still unclear whether the quality of painful thermal sensation is determined only by conduction in specific, dedicated nociceptive channels (i.e. C or A $\delta$  nociceptors) or whether it is a result of integrated activity in both nociceptive and non-nociceptive systems. To evaluate this question, we conducted quantitative and qualitative somatosensory testing in spinal cord injury subjects who suffered from partial or complete loss of thermal sensibility. Testing was performed in skin areas, below the level of the lesion, which were either lacking any thermal sensibility, lacking only one thermal sensation (either heat or cold) or having normal thermal sensations. We found that, in areas lacking any thermal sensibility, warm and cold stimuli produced a sensation of pricking pain, which had no thermal quality and was detected at significantly higher thresholds than in normal controls ( $48.5 \pm 1.8$  and  $9.7 \pm 5.1^\circ\text{C}$  for noxious heat- and noxious cold-induced pricking pain, respectively). Normal thermal pain sensations, consisting of normal perception of thermal quality and normal mean pain thresholds, were present both in normal skin areas ( $42.1 \pm 1.9$  and  $27.6 \pm 2.25^\circ\text{C}$  for heat and cold pain, respectively) and in areas in which only one thermal

modality remained intact, when tested for that modality. Thus, testing for heat pain in areas in which only warm sensation was intact, or cold pain when only cold was intact produced normal qualities and thresholds of pain ( $42.8 \pm 3.4$  and  $24.4 \pm 6.2^\circ\text{C}$  for heat and cold pain, respectively). No spatial summation of pricking pain was observed, in contrast to the marked summation of heat pain in normal areas. In areas with only a single intact thermal modality, the quality of the perceived non-painful sensation was not determined by the thermal stimulus but by the intact modality (paradoxical sensation). Cold stimuli were perceived as warm in areas in which only warm sensation was preserved, and vice versa. A similar pattern was also seen for pain perception in areas with intact warm sensation. In these areas, both noxious heat and cold elicited a sensation of heat pain. No consistent pattern of heat-elicited pain was observed in areas in which only cold sensation was intact. These data suggest that the integrity of non-noxious thermal systems is essential for the normal perception of thermal pain, and that the subjective sensation of pain depends on the integration of information from nociceptive and non-nociceptive channels.

**Keywords:** thermal pain; pain quality; paradoxical sensations; specificity

## Introduction

Pain is a multifaceted sensation. Different qualities are attributed to painful sensations, such as burning, pricking, pressing and others (Melzack and Torgerson, 1971; Melzack, 1975). While the physical stimuli producing different acute pain qualities are often readily definable, the neural processes determining the quality of perceived pain are not clear. Several hypotheses have been developed in the attempt to explain these processes. One early view is the 'pattern theory of pain' (Goldscheider, 1894; Sinclair, 1955). This theory proclaims that pain is signalled via non-specific channels concerned with conduction of both nociceptive and non-nociceptive events. Painful, as opposed to non-painful sensations are thus signalled by means of different frequen-

cies and patterns of activation of these channels. This 'pattern theory of pain' was discarded rapidly once specific receptor organs specializing in the detection of noxious stimuli were identified (Vallbo and Hagbarth, 1968; Van Hees and Gybels, 1972; Torebjörk and Hallin, 1979; Willis, 1985). Furthermore, intense stimulation of the known non-nociceptive pathways under normal circumstances never induces painful sensations, as predicted by the pattern theory (Vallbo, 1981; Schady *et al.*, 1983; Torebjörk and Ochoa, 1983; Willis, 1985).

A contradictory view was developed later following the 'law of specific sense energies' introduced by Muller (1826) and accepted by many scientists. According to this view, the

coding mechanism for the modality of an entire sensory pathway from the receptor to the cortex is defined by receptor and nerve fibre specificity (Kandel *et al.*, 1995). Since this theory of a 'labelled-line code' maintains that pain is processed by dedicated pain pathways, it predicts that excitation of a particular nociceptor by a stimulus always elicits the same quality of pain, regardless of the stimulus energy.

An alternative and third view is that the perception of pain is not monopolized by the peripheral receptor properties of nociceptors. Rather, central processes integrate sensory information including those derived from the response of nociceptors to produce the threshold, intensity and quality of sensations, of which pain is one (Wall and McMahon, 1986).

The labelled-line theory of pain perception is the one espoused by most pain researchers (Perl, 1998). However, despite its wide acceptance, no conclusive evidence for the validity of this approach is available. Confirmation of this theory can be obtained on two conditions: (i) selective and exclusive stimulation of given nociceptors will invariably produce the same sensation; and (ii) activation or elimination of non-noxious sensations will not affect the quality of nociception elicited by stimulation of nociceptors.

The present study examines the quality of thermal nociception in spinal cord injury patients in whom non-noxious thermal sensations (either warmth, cold or both) are absent (condition B), but who still perceive noxious stimuli. Our results show that the quality and intensity of nociception in these patients are highly dependent on conduction in non-noxious channels. Thus, our results lend strong support to the notion that the quality of pain is determined by central integrative processes utilizing sensory information conveyed, simultaneously, by both dedicated pain pathways and non-nociceptive pathways.

## Material and methods

### Subjects

A total of 77 subjects, both male and female, participated in this study. Twenty-eight of the subjects suffered from partial spinal cord injuries at the level of L1–T4 (average age  $37.9 \pm 8.2$  years). Thirty-one suffered from complete spinal cord injury (average age  $38.3 \pm 9.5$  years). Eighteen subjects were intact, healthy volunteers (average age  $35.6 \pm 7.4$  years). Spinal cord injury subjects included in this study were recruited from the out-patient population of the Sheba rehabilitation centre (Tel Hashomer, Israel) on a voluntary basis. They were all paraplegics subsequent to traumatic spinal injuries (mainly due to car accidents). All spinal cord injury patients underwent a thorough neurological examination, prior to testing, to determine their sensory profile and extent of spinal damage (Ditunno, 1994). Patients suffering from disease causing potential neural damage (e.g. diabetes), systemic illness, skin lesions and mental disorders were excluded from this study. Subjects with communication

difficulties, such as language problems, hearing or speech disorders, were also excluded. Those spinal cord injury subjects who regularly used analgesic medications were asked to refrain from using such medication on the day of testing.

Experiments were approved by both the Tel Aviv University and the Sheba Medical Center human rights committees. All subjects participated in this study on a voluntary basis. Informed consent was obtained from all subjects after receiving a full explanation of the goals and protocols of the study.

