

Spatial discrimination thresholds for pain and touch in human hairy skin

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Abstract

The traditional concept that pain is poorly localized has been challenged by recent studies, where subjects were able to point to the stimulated spot on the skin with an accuracy of 10–20 mm. Pointing movements themselves, however, have errors of about 15 mm. To determine the limits of sensory performance of the nociceptive system independent of motor performance, point localization of heat pain (540 mJ punctate laser stimuli, 5 mm diameter), mechanical pain (256 mN punctate probe, 200 μ m diameter), and touch (16 mN von Frey probe, 1.1 mm diameter) were tested in a two-alternative forced-choice paradigm in 12 healthy subjects. Stimuli were applied in randomized order to two parallel lines on the back of the hand (4–32 mm distance). The cumulative distribution functions for correct localization were of similar sigmoid shape for all test stimuli, indicating logarithmic normal distributions. The 75% correct localization threshold for painful heat was 8.6 mm ($3.1 \pm 0.1 \log_2$ units) and did not differ significantly from that of non-painful touch (9.0 mm, $3.2 \pm 0.2 \log_2$ units). Localization of mechanically-induced pain (5.1 mm, $2.4 \pm 0.2 \log_2$ units) was significantly more accurate than both heat pain and touch, possibly due to a synergism of two different sensory channels, the tactile channel and the nociceptive channel, which were activated simultaneously. For all three stimuli, discrimination was significantly better in radial–ulnar compared to proximal–distal direction, which might be related to oval receptive field shapes. Sequential spatial discrimination for touch was significantly better than simultaneous spatial discrimination tested with a grating orientation task (18.9 mm), but both were one order of magnitude worse than at the finger tip (1.3 mm, $0.4 \pm 0.1 \log_2$ units). In conclusion, pain evoked by radiant heat pulses and touch evoked by von Frey probes were localized with similar precision on the back of the hand. These findings indicate that outside the tactile fovea at finger tips or lips the spatial discrimination capacities of the nociceptive and tactile systems are about equal. © 2001 International Association for the Study of Pain. Published by Elsevier Science B.V. All rights reserved.

Keywords: Pain; Spatial discrimination; Localization accuracy; Laser; Touch; Pin prick

1. Introduction:

In contrast to vision and touch, nociception is generally considered to provide only poor spatial resolution. This concept is largely due to the poor spatial discrimination abilities for visceral pain and muscle pain, where pain sensation may be perceived at multiple sites far remote from the injured tissue as it is known from referred pain (Head, 1893; Marchettini, 1993; Mense, 1993). On the other hand, patients' reports of pain localization are often used clinically to guide the diagnosis ('where does it hurt?'). This standard clinical procedure is only possible, because patients are able to localize cutaneous pain remarkably precisely. The difference in spatial resolution between cutaneous and deep (somatic and visceral) pain has been pointed out both in classical reports (e.g. Lewis and Kellgren, 1939) and in more recent studies (Arendt-Nielsen, 1997).

Observations from microneurographic studies in humans have renewed the interest in the spatial resolution of cutaneous pain (Torebjörk and Ochoa, 1983; Ochoa and Torebjörk, 1989). There was a remarkable spatial matching of the receptive field of given C-fiber nociceptors with the projected field of the pain sensation evoked by intraneural microstimulation at the recording site with threshold intensity for conscious sensation (66% were within 10 mm of each other). In subsequent studies, blindfolded subjects were asked to point to the spot on the skin that had been stimulated with one of several noxious stimuli (locognosia). For the skin of the hand, these studies showed pointing errors of 10–16 mm (Koltzenburg et al., 1993; Moore and Schady, 1995). These errors were remarkably small and were of the same order of magnitude as the errors of tactile locognosia in the same skin area.

These previous studies of nociceptive locognosia used a point localization task that included a motor component (finger pointing movement) in addition to the sensory component (identification of the stimulated spot). Finger pointing movements, however, have errors of about 15–17

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mm (Prablanc et al., 1986; Neggers and Bekkering, 1999). Thus, sensory performance in those studies was confounded with motor performance.

