Modality-specific Somatosensory Changes in a Human Surrogate Model of Postoperative Pain

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ABSTRACT

Background: Postoperative pain remains a challenging problem in part because the underlying mechanisms are still not well understood. There is a compelling need for translational studies in human models of postoperative pain to bridge the gap between animal models and human clinical studies.

Methods: Somatosensory changes using Quantitative Sensory Testing for up to 72 h after an experimental 4-mm incision were characterized in 20 male volunteers.

Results: During incision, perceived pain was 29 on a 100-point numeric rating scale and declined rapidly over the next 60 min. After incision, thresholds at the site of incision were lowered to painful heat (primary heat hyperalgesia; \( P < 0.01 \), effect size: 0.68) but not to painful cold (\( P > 0.05 \), effect size: 0.00). Remote to the incision, mechanical pain thresholds were lowered, pain ratings were increased, and an area of hyperalgesia occurred (\( P < 0.05 \), effect size: 0.56; \( P < 0.01 \), effect size: 0.70; \( P < 0.01 \), respectively; secondary mechanical hyperalgesia). All signs of heat and mechanical hyperalgesia declined until full resolution at 27–72 h after incision. Increased mechanical pain ratings remote to the incision (\( r = 0.47; P < 0.01 \)) but not the area of hyperalgesia (\( r = 0.28 \)) or heat hyperalgesia (\( r = 0.12 \)) correlated with incision-induced pain.

Conclusions: Ongoing activity of nociceptors underlying non-evoked pain after incision in humans may not be explained by sensitization of nociceptors to heat but triggers the increased painfulness of mechanical stimuli in the area of secondary hyperalgesia. However, the spatial expansion of hyperalgesia seems to rely on at least partly different mechanisms. These findings may contribute to the understanding of pain and hyperalgesia after surgery.

What We Already Know about This Topic

- Mechanisms for postoperative pain, either at rest or with movement, are poorly understood.

What This Article Tells Us That Is New

- In normal volunteers with a superficial incision, ongoing pain was not related to heat hyperalgesia, suggesting that pain at rest is not related to skin temperature and activation of heat-sensitive nociceptors.

SEVERAL surveys in Europe\(^1\) and the United States\(^2\) have demonstrated that pain in the perioperative period is still poorly managed, indicating that postoperative pain remains a challenging problem.\(^3\) Ample evidence from preclinical studies demonstrates that pain and hyperalgesia after a surgical incision are different from other pain conditions because of the specific combination of nociceptive and inflammatory responses, including edema, hyperemia, and pain, as well as nerve damage concomitant with the surgical procedure.\(^4−7\) Data from well-established animal models of incisional pain have shown that peripheral sensitization of nociceptive afferents after skin incision contributes to ongoing pain\(^8,9\) and increased sensitivity restricted to the site of incision (primary hyperalgesia).\(^10\) Amplified activation of

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nociceptive afferents triggers plastic changes at synapses of
central nociceptive neurons in the spinal cord (central sensi-
tization), leading to an increased sensitivity in an area re-
from the incision (secondary hyperalgesia). Generally, enhanced synaptic strength has been suggested to
depond on long-term potentiation of synaptic transmission
in the spinal cord. However, recent animal data suggest
that central sensitization has to be maintained by ongoing
afferent input from the incision. The preclinical data sug-
ggest that the interaction of peripheral and central pain-
Enhancing mechanisms may be crucial for the experience of
postoperative pain.

The translation of these preclinical results obtained
mainly in rodents into the clinic (postoperative patients) is,
however, difficult and requires an area of translational hu-
man research that joins elements of both preclinical and clin-
ical research. Human surrogate models of acute and chronic
pain are considered to be a valuable approach to study mech-
nism underling, e.g., neuropathic or inflammatory pain.