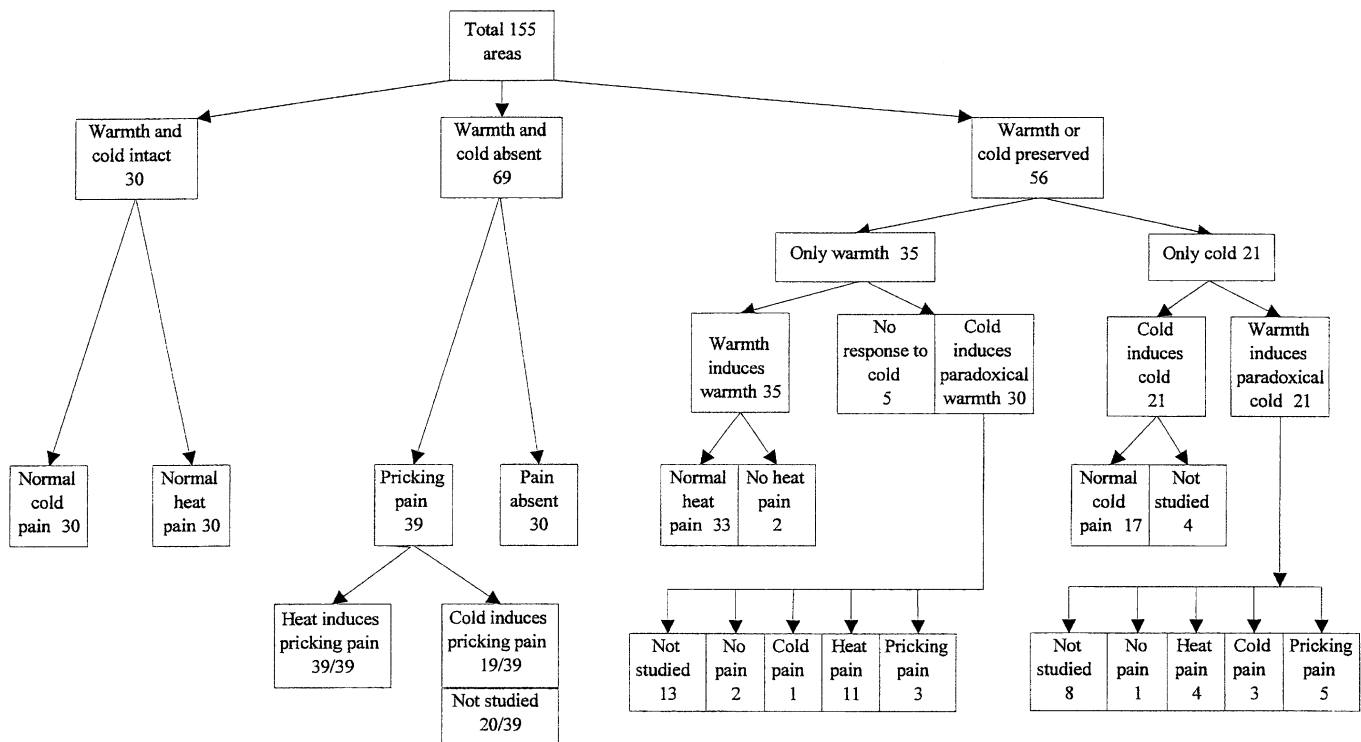
Testing took place in a quiet room. The temperature in the room was maintained at  $22 \pm 2^\circ\text{C}$ . The subjects were seated in their wheelchairs or a comfortable armchair with the tested limb resting on a supporting structure. Testing was repeated three times on each subject with a minimal interval of 1 week separating the trials.

Sensory testing was conducted on the back of the hand, and in the legs (mid thigh, shin, and the dorsal part of the foot). None of the spinal cord injury subjects had either sensory or motor impairments of the hand; therefore, the hand testing area was used as the 'normal' reference area for all subjects. In intact subjects, sensory threshold values did not vary between the three leg areas and were therefore treated as one test zone. In those patients suffering from partial spinal cord injury, the leg areas comprised regions with complete or partial sensory damage and regions with completely normal sensory function (Defrin *et al.*, 2001). Comparisons were, therefore, performed between normal and abnormal skin areas. A total of 367 skin areas were examined; 154 of them in the back of the hand (36 in intact controls and 118 in spinal cord injury patients) and 213 in the leg areas (58 in intact controls and 155 in partial spinal cord injury patients).

### Thermal testing

Sensations of warm, cold, heat pain and cold pain were tested to evaluate spinothalamic function (Willis, 1985; Nathan *et al.*, 1986). The threshold of each thermal sensation was measured by means of a Peltier-based computerized thermal stimulator (TSA 2001; Medoc Inc., Ramat Ishai, Israel), with a  $4.8 \times 3.2$  cm contact probe. The principles of the Peltier stimulator have been described elsewhere (Fruhstorfer *et al.*, 1976; Wilcox and Giesler, 1984; Verdugo and Ochoa, 1992). Briefly, passage of current through the Peltier element produced temperature changes at rates determined by an active feedback system. As soon as the target temperature was attained, probe temperature actively reverted to a pre-set adaptation temperature by passage of an inverse current.

Warm, cold, heat pain and cold pain thresholds were measured using the method of limits (Gescheider, 1985). The contact probe was attached to the skin of the subject by means of a Velcro band. For warm and cold threshold determination, subjects received four successive ramps of gradually increas-



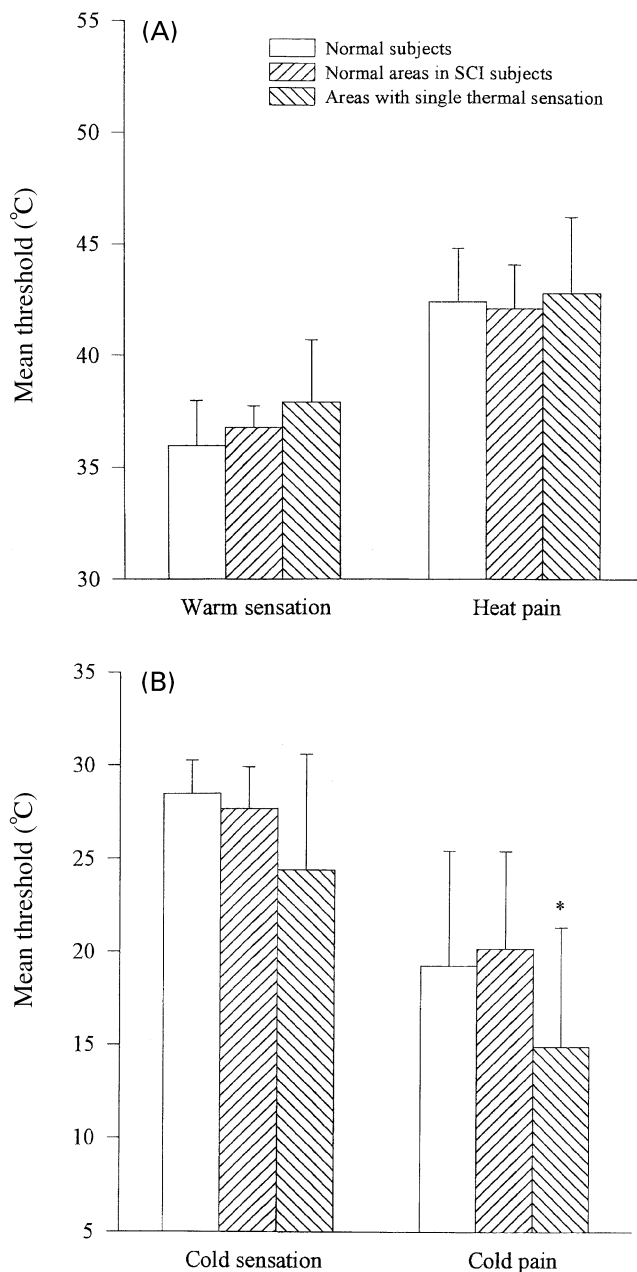
**Fig. 1** Thermal sensations below the level of injury in skin areas of patients suffering from partial spinal cord damage. The numbers denote skin areas.