To determine the limits of sensory performance of the nociceptive system independent of motor performance, we developed a point localization task in a two-alternative forced-choice paradigm, where blindfolded subjects had to decide which one of two pre-defined parallel lines on the back of the hand had been stimulated. For activation of the nociceptive system, we used laser radiant heat pulses (Spiegel et al., 2000) and punctate mechanical stimuli (Ziegler et al., 1999). For comparison of the nociceptive and tactile systems, the same measurements were also performed using von Frey probes with a blunt rounded tip (Magerl et al., 1998b).

Spatial resolution of the tactile system is usually reported as thresholds for two-point discrimination, which represents simultaneous spatial discrimination, whereas point localization tasks test sequential spatial discrimination. Sequential spatial discrimination is known to be more precise than simultaneous spatial discrimination (Weinstein, 1968). For comparison with standard data, we therefore also assessed simultaneous spatial discrimination for touch using a grating orientation task (Van Boven and Johnson, 1994). Some of the results of this study were presented in abstract form (Schlereth et al., 1998).

2. Methods

2.1. Subjects

The study was performed in 12 healthy volunteers, nine females and three males (age 22–47 years, mean: 28 years), who gave written informed consent for participation. The study was approved by the local ethics committee. Subjects were comfortably seated in a noise-reduced room at an ambient temperature of 24°C. All subjects except one were right handed.

2.2. Stimuli

Painful and tactile stimuli were applied to the back of the left and right hands. Painful stimuli were applied in two different ways: heat-induced pain by an energy-controlled infra-red thulium laser (2.01 μm wavelength, 5 mm beam diameter, 3 ms stimulus duration; Spiegel et al., 2000), and mechanically-induced pain by a punctate cylindrical probe of 200 μm diameter eliciting a sensation of pricking pain (Ziegler et al., 1999). The tactile stimulus was a von Frey probe with a rounded tip of 1.1 mm diameter (Magerl et al., 1998b). Stimulus intensities were chosen in such a way that detection probability within their specific sensory channel was equal ($\geq 98\%$). According to results from studies quoted above, these intensities were 540 mJ for laser-evoked heat pain, 256 mN for mechanical pain, and 16 mN for touch.

2.3. Experimental protocol

Sequential spatial discrimination thresholds were determined in a two-alternative forced-choice paradigm. For this purpose, pairs of parallel lines were marked onto the back of the left and right hand with felt tip pens (Fig. 1). The line spacings were 2, 4, 8, 16 and 32 mm, and line orientation was either from the fingers to the wrist (radial–ulnar discrimination task) or from the radial to the ulnar part of the hand (proximal–distal discrimination task). Within a run of 20 stimuli, each stimulus was randomly applied to one of a pair of parallel lines (12 different standard sequences were used, there were never more than three successive stimuli on the same line). The subject's task was to decide to which one of the two lines the stimulus had been applied. The first two stimuli of a run were given under full visual control of the subject as a demonstration of the relative position of each line. Then the subject's eyes were covered with a blindfold to avoid the use of visual cues for stimulus location. The remaining 18 stimuli were used to determine the 75% correct detection threshold (see below). Interstimulus intervals were 6–12 s, and each stimulus was signaled by an auditory cue one second prior to stimulation.

Experiments were done in two experimental sessions on two different days to warrant sufficient vigilance of the subjects, and to test reliability of results (session 1: spacings of 4–32 mm, session 2: 2–16 mm). Within each session, one hand was tested for the radial–ulnar discrimination task and the other for the proximal–distal discrimination task, and each hand was tested with 12 runs (4 spacings \times 3 stimulus types). Across subjects, the testing sequence was fully balanced for order of stimulus type, line orientation, line spacing and left/right hand to eliminate confounding effects of habituation, fatigue or learning.

The simultaneous spatial discrimination threshold for touch was also tested on the back of the hand using a grating orientation task (Van Boven and Johnson, 1994). Briefly, a 5 \times 5 cm block of acrylic, having alternating grooves and ridges of precisely defined width was placed on the back of the hand, and orientation was guessed by the subject. For comparison, grating orientation was also tested on the index finger tips. Groove widths were 4, 6, 8, 12, 16, and 20 mm on the back of the hand, 0.5, 1, 2, and 4 mm on the finger tip (32 stimuli per groove width). The 75% correct detection thresholds were calculated as described below.