The major focus of the current study was to investi-
gate in detail the perceptual characteristics of pain and hy-
peralgesia after experimental skin incision in humans and to
identify associations between underlying mechanisms of sen-
sory changes. Our results show that ongoing pain ratings
caued by an incision were related to perceptual changes of
several different somatosensory modalities and submodalities
quantified by means of a comprehensive, standardized pro-
tocol of Quantitative Sensory Testing (QST). By correlat-
ing the profile of somatosensory changes with ongoing pain
characteristics—the perceptual correlate of spontaneous ac-
tivity of nociceptive afferents—we attempted to explore
whether, first, ongoing pain may be related to sensitization of
nociceptive afferents to heat as has been suggested by preclini-
cal data, and second, whether ongoing pain after incision
contributes to the initiation and/or maintenance of central
sensitization processes after incision in humans.

Materials and Methods

Subjects
The study was conducted at the University Hospital Münster
after approval of the local Ethics Committee of the Medical
Faculty, Münster, Germany. Experiments were performed in
20 male right-handed volunteers (average age 27 yr, range
22–39 yr). Handedness was determined by the Edinburgh
Handedness Inventory. Individuals with skin lesions in the areas
to be tested or neurologic and dermatologic disorders were ex-
cluded from this study. All volunteers enrolled in this study were
free of any preexisting pain syndromes and did not take analge-
sic medications. Assessments in each individual were performed
in seven experimental sessions distributed over 4 days. Each
subject was familiarized with the experimental procedures and
gave written, informed consent according to the declaration of
Helsinki. All subjects were comfortably seated in a reclining
chair with their forearms on armrests.

Experimental Design

Test Site and Control Site
Somatosensory perception was tested in the ventral forearm by QST (fig. 1). The test stimuli were applied in runs alternating between the site of incision (test site) and a con-
trolateral control site (fig. 1A and C). Thermal submodalities
were only tested directly at the site of incision (i.e., the pre-
sumed site of primary hyperalgesia; primary zone) and a con-
trolateral control site. Mechanical submodalities were only
tested remote to the incision (i.e., the presumed site of sec-
ondary hyperalgesia; secondary zone) and a controlateral
control site. To avoid interactions between the various me-
chanical test stimuli, both sites were subdivided into nine independ-
ent sectors located 10–20 mm from the incision and marked
on the skin by a stamp (fig. 1B). Three separate sectors each
(located at 120° angle) within the secondary zone were used for
the different mechanical test procedures to avoid interference
between different modalities (fig. 1B). The tests were carried out
clockwise in the areas shown in figure 1. The starting point was
always at the top (12 o’clock position).

Experimental Paradigm
After baseline testing with natural test stimuli (QST preincisi-
on), the skin incision was performed on the right forearm.

Skin Incision
A small incision (length, 4 mm) was made through the skin,
fascia, and muscle of the anterior part of the right forearm of
each subject. The blade was pushed 5–7 mm into the skin and
then pulled out. A gauze swab was gently pressed onto
the incision to stop bleeding.

Pain Ratings Related to Incision (Nonevoked Pain)
Subjects rated the magnitude of pain related to the incision
on a numeric rating scale ranging from 0 (nonpainful) to 100
(most intense pain imaginable). Subjects were free to use
integers as well as fractions ad libitum. Mean pain of the first
60 min after incision was calculated by the linear trapezoidal
rule.

Test Stimuli
Skin sensitivity was tested using a standardized test battery
for QST, as inaugurated by the German Research Network
on Neuropathic Pain. The entire battery provides a com-
prehensive profile of somatosensory functions within 30 min
and encompasses thermal as well as mechanical testing pro-
cedures (see the following paragraphs). Testing of pressure
pain thresholds was omitted from the list of test procedures
to avoid undue strain at the site of incision. The QST was

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always alternating between test and control site, and the starting site was balanced across subjects.