ing or decreasing temperature, starting from a baseline temperature of 32°C, at a rate of 2°C/s. Thermal stimuli were applied every 15 s. The subjects were asked to press a switch when a thermal sensation (either warm or cold) was first perceived, thus defining the thermal threshold for that stimulus presentation. Pressing the switch resulted in automatic recording of the threshold temperature and reset the probe temperature to baseline values. In those cases in which subjects did not detect the thermal stimulus, the system returned automatically to baseline levels once temperatures had reached a pre-set value (0 and 54°C for cold and hot stimuli, respectively). Warm and cold thresholds were computed by averaging the reading of four successive stimuli in each session. To determine heat pain and cold pain threshold, we followed a similar protocol. Four successive stimuli were applied at 30-s intervals to minimize tissue damage (Yarnitsky and Ochoa, 1990b; Verdugo and Ochoa, 1992). Baseline temperature was 35°C, and the rate of temperature change was 2°C/s. During each stimulus, the subject was asked to press a switch when the first pain sensation was perceived, defining pain threshold for this trial. Heat pain and cold pain thresholds were computed by averaging the readings of four successive trials in each session.

A subject's response was considered normal if the thermal threshold of that subject was within 2 SD of the group mean of the normal volunteers.

### *Changes in the quality of sensation*

The quality of thermal sensation evoked by the stimuli during threshold testing was assessed. Testing was performed first in intact areas and only then was testing of areas with sensory impairment conducted. Stimuli (warm, cold) were presented randomly, so the subjects did not know which stimulus would be delivered. Once stimulation ended, the subject was requested to report the quality of the sensation produced by the stimulus. A normal response to non-noxious stimuli was one in which the subject detected gradual warming or cooling in response to gradually increasing or decreasing thermal stimuli, respectively. Normal thermal nociception was defined as one in which the subject identified the nature of the painful thermal stimulus correctly (heat pain or cold pain). Paradoxical cold was defined as a perception of cold in response to a gradually increasing thermal stimulus, relative to baseline. Inversely, paradoxical warm was defined as a perception of heat in response to a gradually decreasing thermal stimulus. Similarly to non-painful paradoxical sensations, paradoxical cold pain was defined as a perception of cold pain in response to a gradually increasing thermal stimulus, and paradoxical heat pain was defined as a perception of heat pain in response to a gradually decreasing thermal stimulus. Complete absence of a thermal sensation was established if the subject did not perceive warming or cooling to



**Fig. 2** Innocuous and noxious thermal thresholds in normal subjects, intact skin areas below the lesion in spinal cord injury subjects and areas with a single thermal sensation (either warm or cold) in these subjects. Except for cold pain threshold in areas with a single thermal sensation (\* $P < 0.05$ ,  $t$ -test), thermal thresholds in spinal cord injury subjects were not different from normal thresholds (bars denote group mean  $\pm$  standard deviation).

thermal stimuli up to the cut-off values of the stimulation system (0 and 53°C). Painful sensation, elicited by thermal stimulation in the noxious range, reported by the subject to be one of sharp or pricking pain, and not identified by the subject as possessing a thermal quality, was defined as pain lacking thermal quality.

### *Spatial aspects of pain threshold*

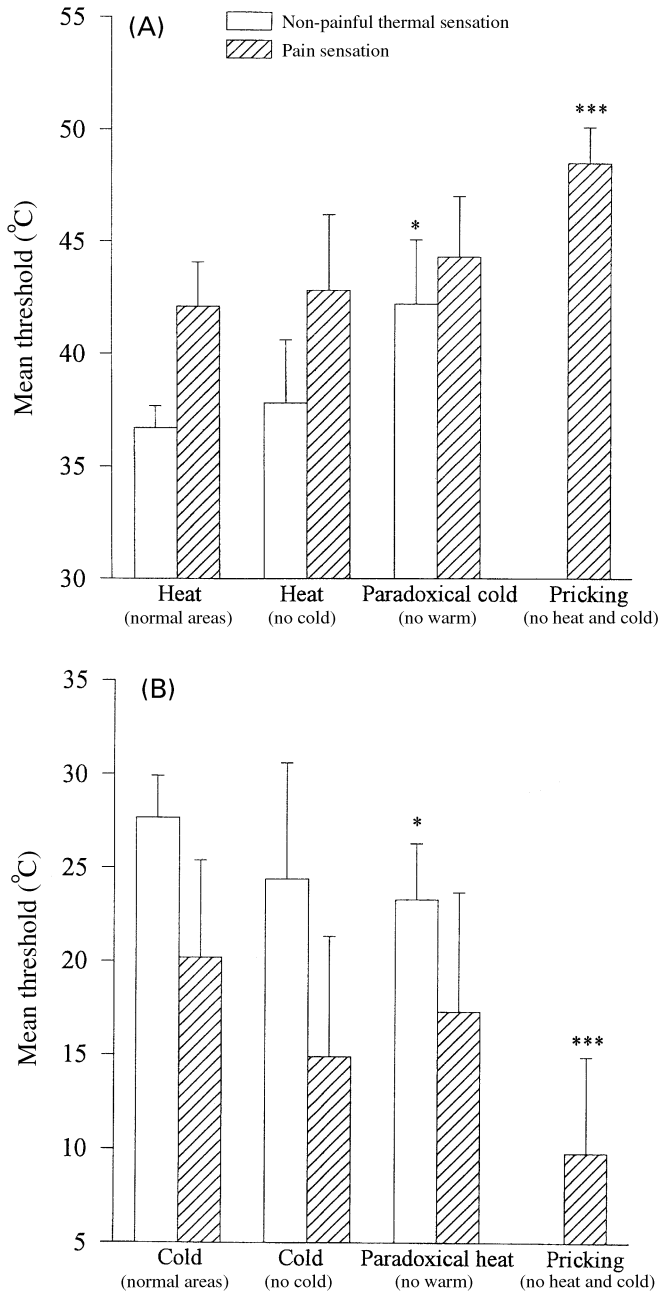
Thermal pain quality has been reported to vary with stimulation area (Melzack and Wall, 1962; Chery-Croze and Duclaux, 1980), and thermal pain thresholds appear to increase with decreased stimulation area (Defrin and Urca, 1996). To examine whether similar effects can be observed in regions in which thermal nociception was impaired, nociception induced by stimuli of different areas was employed. Threshold testing and qualitative assessment were performed as described previously (Defrin and Urca, 1996). Briefly, a  $4.8 \times 3.2$  cm sheet of insulating material (soft plastic insulation material 0.3 mm in thickness), hollowed in the centre, was interposed between the probe and the skin. This thermal insulation material was selected to ensure contact between the exposed part of the probe and the skin. Contact areas of 0.25, 2.25, 6.25 and 15.36 cm<sup>2</sup> were used. Heat pain threshold and qualitative assessment of thermal sensation evoked by heat stimuli were performed for each of the stimulation areas on the back of the hand of all subjects, and below the level of the lesion in partial spinal cord injury patients.