2.4. Data evaluation

The proportions of correct localization responses (hit rates) were calculated separately for each run. Hit rates were analyzed by five-way repeated measures ANOVA with the main factors: stimulus type, line spacing, line orientation, left vs. right hand and experimental session. Psychometric functions were fitted to the population data of these hit rates from both sessions combined by using a logistic

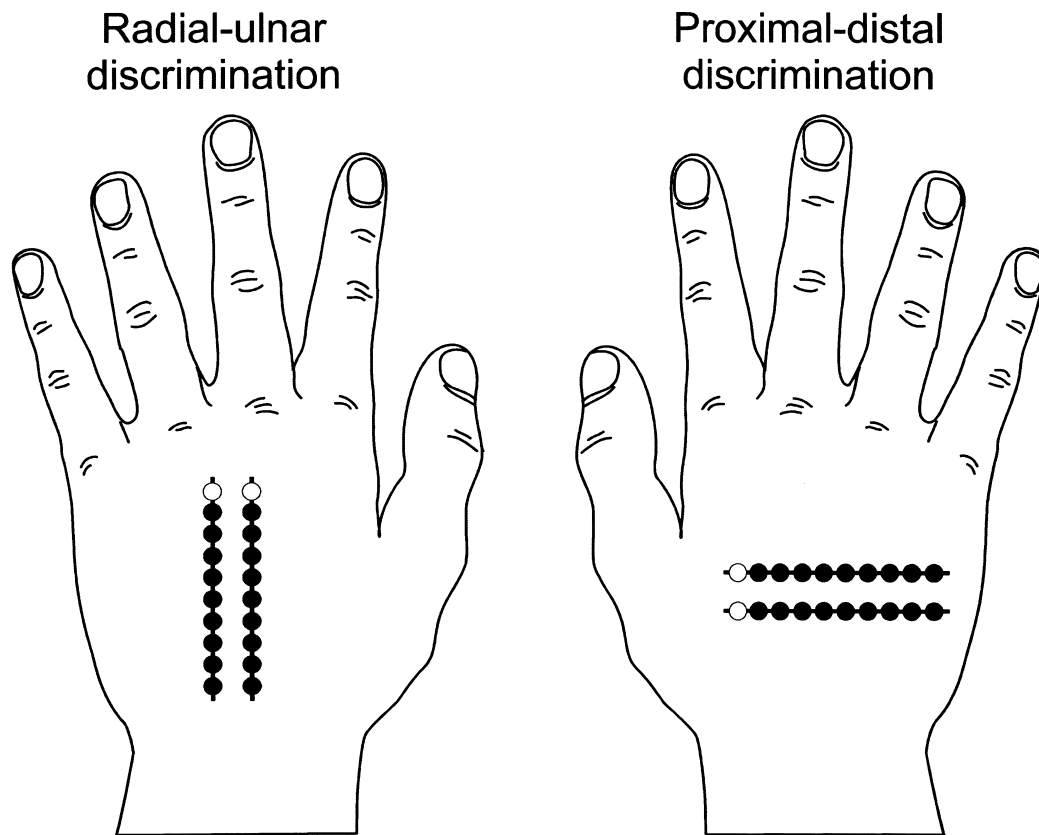


Fig. 1. Stimulus arrangement for testing spatial resolution of touch and pain. Each run consisted of 20 stimuli applied to two parallel lines on the back of the hand with line spacings of 2, 4, 8, 16 and 32 mm. The first two stimuli were given openly for demonstration (open circles). The remaining 18 stimuli were evaluated for correct localization incidence (filled circles). Left: line arrangement for sequential spatial discrimination task in the radial–ulnar direction. Right: line arrangement for sequential spatial discrimination task in the proximal–distal direction.

function assuming 50% hit rate (chance) as the lower and 100% hit rate as the upper boundaries

$$\text{hitrate} = 100\% + (50\% - 100\%)/(1 + (x/x_0)^s)$$

The shape of this function is characterized by its turning point (x_0), which denotes the calculated line spacing allowing for a 75% hit rate, and its slope (s).