**Thermal Testing**

Thermal thresholds were determined using a TSA 2001-II (MEDOC, Ramat Yishai, Israel) thermal sensory testing device with a thermode of Peltier elements (contact area 16 × 16 mm, 32°C baseline temperature, ramped stimuli with 1°C/s). First, thresholds of cold and warm detection were measured in triplicate. The number of paradoxic heat sensations (reports of hot or burning sensations to innocuous cold stimuli) was determined during the thermal sensory limen procedure (the difference limen for alternating warm and cold stimuli), followed by determination of cold pain and heat pain thresholds measured in triplicate. The mean threshold temperature of the three consecutive measurements was calculated.

**Mechanical Testing**

Mechanical testing was performed in a manner similar to that described by Klein *et al.* in 2008. Briefly, vibration detection threshold was assessed with a Rydel–Seiffer tuning fork (64 Hz, 8/8 scale; Arno Barthelmes & Co GmbH, Tuttlingen, Germany). Mechanical detection threshold was assessed using a standardized set of modified von Frey hairs with a rounded tip of 0.5 mm in diameter to avoid nociceptor activation by sharp edges (OptiHair-Set; Marstock Nervtest, Schriesheim, Germany) that exert forces between 0.25 and 512 mN. Mechanical pain threshold (MPT) and stimulus-response function for determining mechanical pain

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**Fig. 1.** Experimental setup. (A) Skin incision was applied to the proximal right volar forearm, and the corresponding area on the left forearm served as the uninjured control site. (B) For mechanical QST, both test site and control site were subdivided into three independent sectors for each mechanical submodality in an area surrounding the incision (primary zone). Thermal submodalities were tested at the site of incision (primary zone). (C) Chronologic order of measurements: Baseline QST measurements (preincision) was followed by the skin incision. After incision, incision-related pain was rated for 1 h before QST was started after skin injury. CDT = cold detection threshold; CPT = cold pain threshold; DMA = dynamic mechanical allodynia; HPT = heat pain threshold; MDT = mechanical detection threshold; MPS = mechanical pain sensitivity; MPT = mechanical pain threshold; PHS = paradoxical heat sensation; QST = quantitative sensory testing; TSL = thermal sensory limen; VDT = vibration detection threshold; WDT = warm detection threshold; WUR = windup ratio. Test site (●), control site (○).
sensitivity (MPS) were assessed using custom-made weighted pinprick stimuli with fixed stimulus intensities (8, 16, 32, 64, 128, 256, and 512 mN; flat contact area of 0.25-mm diameter; The PinPrick, MRC Systems GmbH, Heidelberg, Germany). These punctual stimuli were adequate to excite cutaneous nociceptors.20,21 Mechanical detection and pain thresholds were determined by an adaptive method of limits by series of alternating ascending and descending stimulus intensities yielding five suprathreshold-only and five subthreshold-only estimates.

Pain in response to light touch (dynamic mechanical alldynia) was tested by light stroking with a cotton wisp (3 mN), a cotton wool tip fixed to an elastic strip (100 mN), and a brush (200–400 mN). Each of the seven intensities of pinpricks and of the three intensities of light stroking was applied five times in a randomized sequence. Subjects rated the magnitude of pain related to each stimulus from 0 (nonpainful) to 100 (most intense pain imaginable).

They were instructed to distinguish pain from the perception of touch or pressure by the presence of a sharp or slightly pricking or burning sensation.

To test for temporal pain summation (windup ratio), the perceived magnitude of pain to a series of pinprick stimuli (256 mN, repeated 10 times at a 1/s rate on separate spots perceived magnitude of pain to a series of pinprick stimuli). Each of the seven intensities of pinpricks and of the three intensities of light stroking was applied five times in a randomized sequence. Subjects rated the magnitude of pain related to each stimulus from 0 (nonpainful) to 100 (most intense pain imaginable).