### **Results**

Figure 1 shows the distribution pattern of the thermal sensations below the level of injury in patients suffering from partial spinal cord damage. As can be seen, normal thermal pain sensation was observed in those areas with normal warm and cold sensations. In contrast, in areas completely lacking non-noxious thermal sensations, high intensity noxious thermal stimulation, when eliciting pain, invariably produced a sensation of pricking pain devoid of any thermal characteristics. Furthermore, in those areas showing a loss of only one of the thermal modalities (either warm or cold), the quality of the perceived stimulus was dictated by the intact modality. Thus, if warm sensation was intact in a certain skin area, warm innocuous and noxious stimuli were perceived correctly. In the same region, cold stimuli elicited paradoxical sensations of warmth and heat pain, respectively. A similar (though inverse) pattern of paradoxical innocuous cold sensations was elicited by warming in all the areas in which only cold sensation was intact. In contrast, paradoxical cold pain sensation was detected only in a few patients.

Thresholds for warm and heat pain sensations were almost identical in the legs of intact subjects and in 'normal' skin regions of partial spinal cord injury patients (Fig. 2A). Warm and heat pain thresholds, in impaired areas in which only warm sensation was intact, were almost identical to those seen in 'normal' regions ( $37.8 \pm 2.8$  and  $36.7 \pm 0.9^\circ\text{C}$  for warm, and  $42.8 \pm 3.4$  and  $42.1 \pm 1.9^\circ\text{C}$  for heat pain, respectively) (Fig. 2A). Cold stimulation of most of the impaired areas (30 of 35) elicited paradoxical warm sensations (mean threshold of  $23.3 \pm 2.6^\circ\text{C}$ ) (Fig. 3B). Of those areas in which additional testing was conducted ( $n = 17$ ),

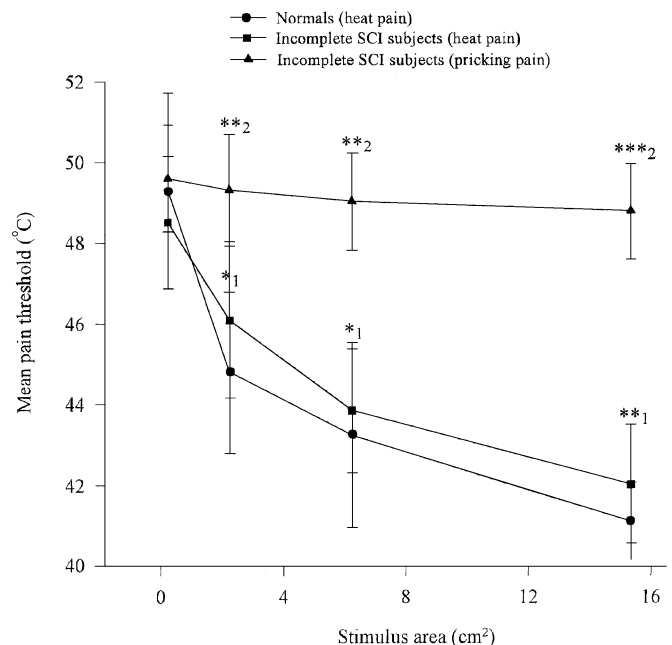
most areas ( $n = 11$ ) responded to further cooling with a sensation of paradoxical heat pain ( $17.3 \pm 6.4^\circ\text{C}$ ) (Fig. 3B). In three of the remaining areas, further cooling produced pricking pain ( $18.4 \pm 9.2^\circ\text{C}$ ), cold pain was elicited in one



**Fig. 3** Innocuous and noxious thermal thresholds in spinal cord injury subjects. Both innocuous and noxious thermal thresholds of the intact modality, in areas with a single sensation, were normal. However, stimulation of the missing modality (e.g. cold in areas with only heat sensation) produced a paradoxical thermal sensation with a higher threshold than normal ( $*P < 0.05$ ,  $t$ -test) and paradoxical pain. Thermal stimulation of areas with no thermal sensations produced pricking pain with thresholds higher than those of normal thermal pain ( $***P < 0.001$ ,  $t$ -test) (bars denote group mean  $\pm$  standard deviation).

area, and two areas supported no painful sensation in response to noxious cold stimulation (not shown).

Cold and cold pain sensations were also normal in intact skin areas of partial spinal cord injury patients (Fig. 2B). In areas in which only cold sensation was preserved, a similar pattern to the one previously described could be discerned. Thus, in all areas ( $n = 21$ ), a decrease in temperature was perceived as cold and an increase in temperature was also perceived as cold. Cold thresholds for cooling were elevated when compared with those in normal skin areas in the same patients, though not significantly ( $24.4 \pm 6.2$  and  $27.6 \pm 2.25^\circ\text{C}$ , respectively) (Fig. 3B). Further cooling, in those areas tested ( $n = 17$ ), produced a sensation of cold pain. Cold pain threshold temperatures were significantly lower when compared with those of normal skin areas in the same patients ( $14.9 \pm 6.4$  compared with  $20.2 \pm 5.2^\circ\text{C}$ , respectively,  $P < 0.05$ ) (Fig. 3B). Paradoxical responses could also be observed in these areas in response to warming. Thus, warming produced sensations of paradoxical cold in all subjects with no warm sensation ( $n = 21$ , mean threshold of  $42.2 \pm 2.8^\circ\text{C}$ ). Paradoxical cold pain, however, was only observed in three of the 13 sites tested ( $44.3 \pm 2.7^\circ\text{C}$ ) (Fig. 3A). The sensation produced by warming in five additional sites was that of pricking pain (mean threshold  $48.3 \pm 1.3^\circ\text{C}$ )



**Fig. 4** Spatial summation of heat pain (in normal subject and in intact areas below the lesion of spinal cord injury subjects) and lack of spatial summation of pricking pain [areas in spinal cord injury (SCI) subjects with no thermal sensations]. Heat pain thresholds decreased with the increase in stimulus area ( $*P < 0.05$ ,  $**P < 0.01$ ,  $t$ -test) and were significantly lower than pricking pain thresholds ( $**P < 0.01$ ,  $***P < 0.001$ ,  $t$ -test) only with the larger stimulus areas ( $2.25$ – $15.36 \text{ cm}^2$ ) (values denote group mean  $\pm$  standard deviation).

(Fig. 3A), cold pain was produced at one site and warming of the remaining sites did not produce pain (not shown).