Individual spatial discrimination thresholds at 75% correct localization were interpolated from adjacent line spacings giving hit rates just below and above this threshold criterion. The histograms of individual thresholds were analyzed for distribution properties. Differences between stimulus types and spatial orientation of the discrimination task (radial–ulnar vs. proximal–distal) were analyzed by two-way repeated measures ANOVA on individual discrimination thresholds (main factors: stimulus type and orientation). The significance of differences was tested by least squares differences (LSD) post-hoc tests. Data are presented as mean \pm standard error of the mean (SEM). Probabilities of $P \leq 0.05$ were considered as being statistically significant.

3. Results

The stimulus intensities in this study were well above the

respective detection thresholds, as shown by the percentage of stimuli that were perceived by the subjects: $99.7 \pm 0.7\%$ for laser heat pain, 100% for pin prick pain, and $99.2 \pm 1.2\%$ for touch. The percentages of correctly localized stimuli (hit rates) for the three line spacings that were used in both experimental sessions were reproducible (correlation coefficients $r = 0.54$ for painful laser heat stimuli, $r = 0.64$ for pin prick stimuli, and $r = 0.51$ for touch, $P < 0.001$ each). Five way repeated measures ANOVA on hit rates (Table 1) revealed that there was no difference between sessions ($F_{1,180} = 1.5$, $P > 0.20$), or between left and right hand ($F_{1,180} = 0.7$, $P > 0.40$). There were no significant interactions between main effects (for impact of stimulus type, line spacing and line orientation, see below). Thus, the data from both sessions and both hands were pooled for further analysis. In addition we did not observe any training effect within sessions as disclosed by analysis of covariance (number of testing sequence within a session as a covariate), which revealed that trial number was not a statistically relevant predictor ($F_{1,515} = 0.05$, $P = 0.81$).

The probability of correct localization depended highly significantly on line spacing ($F_{2,180} = 136.5$, $P < 0.001$). Generally, the probability of correct localization increased

Table 1

Five-way repeated measures ANOVA on percentages of correct localization (hit rates) for sequential spatial discrimination of pain and touch

Main factors	d.f. (effect, error)	F-value	P level
Stimulus type	2, 180	16.4	< 0.001
Line spacing	2, 180	136.5	< 0.001
Line orientation	1, 180	15.8	< 0.001
Left vs. right hand	1, 180	0.7	0.41
Experimental sessions	1, 180	1.5	0.22
No significant interactions			

with increasing line spacing, and matched a cumulative Gaussian function over the logarithm of line spacing for all stimulus types, i.e. it was best approximated by a log-normal distribution (Fig. 2, top row). Additionally, correct localization depended highly significantly on stimulus type

($F_{2,180} = 16.4$, $P < 0.001$). The average spatial discrimination threshold estimated from the pooled data of all subjects was 8.1 mm for painful laser heat stimuli (Fig. 2, top left). A similar discrimination threshold of 8.2 mm was found for touch by von Frey probe (Fig. 2, top right). In contrast, spatial discrimination threshold of 5.2 mm for pin prick pain by the 200 μm punctate probe (Fig. 2, top center) was considerably lower than for both heat pain and touch. Despite these differences the shapes of psychometric functions were almost the same for all stimulus paradigms as demonstrated by their similar rates of rise: the slope s of the logistic function was 0.46 ± 0.04 for laser heat pain, 0.43 ± 0.04 for pin prick pain, and 0.43 ± 0.04 for touch (all differences $P > 0.60$).