In those areas devoid of any innocuous thermal sensation, intense thermal stimuli produced a pricking pain without any thermal correlates in half of the sites (39 of 69). No pain could be elicited from the remaining 30 sites. The threshold for heat-induced pricking pain ( $48.5 \pm 1.8^\circ\text{C}$ ) was significantly higher than the threshold for thermal pain induced in normal skin areas ( $42.1 \pm 2.8^\circ\text{C}$ ,  $P < 0.001$ ) (Fig. 3A). Thresholds for cold-induced pricking pain were determined in only 19 of the areas and the mean threshold was found to be  $9.7 \pm 5.1^\circ\text{C}$ , significantly lower in temperature than normal cold pain ( $20.2 \pm 5.2^\circ\text{C}$ ,  $P < 0.001$ ; Fig. 3B).

Spatial summation of heat pain could be demonstrated both in normal subjects and in normal skin areas of incomplete spinal cord injury patients (Fig. 4). In contrast, no spatial summation was observed by heat-elicited pricking pain in areas lacking thermal sensibilities. Thus, pain thresholds in normal skin areas were significantly lower when compared with areas with no thermal sensibilities at larger stimulation areas ( $15.36\text{--}2.25\text{ cm}^2$ ). A significant elevation in threshold temperature was seen with decreasing stimulus size in normal areas of both normal and spinal cord injury subjects, an effect not seen in the areas lacking innocuous thermal sensations. With the smallest stimulation area ( $0.25\text{ cm}^2$ ), the heat pain threshold for intact areas was elevated and was almost identical to that of impaired skin (Fig. 4).

Qualitative evaluation of noxious thermal stimulation in normal skin areas showed that with a decrease in stimulation areas, pain was described as having more of a pricking quality and was perceived as much less burning or hot.

## Discussion

The results of our study show that the quality of thermal pain and its threshold are strongly dependent on the integrity of the non-noxious thermal pathways. In skin areas in which non-noxious thermal sensibilities are absent, thermal noxious stimulation (cold and hot) invariably elicits a sensation of pricking, non-thermal pain irrespective of the size of the area stimulated. Pricking pain thresholds in these skin areas are markedly higher than in normal skin and are independent of the size of the area stimulated. High threshold pricking pain evoked using noxious heat stimuli was also present in normal skin, when the stimulation area was limited to  $0.25\text{ cm}^2$ . Increasing the area of skin exposed to noxious heat reduces thermal thresholds, and the pain elicited acquires a clear thermal quality.

When only one thermal sensibility was intact, noxious thermal stimulation of the intact modality produced sensations identical to those found in normal skin. Thus, noxious heat elicited heat pain in areas in which warm sensation was preserved, and cold elicited cold pain when cold sensation was preserved. Furthermore, pain thresholds were identical to those observed in normal skin. When only non-noxious cold sensation was absent, noxious cold stimuli produced a

sensation of paradoxical heat pain in most cases. No consistent pattern was seen for noxious heat stimuli in areas devoid of warm sensibility, as these produced either heat pain, pricking pain or cold pain.

The dependence of thermal nociception on the integrity of thermal, non-nociceptive pathways and the lack of spatial summation of nociception when such pathways are not functional strongly suggest that pain quality and threshold are a function of simultaneous activation of both nociceptive and non-nociceptive systems. Thus, it appears that the quality of pain is determined by central neurones that integrate sensory information arriving from specific nociceptive and non-nociceptive thermal pathways. This central integration enables the non-noxious modality (e.g. warmth, cold) to 'colour' the pain sensation otherwise lacking any thermal quality ('pure pricking pain').

The proposed interpretation of our results posits that nociceptors are essential for pain perception, but the quality of the elicited sensation results from the integration of data from both nociceptive and non-nociceptive channels. The labelled-line (specificity) theory, on the other hand, states that the relevant information for the determination of pain threshold and quality is conveyed via dedicated labelled-line nociceptive channels, each responsive to one discrete stimulus energy or more. Their activation is thought to excite cortical centres whose activation, predictably, evokes a distinct subjective quality of pain. Consequently, the determination of pain quality should be relatively uninfluenced by the traffic in non-nociceptive pathways. According to this approach, activation of C nociceptors evokes a sensation of burning pain, while pricking pain is the result of activation of A $\delta$  nociceptors. (Fruhstorfer *et al.*, 1976; Price *et al.*, 1977; Torebjörk and Ochoa, 1980; Martin, 1991; Kandel *et al.*, 1995).

According to the most basic presentation of the labelled-line approach, loss of thermal (hot) quality of noxious stimuli implies that all C nociceptors were lost. The pricking pain evoked by heat and cold would, therefore, be the result of activation of remaining A $\delta$  nociceptive pathways. However, such an approach cannot account for the fact that pricking pain in our subjects was elicited only when both warm and cold sensations were eliminated.

This basic version of the labelled-line theory also fails to account for the paradoxical thermal pain sensations observed in the present study. Indeed, similar paradoxical effects (Mackenzie *et al.*, 1975; Yarnitsky and Ochoa, 1990a; Craig and Bushnell, 1994) have led to modifications of the labelled-line approach previously. According to the modified approach, interactions exist between heat and cold nociceptive channels, and the quality of the elicited sensation is a result of such an interaction. Thus, experiments using compression block of A fibres, in which cold stimuli induced burning pain, have led to two assumptions, the first being that noxious cold stimuli activate both A $\delta$  cold nociceptors and C polymodal nociceptors, and the second that loss of transmission in cold and cold pain pathways releases the masked

burning component of C nociceptors (Fruhstorfer, 1984; Wahren *et al.*, 1989; Yarnitsky and Ochoa, 1990a). The Thunberg's thermal grill illusion (Thunberg, 1896), in which simultaneous presentation of interlaced warm (40°C) and cold (20°C) bars produced a sensation of painful heat, was also used to demonstrate that cold pain sensation is a blend of cold and heat pain and that only inhibition of the cold channel reveals the heat C polymodal component (Craig and Bushnell, 1994). Thus, in its present form, the labelled-line approach is a far cry from its original formulation. It is, in fact, an integrative approach, which posits interaction between nociceptive systems in determining stimulus qualities without addressing the contribution of non-nociceptive systems.

The determination that pure C pain is burning and pure A $\delta$  pain is pricking relies on studies claiming selective activation of nociceptors. The bulk of the literature concerning such selective activation relies on microstimulation of nerve fibres. Considerable controversy exists concerning the true selectivity of this technique (Wall and McMahon, 1985). However, irrespective of technical considerations, the results obtained using this method are far from unequivocal. While several studies have demonstrated that microneural stimulation of C nociceptive fibres induced burning pain, and stimulation of fibres of the A $\delta$  range induced sharp, pricking pain (Torebjörk and Hallin, 1973; Mackenzie *et al.*, 1975; Ochoa and Torebjörk, 1983), microstimulation of C polymodal fibres also produced dull pain (Ochoa and Torebjörk, 1989) depending on the skin areas they innervate.