Analysis was further detailed by estimation of thresholds of individual subjects (see Section 2). Inspection of threshold histograms showed that also individual thresholds were

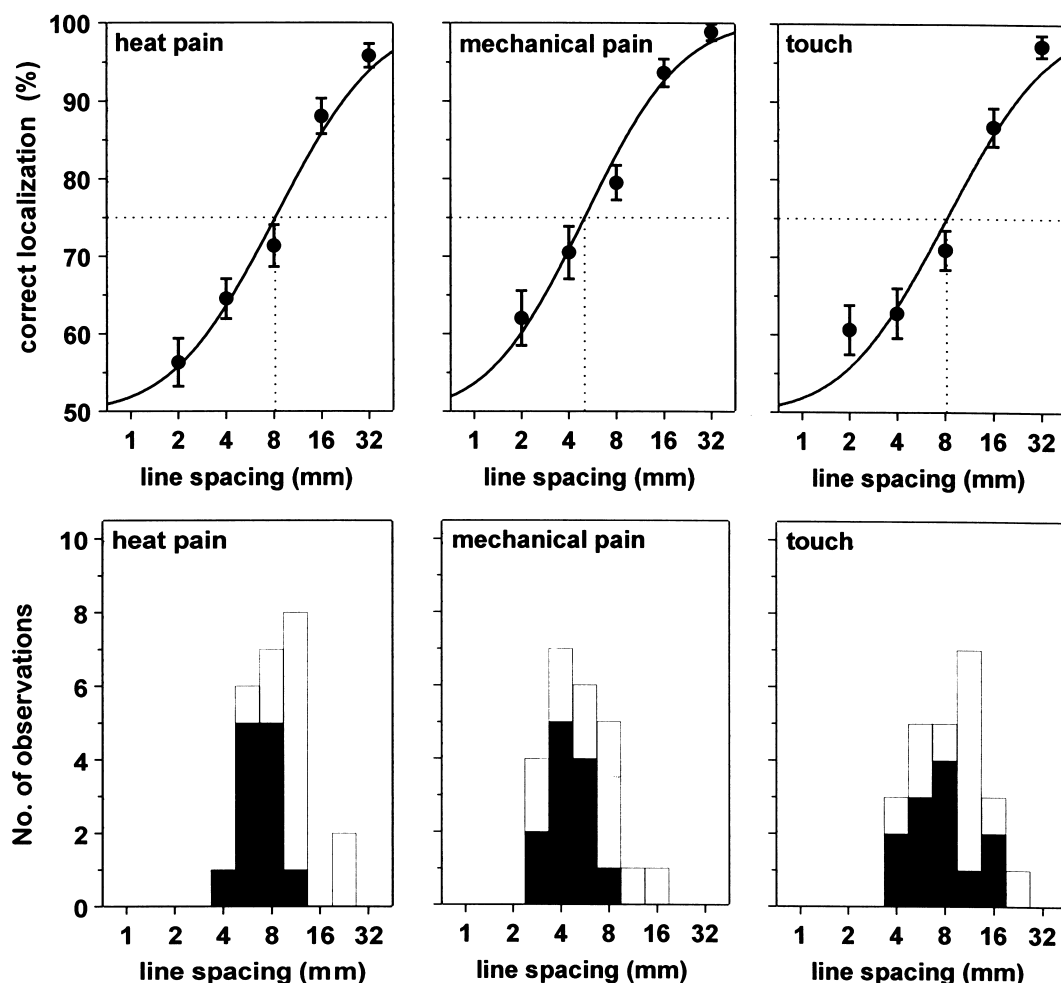


Fig. 2. Spatial thresholds for heat pain (left column), pin prick pain (center column), and touch (right column) on the back of the hand. Top row: Stimulus-response functions depicting the probability of correct point localization as a function of line spacing (mean \pm SEM). Data of all 12 subjects for both discrimination directions combined (radial-ulnar and proximal-distal). The stimulus-response functions were modeled by sigmoid curves (logarithmic cumulative Gaussian distribution). The spatial threshold is the point where the hit rate equals 75%. The 75% correct identification thresholds of heat pain and touch were similar (8.1 and 8.2 mm, respectively), whereas that of mechanically induced pain (5.2 mm) was lower than either of them. Bottom row: distribution of individual thresholds. Numbers of observations for each line spacing. Individual spatial thresholds were log-normally distributed. Sequential spatial discrimination in the radial-ulnar direction (filled bars) yielded lower thresholds than in the proximal-distal direction (open bars). For statistics, see Table 1.