Even less compelling is the attempt at selective chemical activation of nociceptors. Topical application of capsaicin, the most commonly used chemical agent, produces burning pain, which has been attributed to the activation of C nociceptive fibres (Simon *et al.*, 1989; LaMotte *et al.*, 1991; Caterina *et al.*, 1997; Schmelz *et al.*, 2000). Such activation is thought to occur via the VR1 (Vanilloid type 1) receptor located on peripheral primary afferent terminals (Caterina *et al.*, 1997; Schmelz *et al.*, 2000). However, topical capsaicin, in addition to producing burning pain, also produces a sensation of warmth, suggesting that the burning pain produced by capsaicin is a result of co-activation of both innocuous and noxious thermoreceptive neurones by this compound. Although, *in vitro*, VR1 receptor-bearing neurones respond only to noxious heat (Caterina *et al.*, 1997; Schmelz *et al.*, 2000), no *in vivo* examination of the sensitivity of warmth receptors to capsaicin has been attempted. Further proof against the specific nature of capsaicin's action is the fact that following repeated application of capsaicin, all modes of acute nociception are impaired (Chung *et al.*, 1985; Szolcsanyi *et al.*, 1988; Seno and Dray, 1993; Ringkamp *et al.*, 1997). In addition, a subpopulation of C fibres, which are capsaicin-insensitive, has been identified recently (Caterina *et al.*, 2000; Magerl *et al.*, 2001).

Even more problematic for the labelled-line approach is the use of selective neural block for the study of nociception. Although widely used and considered as a selective A fibre

block, compression ischaemia was reported to affect the conduction in C fibres as well (Gasser and Erlanger, 1935; Torebjörk and Hallin, 1973; Mackenzie *et al.*, 1975; Hari *et al.*, 1985; Kojo and Pertovaara, 1986; Yarnitsky and Ochoa, 1991). Selective conduction block in C fibres with either local anaesthetics (Torebjörk and Hallin, 1973; Mackenzie *et al.*, 1975) or irrigation with distilled water (Dodt *et al.*, 1983) is even more problematic (Dodt *et al.*, 1983; King *et al.*, 1977), and a distinction between subpopulations of C fibres (nociceptive versus non-nociceptive) is impossible. Thus, simultaneous elimination of cold and warm sensation while leaving nociception intact cannot be attained.

The spinal cord injury subjects in this study exhibit a unique sensory profile due to their injury, in which the non-nociceptive thermal pathways (warmth, cold or both) are selectively absent, but who still perceive noxious stimuli. This sensory profile allows us to examine the quality and intensity of pain in a condition where non-nociceptive channels are selectively blocked. Since it is unreasonable to assume that in all our spinal cord injury subjects, only the A $\delta$  pathways were preserved after injury, pricking pain in areas devoid of thermal sensations must, therefore, result from the lack of integration between nociceptive and non-nociceptive pathways.

Further support for this approach can be found in data obtained from normal subjects. Pricking pain was produced in normal skin, when both C and A $\delta$  nociceptive pathways were intact, using a small stimulus area. The thermal quality of pain was regained only by increasing the stimulus area. Previous studies using punctate noxious hot, cold or mechanical stimuli applied to normal skin provide similar results. Thus, when noxious stimuli were confined to relatively small areas, they were reported as pricking pain. Enlarging the stimulus area enabled subjects to identify the different pain qualities, i.e. burning, cold or pressure pain sensation, respectively (Melzack and Wall, 1962; Chery-Croze and Duclaux, 1980). Labelled-line theories cannot account for this phenomenon, unless it is posited that small stimuli invariably activate A $\delta$  nociceptors without affecting C nociceptors. In contrast, assuming interactions between nociceptive and non-nociceptive systems provides a simple explanation of this phenomenon.

Early studies assessing the spatial characteristics of thermal sensation maintained that warm sensation is subject to considerable spatial summation (Stevens and Marks, 1971; Marks and Stevens, 1973; Stevens *et al.*, 1974; Marks, 1974). In contrast, minimal or no spatial summation has been reported for nociception (Green and Hardy, 1958; Stevens and Marks, 1971; Stevens *et al.*, 1974). It would therefore appear that for nociception to acquire its thermal quality, a minimal quantity of warm receptors has to be activated. Further support for this approach is the report that in normal skin areas devoid of warm sensation, noxious thermal stimulation produces a pricking sensation (Green and Cruz, 1998). Thus, it appears that co-activation of nociceptors and

warm receptors determines the perceived quality of heat pain. Furthermore, the spatial summation of pain threshold seen in this and previous studies (Defrin and Urca, 1996; Nielsen and Arendt-Nielsen, 1997), which is not observed when non-noxious thermal sensations are impaired, may be the result of convergence of nociceptive and non-nociceptive information on a common nociceptive conduction system.

Paradoxical thermal sensations have been reported previously in both normal (Dodt and Zotterman, 1952; Mackenzie *et al.*, 1975; Hämäläinen *et al.*, 1982; Wahren *et al.*, 1989; Yarnitsky and Ochoa, 1990a; Harrison and Davis, 1999) and pathological (Yosipovitch *et al.*, 1995; Hansen *et al.*, 1996) subjects. However, the distinction between innocuous and noxious paradoxical sensations is not always clear, since terms such as 'paradoxical heat', used by these authors, do not reveal if the 'heat' perceived by the subject was painful or not.

Paradoxical sensations are usually attributed to the 'inappropriate' activation of thermal channels by cold and warm stimuli. Thus, paradoxical cold sensation can be elicited, in normal subjects, when cold spots on the skin are stimulated by high temperatures (Lehmann, 1892; Von Frei, 1904). This paradoxical sensation can be explained by the demonstration that cold receptors are activated, under the appropriate conditions, by noxious heat (Dodt and Zotterman, 1952; Kenshalo and Duclaux, 1977; Long, 1977). Similarly, paradoxical heat sensations can be produced by low temperature stimulation of the skin (Dodt and Zotterman, 1952; Hämäläinen *et al.*, 1982; Wahren *et al.*, 1989; Harrison and Davis, 1999; Susser *et al.*, 1999). While such sensations are usually attributed to the activation of C polymodal nociceptors (LaMotte and Thalhammer, 1982; Campero *et al.*, 1996), activation of C fibre warmth receptors is also a viable possibility (Dodt and Zotterman, 1952; Zotterman, 1953). These investigators have shown that non-noxious warm fibres in the cat's tongue respond to phasic cooling with a burst of activity. Such activation of warm fibres can, paradoxically, be perceived as warming. Surprisingly, this finding has not been followed up in subsequent studies.