Table 2
Spatial discrimination thresholds on the back of the hand^a

	Heat pain	Pin prick	Touch
Pooled data ($n = 24$)	8.6 mm (3.11 ± 0.12)	5.1 mm (2.35 ± 0.15) ^b	9.0 mm (3.17 ± 0.15)
Radial–ulnar direction ($n = 12$)	6.7 mm (2.75 ± 0.13) ^c	4.5 mm (2.16 ± 0.13) ^{b,d}	7.8 mm (2.96 ± 0.18) ^d
Proximal–distal direction ($n = 12$)	11.1 mm (3.47 ± 0.14)	5.9 mm (2.55 ± 0.26) ^b	10.4 mm (3.37 ± 0.24)

^a Since data were log-normally distributed, they are presented as mean \pm SEM of \log_2 transformed values, as well as the equivalent line spacings of the means in mm.

^b Significantly different from heat pain and touch ($P < 0.005$, each).

^c Significantly smaller than proximal–distal ($P < 0.001$).

^d Significantly smaller than proximal–distal ($P < 0.05$).

log-normally distributed irrespective of the stimulus type (Fig. 2, bottom row). Estimated means of spatial discrimination thresholds across both orientation conditions were very similar to those estimated from the population function (see Table 2). Two way ANOVA revealed that there was a highly significant main effect of the stimulus type on spatial discrimination thresholds ($F_{2,22} = 19.9$, $P < 0.001$). Post-hoc analysis showed that the mean spatial discrimination threshold for painful laser heat stimuli was 3.11 ± 0.12 \log_2 -units, equivalent to 8.6 mm (Fig. 2, bottom left). This value was similar to the spatial discrimination threshold for touch by von Frey probes (3.17 ± 0.15 \log_2 -units, equivalent to 9.0 mm; Fig. 2, bottom right). In contrast, spatial

discrimination thresholds for pin prick pain were significantly lower than for both heat pain and touch (2.35 ± 0.15 \log_2 -units, equivalent to 5.1 mm, $P < 0.001$; Fig. 2, bottom center).

Generally, spatial discrimination thresholds were lower in the radial–ulnar than proximal–distal discrimination direction (two way-ANOVA: $F_{1,11} = 10.6$, $P < 0.01$) for all stimulus types, which was statistically evidenced by the absence of any significant interaction between line orientation and stimulus type ($F_{2,22} = 1.2$, $P < 0.33$). Spatial discrimination thresholds of the proximal–distal discrimination task exceeded radial–ulnar discrimination threshold by 33% for touch and by 31% for pin prick pain (both $P < 0.05$; post-hoc LSD test), and by 65% for heat pain ($P < 0.001$, Table 2).

For touch, the spatial discrimination thresholds obtained by sequential presentation of single stimuli were also compared with more conventional simultaneous spatial discrimination. The latter was tested by a subject's ability to identify the orientation of gratings with different groove widths. Individual thresholds at 75% correct responses could only be obtained from the majority (9/12 subjects), but not all subjects (wider groove widths could not be tested due to the size of the back of the hand). Thus, the average threshold was only estimated from the psychometric function of the population data as 18.9 mm for the back of the hand (Fig. 3). For comparison, the same threshold was tested at the tip of the index finger, where it was 1.3 mm (0.38 ± 0.09 \log_2 -units).

Notably, the spatial discrimination threshold on the back of the hand was significantly wider when estimated by grating orientation, a simultaneous spatial discrimination task, than when estimated by point localization, a sequential spatial discrimination task ($P < 0.01$). However, despite their difference in estimated threshold, the shape of the psychometric function for the grating orientation task at the back of the hand (slope s : 0.46 ± 0.13) matched the ones of the point localization task for laser heat pain, pin prick pain, and touch (cf. Fig. 2, all differences $P > 0.80$). In contrast, the psychometric function of the grating orientation task at the finger tip was much steeper than at the back of the hand (1.36 ± 0.20 , $P < 0.001$).