As far as the non-noxious sensations are concerned, our data support a labelled-line approach. Non-noxious thermal sensations are determined by the intact thermal modality. Whenever only warm pathways were intact, innocuous cold produced a sensation of warmth. Similarly, when only cold sensation was intact, warm stimuli elicited a sensation of cold. Paradoxical noxious sensation, however, did not follow such a clear pattern. Further cooling of the skin in areas devoid of cold sensation resulted in paradoxical heat pain. However, the quality of paradoxical pain sensation did not follow an identical pattern in the areas lacking warm sensibility. Further warming the skin to high intensity heat stimuli produced either paradoxical cold pain, heat pain or pricking pain. Paradoxical heat pain can be explained both by assuming co-activation of nociceptors and C warm receptors and by the 'inappropriate' activation of C nociceptors, as posited by the labelled-line theory. Neither approach can

explain the inconsistent 'paradoxical' pattern elicited by noxious heat in patients lacking warm sensation.

The experiments presented in this paper demonstrate that the characteristics of thermal pain (heat pain and cold pain) are dependent on the integrity of non-noxious thermal sensations. In those cases in which a thermal sensation is completely disrupted, noxious thermal stimulation completely loses its thermal quality and elicits a sensation of pricking pain. The threshold for this painful sensation is considerably elevated when compared with normal thermal pain sensations, and is well within the frankly noxious range. Furthermore, when only one thermal sensory modality is intact, both innocuous and noxious stimuli acquire the characteristics of that intact modality resulting in paradoxical sensations. It appears, therefore, that the quality of thermal nociception is a result of both activation of dedicated sensory channels and the interaction between those conveying innocuous thermal sensibilities and those channels conveying information from channels responsive to frankly noxious thermal stimulation.

## References

- Campero M, Serra J, Ochoa JL. C-polymodal nociceptors activated by noxious low temperature in human skin. *J Physiol (Lond)* 1996; 497: 565–72.
- Caterina MJ, Schumacher MA, Tominaga M, Rosen TA, Levine JD, Julius D. The capsaicin receptor: a heat-activated ion channel in the pain pathway. *Nature* 1997; 389: 816–24.
- Caterina MJ, Leffler A, Malmberg AB, Martin WJ, Trafton J, Petersen-Zeitz KR, et al. Impaired nociception and pain sensation in mice lacking the capsaicin receptor. *Science* 2000; 288: 306–13.
- Chery-Croze S, Duclaux R. Discrimination of painful stimuli in human beings: influence of stimulation area. *J Neurophysiol* 1980; 44: 1–10.
- Chung JM, Lee KH, Hori Y, Willis WD. Effects of capsaicin applied to a peripheral nerve on the responses of primate spinothalamic tract cells. *Brain Res* 1985; 329: 27–38.
- Craig AD, Bushnell MC. The thermal grill illusion: unmasking the burn of cold pain. *Science* 1994; 265: 252–5.
- Defrin R, Urca G. Spatial summation of heat pain: a reassessment. *Pain* 1996; 66: 23–9.
- Defrin R, Ohry A, Blumen N, Urca G. Characterization of chronic pain and somatosensory function in spinal cord injury subjects. *Pain* 2001; 89: 253–63.
- Ditunno JF, Young W, Donovan WH, Creasey G. The international standards booklet for neurological and functional classification of spinal cord injury. *Paraplegia* 1994; 32: 70–80.
- Dodt E, Zotterman Y. The discharge of specific cold fibres at high temperatures (the paradoxical cold). *Acta Physiol Scand* 1952; 26: 358–365.
- Dodt HU, Forke D, Zimmermann M. Persisting selective block of unmyelinated fibers in cutaneous nerves of the cat by distilled water. *Neurosci Lett* 1983; 35: 203–7.



- Frey M von. Vorlesungen über Physiologie. Berlin: Springer; 1904.
- Fruhstorfer H. Thermal sensibility changes during ischemic nerve block. *Pain* 1984; 20: 355–61.
- Fruhstorfer H, Lindblom U, Schmidt WC. Method for quantitative estimation of thermal threshold in patients. *J Neurol Neurosurg Psychiatry* 1976; 39: 1071–5.
- Gasser HS, Erlanger J. Conduction in nerves in relation to fiber types. *Res Publ Ass nerv ment Dis* 1935; 15: 35–9.
- Gescheider GA. *Psychophysics: method, theory and application*. 2nd edn. Hillsdale (NJ): Lawrence Erlbaum; 1985.
- Goldscheider A. Ueber den Schmerz in physiologischer und klinischer Hinsicht. Berlin: Hirschwald; 1894.
- Green BG, Cruz A. 'Warmth-insensitive fields': evidence of sparse and irregular innervation of human skin by the warmth sense. *Somatosens Mot Res* 1998; 15: 269–75.
- Green LC, Hardy JD. Spatial summation of pain. *J Appl Physiol* 1958; 13: 457–65.
- Hämäläinen H, Vartiainen M, Karvanen L, Jarvilehto T. Paradoxical heat sensations during moderate cooling of the skin. *Brain Res* 1982; 251: 77–81.
- Hansen C, Hopf HC, Treede RD. Paradoxical heat sensation in patients with multiple sclerosis. Evidence for a supraspinal integration of temperature sensation. *Brain* 1996; 119: 1729–36.
- Hari R, Pertovaara A, Kemppainen P, Salminen J. The effect of tourniquet-induced ischemia on somatically evoked cerebral magnetic fields in man. *Acta Neurol Scand* 1985; 72: 419–26.
- Harrison JL, Davis KD. Cold-evoked pain varies with skin type and cooling rate: a psychophysical study in humans. *Pain* 1999; 83: 123–35.
- Kandel ER, Schwartz JH, Jessell TM. The sensory systems. In: Kandel ER, Schwartz JH, Jessell TM, editors. *Essentials of neural science and behavior*. New York: McGraw-Hill; 1995. p. 369–86.
- Kenshalo H, Duclaux R. Response characteristics of cutaneous cold receptors in the monkey. *J Neurophysiol* 1977; 40: 319–32.
- King JS, Jewett DL, Rutkin B, Wilson CB. On attempting selective blockade of dorsal root C fibers in the treatment of chronic pain problems. *Exp Neurol* 1977; 56: 241–51.
- Kojo I, Pertovaara A. Effect of tourniquet-induced ischemia on cutaneous thermal thresholds. *Acta Neurol Scand* 1986; 74: 383–6.
- LaMotte RH, Thalhhammer JG. Response properties of high-threshold cutaneous cold receptors in the primate. *Brain Res* 1982; 244: 279–87.
- LaMotte RH, Shain CN, Simone DA, Tsai EF. Neurogenic hyperalgesia: psychophysical studies of underlying mechanisms. *J Neurophysiol* 1991; 66: 190–211.
- Lehmann AG. *Die Hauptgesetze des menschlichen Gefühlsleben*. Leipzig: Reisland; 1892.
- Long DR. Sensitivity of cutaneous cold fibers to noxious heat: paradoxical cold discharge. *J Neurophysiol* 1977; 40: 489–502.
- Mackenzie RA, Burke D, Skuse NF, Lethlean AK. Fibre function and perception during cutaneous nerve block. *J Neurol Neurosurg Psychiatry* 1975; 38: 865–73.
- Magerl W, Fuchs PN, Meyer RA, Treede RD. Roles of capsaicin-insensitive nociceptors in cutaneous pain and secondary hyperalgesia. *Brain* 2001; 124: 1754–64.
- Marks LE. Spatial summation in relation to the dynamics of warmth sensation. *Int J Biometeorol* 1971; 15: 106–10.
- Marks LE, Stevens JC. Spatial summation of warmth: influence of duration and configuration of the stimulus. *Am J Psychol* 1973; 86: 251–67.
- Martin JH. Coding and processing of sensory information. In: Kandel ER, Schwartz JH, Jessell TM, editors. *Principles of neural sciences*. 3rd edn. East Norwalk (CO): Appleton & Lange; 1991. p. 329–40.
- Melzack R. The McGill Pain Questionnaire: major properties and scoring methods. *Pain* 1975; 1: 277–99.
- Melzack R, Torgerson WS. On the language of pain. *Anesthesiology* 1971; 34: 50–9.
- Melzack R, Wall PD. On the nature of cutaneous sensory mechanisms. *Brain* 1962; 85: 331–56.
- Nathan PW, Smith MC, Cook AW. Sensory effects in man of lesions of the posterior columns and of some other afferent pathways. *Brain* 1986; 109: 1003–41.
- Nielsen J, Arendt-Nielsen L. Spatial summation of heat induced pain within and between dermatomes. *Somatosens Mot Res* 1997; 14: 119–25.
- Ochoa J, Torebjörk E. Sensations evoked by intraneural microstimulation of single mechanoreceptor units innervating the human hand. *J Physiol (Lond)* 1983; 342: 633–54.
- Ochoa J, Torebjörk E. Sensations evoked by intraneural microstimulation of C nociceptor fibres in human skin nerves. *J Physiol (Lond)* 1989; 415: 583–99.
- Perl ER. Getting a line on pain: is it mediated by dedicated pathways? *Nat Neurosci* 1998; 1: 177–8.
- Price DD, Dubner R. Mechanisms of first and second pain in the peripheral and central nervous systems. [Review]. *J Invest Dermatol* 1977; 69: 167–71.
- Ringkamp M, Peng YB, Campbell JN, Meyer RA. Intradermal capsaicin produces a vigorous discharge in mechanically-insensitive A-fiber nociceptors of the monkey [abstract]. *Soc Neurosci Abstr* 1997; 23: 1258.
- Schady WJ, Torebjörk HE, Ochoa JL. Peripheral projections of nerve fibres in the human median nerve. *Brain Res* 1983; 277: 249–61.
- Schmelz M, Schmid R, Handwerker HO, Torebjörk HE. Encoding of burning pain from capsaicin-treated human skin in two categories of unmyelinated nerve fibres. *Brain* 2000; 123: 560–71.
- Seno N, Dray A. Capsaicin-induced activation of fine afferent fibres from rat skin in vitro. *Neuroscience* 1993; 55: 563–9.
- Simon DA, Baumann TK, LaMotte RH. Dose-dependent pain and mechanical hyperalgesia in humans after intradermal injection of capsaicin. *Pain* 1989; 38: 99–107.

- Sinclair DC. Cutaneous sensation and the doctrine of specific energy. *Brain* 1955; 78: 584–614.
- Stevens JC, Marks LE. Spatial summation and the dynamics of warmth sensation. *Percept Psychophys* 1971; 9: 391–8.
- Stevens JC, Marks LE, Simonson DC. Regional sensitivity and spatial summation in the warmth sense. *Physiol Behav* 1974; 13: 825–36.
- Susser E, Sprecher E, Yarnitsky D. Paradoxical heat sensation in healthy subjects: peripherally conducted by A $\delta$  or C fibres? *Brain* 1999; 122: 239–246.
- Szolcsanyi J, Anton F, Reeh PW, Handwerker HO. Selective excitation by capsaicin of mechano-heat sensitive nociceptors in rat skin. *Brain Res* 1988; 446: 262–8.
- Thunberg T. Förmimmelserne vid till samma ställe lokaliserad, samtidigt pågående köld-och värmeretning. *Uppsala Läkfören Förh* 1896; 1: 489–95.
- Torebjörk HE, Hallin RG. Perceptual changes accompanying controlled preferential blocking of A and C fibre responses in intact human skin nerves. *Exp Brain Res* 1973; 16: 321–32.
- Torebjörk HE, Hallin RG. Microneurographic studies of peripheral pain mechanisms in man. *Adv Pain Res Ther* 1979; 3: 121–31.
- Torebjörk HE, Ochoa JL. Specific sensations evoked by activity in single identified sensory units in man. *Acta Physiol Scand* 1980; 110: 445–7.
- Torebjörk HE, Ochoa JL. Selective stimulation of sensory units in man. *Adv Pain Res Ther* 1983; 5: 99–104.
- Vallbo AB. Sensations evoked from the glabrous skin of the human hand by electrical stimulation of unitary mechanosensitive afferents. *Brain Res* 1981; 215: 359–63.
- Vallbo AB, Hagbarth KE. Activity from skin mechanoreceptors recorded percutaneously in awake human subjects. *Exp Neurol* 1968; 21: 270–89.
- Van Hees J, Gybels JM. Pain related to single afferent C fibers from human skin. *Brain Res* 1972; 48: 397–400.
- Verdugo R, Ochoa JL. Quantitative somatosensory thermostest. A key method for functional evaluation of small calibre afferent channels. *Brain* 1992; 115: 893–913.
- Wahren LK, Torebjörk E, Jörum E. Central suppression of cold-induced C fibre pain by myelinated fibre input. *Pain* 1989; 38: 313–9.
- Wall PD, McMahon SB. Microneurography and its relation to perceived sensation. A critical review. *Pain* 1985; 21: 209–29.
- Wall PD, McMahon SB. The relationship of perceived pain to afferent nerve impulses. *Trends Neurosci* 1986; 9: 254–5.
- Wilcox GL, Giesler GJ. An instrument using a multiple layer Peltier device to change skin temperature rapidly. *Brain Res Bull* 1984; 12: 143–6.
- Willis WD. *The pain system*. Basel: Karger; 1985.
- Yarnitsky D, Ochoa JL. Release of cold-induced burning pain by block of cold-specific afferent input. *Brain* 1990a; 113: 893–902.
- Yarnitsky D, Ochoa JL. Studies of heat pain sensation in man: perception thresholds, rate of stimulus rise and reaction time. *Pain* 1990b; 40: 85–91.
- Yarnitsky D, Ochoa JL. Differential effect of compression-ischaemia block on warm sensation and heat-induced pain. *Brain* 1991; 114: 907–13.
- Yosipovitch G, Yarnitsky D, Mermelstein V, Sprecher E, Reiss J, Witenberg C, et al. Paradoxical heat sensation in uremic polyneuropathy. *Muscle Nerve* 1995; 18: 768–71.
- Zotterman Y. The special senses: thermal receptors. *Annu Rev Physiol* 1953; 15: 357–72.

*Received June 20, 2000. Revised December 4, 2000.  
Second revision September 27, 2001. Accepted October 5, 2001*