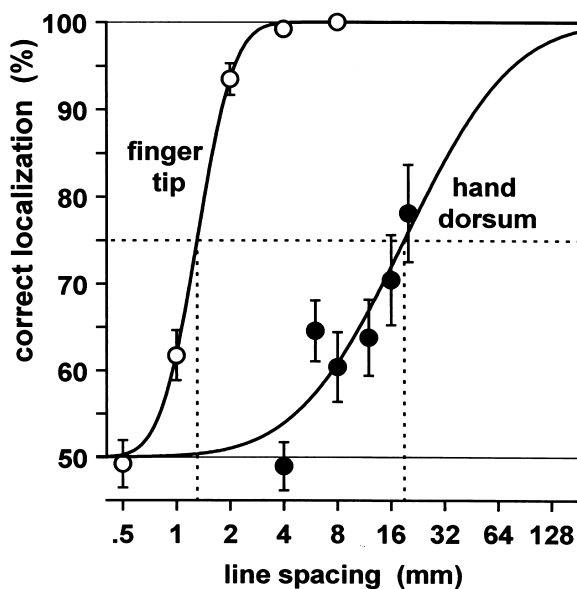


Fig. 3. Simultaneous spatial discrimination in the tactile grating orientation task. Stimulus-response functions for the grating orientation task depicting the probability of correct identification of grating orientation as a function of groove width (mean \pm SEM, $n = 12$). The stimulus-response functions were modeled by sigmoid curves (logarithmic cumulative Gaussian distribution). The stimulus-response function for the tip of the index finger had a steeper slope and was shifted about one order of magnitude to the left of the stimulus-response function for the back of the hand. The 75% correct identification thresholds of the population data were 1.3 mm at the index finger (open circles) and 18.9 mm at the back of the hand (filled circles).

4. Discussion

This study has shown that in the hairy skin of the back of the hand the sequential spatial discrimination threshold for heat pain is about 8.6 mm, which is comparable to that of touch in the same area (9.0 mm). This number is likely to represent the sensory limits of nociceptive spatial resolution in humans, because the two-alternative forced-choice task used is independent of motor performance and has been modeled according to the established procedure to determine the limits of tactile spatial resolution (Van Boven and Johnson, 1994).

The capacity to localize cutaneous noxious stimuli has traditionally been ascribed to simultaneous activation of tactile afferents. Such a coactivation can be excluded for the laser radiant heat pulses used in this study, because microneurographic recordings showed that these stimuli do not activate mechanoreceptors in the hairy skin of the human hand (Bromm et al., 1984). Moreover, detection of these stimuli was eliminated by topical treatment of the skin with capsaicin (Beydoun et al., 1996; Magerl et al., 1998a) and in patients with a dissociated sensory loss due to syringomyelia (Treede et al., 1991; Hansen and Treede, 1995) or brainstem infarction (Hansen et al., 1996; Urban et al., 1999).

The spatial resolution of pin prick pain (5.1 mm) was significantly higher than that of both heat pain and touch. The diameter of the laser heat stimulus (5 mm) may have been a limiting factor, but certainly the diameter of the tactile stimulus (1.1 mm) was not. The pin prick stimulus used in this study was designed to activate the nociceptive system (cf. Greenspan and McGillis, 1991; Chan et al., 1992), but mechanical stimuli also activate the tactile system. Thus, a central cooperative interaction between these two systems may explain the enhanced performance, e.g. by improving the signal to noise ratio (expected effect size: by a factor of $\sqrt{2}$).

We observed that it was easier to discriminate stimulus location in the radial–ulnar direction than in the proximal–distal direction on the back of the hand (threshold ratio about 2/3). Such a difference could be due to oval-shaped receptive fields that are oriented in the longitudinal direction. Receptive fields of nociceptors innervating the hairy skin often have an oval shape for both mechanical and heat stimuli (Treede et al., 1990), but the direction of the larger diameter appears to vary more or less randomly (Schmidt et al., 1997). The elongated receptive fields of Merkel and Meissner receptors, which are involved in spatial discrimination of touch, are known to be preferentially oriented in the longitudinal direction of the hand (Johansson, 1978; Schady and Torebjörk, 1983).

For the tactile system, spatial resolution on the back of the hand is about one order of magnitude less than in the ‘tactile foveal areas’ finger tips and lips (Weinstein, 1968; Sato et al., 1999). The difference in spatial resolution has been related to a distal-proximal gradient in innervation density

by Merkel and Meissner receptors and the size of the representation areas in the primary somatosensory cortex (Johansson and Vallbo, 1979). The innervation density of the skin by free intraepidermal nerve endings (presumably mostly nociceptive), however, does not show the same distal-proximal gradient of decreasing density as for tactile receptors and the size of the nociceptive representation in the primary somatosensory cortex is unknown. Instead, innervation density of the epidermis tends to be even higher in proximal limbs and the trunk than on the finger tip (Johansson et al., 1999; Lauria et al., 1999). There is only limited data on the spatial resolution of heat pain in different skin areas, and those studies were confounded by the accuracy of motor performance. Since all studies used a similar design (pointing to the stimulated spot), these errors are likely to be similar across studies, and hence results are worthwhile to compare. The average mislocalization for heat pain was 17.1 mm on the foot (Jørum et al., 1989), 9.5–16.0 mm on the back of the hand (Koltzenburg et al., 1993; Moore and Schady, 1995), 10.5 mm on the palm of the hand and 7.5 mm on the fingers (Ochoa and Torebjörk, 1989). These data suggest relatively homogenous spatial resolution for nociception throughout the whole skin surface with only a moderate distal-proximal gradient.

In our own data, tactile resolution on the finger tip was one order of magnitude better than on the back of the hand, where it was similar to nociceptive spatial resolution. This observation suggests that tactile and nociceptive spatial resolution are similar throughout most of our skin surface, but nociception unlike tactile perception lacks a fovea of enhanced spatial detail. The detailed spatial information from the finger tips is evidently related to the manipulative functions of the human hand (Van Boven et al., 2000). On the remaining skin surface, the function of our tactile sense may mostly be to supply a warning signal (e.g. about crawling insects), which is similar to the functions of the nociceptive system. From a general sensory physiology point of view, foveal vision provides detailed spatial information, whereas the visual periphery and the auditory system are more involved in orienting reactions.

The cortical representation of touch in the primary somatosensory cortex reflects the close relationship with manipulative skills (Elbert et al., 1995). A survey of PET-studies on the cortical representation of heat pain shows that 63% of these studies show activation of SI and they discuss a role of SI in discriminative aspects (Bushnell et al., 1999). Also animal experiments found that SI neurons participate in intensity coding of noxious stimuli (Kenshalo et al., 1988). The number of nociceptive neurons in SI, however, is small. Nevertheless, somatotopic arrangement is evident in animal and human studies. Receptive fields of nociceptive neurons show somatotopic organization in the dorsal horn (Swett and Woolf, 1985), lateral thalamus (Albe-Fessard et al., 1985; Lenz et al., 1994) and the primary somatosensory cortex (Lamour et al., 1983; Kenshalo et al., 2000). In the human primary somatosensory cortex,

nociceptive face, hand, and foot areas in PET (Andersson et al., 1997) and dipole source analysis (Tarkka and Treede, 1993) were found in places predicted by the tactile homunculus. Thus, all existing evidence favors the view that SI is involved in stimulus localization for the nociceptive system as well as the tactile system. The lateral nociceptive system, which is considered to process sensory-discriminative aspects of pain (for a recent review see Treede et al., 1999), overlaps considerably with the tactile system in the thalamus and cerebral cortex (e.g. SI and SII). In contrast, the medial nociceptive system, which is considered to process affective-motivational aspects of pain, provides a separate and direct access to cortical and subcortical limbic areas (including cingulate gyrus, amygdala and hypothalamus). The medial nociceptive system is very important for many clinical aspects of pain but lacks spatial resolution.

In summary, innervation density of nociceptive afferents in hairy skin, somatotopic representation of pain in the central nervous system, and sensory performance in spatial discrimination tasks reveal relatively small differences compared with those parts of the tactile system that innervate the same skin area. These findings suggest that both the tactile and the nociceptive system subserve a similar function in hairy skin, which may be to warn the central nervous system about potentially dangerous skin contact. This warning function is usually attributed to the nociceptive system, but may also be true for parts of the tactile system. The tactile system in addition has developed an area on the finger tips with detailed spatial resolution, which is functionally equivalent to the fovea in the visual system. The nociceptive system lacks such a foveal area, which may explain its relatively minor representation in the hand area of SI.

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