To be able to compare QST parameters independent of their physical dimensions, all changes of somatosensory perception (taken from the average of three assessments at 1, 3, and 9 h after incision) were weighted by transformation into a standard normal distribution (Z-transformation) except for dynamic mechanical allodynia and paradoxic heat sensation:

\[ Z = \frac{\text{single value}_{\text{test site}} - \text{mean}_{\text{reference}}}{\text{SD}_{\text{reference}}} \]

The Z-scores indicate how far and in what direction the QST parameters deviated from unconditioned skin (= reference values), expressed in units of SD (Z).17 Z-values greater than 0 indicate a gain of function (more sensitive), whereas Z-values less than 0 indicate a loss of function (less sensitive). Z-values were analyzed by two-tailed paired Student t tests. Dynamic mechanical allodynia and paradoxic heat sensations could not be transformed into Z-scores because they were absent in normal skin condition (i.e., mean and SD were 0). Because neither original nor log-transformed data achieved normal distribution, allodynia and paradoxic heat sensation were analyzed by nonparametric Friedman analysis of variance (ANOVA). Effect sizes on Z-scores were defined as

\[ \text{mean}_{\text{difference}_{\text{test site}}} - \text{mean}_{\text{control site}} / \text{SD}_{\text{difference}_{\text{test site}}} - \text{SD}_{\text{control site}} \]

**Analyzing the Time Course of Perceptual Changes and Pain Ratings Related to Incision.** Sensory modalities and submodalities, which showed a significant gain of sensitivity in Z-scores, were further analyzed regarding their time course. Therefore, warm detection threshold, mechanical pain detection threshold, and pain to suprathreshold mechanical sensitivity were quantified as the difference of log-transformed thresholds and pain ratings between the test and unconditioned contralateral control site. This procedure is equivalent to building a ratio of original thresholds, and it avoids the skewed nonnormal distribution of ratio data. Because there was no area of hyperalgesia at the control site, only log-transformed radii at the test site were used. Because heat pain thresholds are interval data, the differences of raw data between test and control site were used. The time courses were analyzed by one-way repeated measures ANOVA (factor: time); post hoc Scheffé F test was used to compare increased sensitivity or pain ratings at different time points.

\[ P \text{ values less than 0.05 were generally considered statistically significant.} \]

Correlation analyses were performed by Pearson Product Moment Correlation.

Data in the text and tables are expressed as log mean ± SD as well as retransformed means. In the figures mean ± SEM are presented.

**Statistical Analysis**

All QST values with the exception of cold and heat pain threshold, vibration detection threshold, and paradoxic heat sensation were transformed into decadic logarithm to achieve a (secondary) normal distribution. To avoid a loss of zero values, a small constant (0.1) was added to all pain ratings (MPS, dynamic mechanical allodynia, and pain to incision) and the area of hyperalgesia before log transformation.22

**Z-Transformation of QST Data to Create Profiles of Sensory Changes.** To be able to compare QST parameters independent of their physical dimensions, all changes of somatosensory perception (taken from the average of three assessments at 1, 3, and 9 h after incision) were weighted by transformation into a standard normal distribution (Z-transformation) except for dynamic mechanical allodynia and paradoxic heat sensation:

\[ Z = \frac{\text{single value}_{\text{test site}} - \text{mean}_{\text{reference}}}{\text{SD}_{\text{reference}}} \]

The Z-scores indicate how far and in what direction the QST parameters deviated from unconditioned skin (= reference values), expressed in units of SD (Z).17 Z-values greater than 0 indicate a gain of function (more sensitive), whereas Z-values less than 0 indicate a loss of function (less sensitive). Z-values were analyzed by two-tailed paired Student t tests. Dynamic mechanical allodynia and paradoxic heat sensations could not be transformed into Z-scores because they were absent in normal skin condition (i.e., mean and SD were 0). Because neither original nor log-transformed data achieved normal distribution, allodynia and paradoxic heat sensation were analyzed by nonparametric Friedman analysis of variance (ANOVA). Effect sizes on Z-scores were defined as

\[ \text{mean}_{\text{difference}_{\text{test site}}} - \text{mean}_{\text{control site}} / \text{SD}_{\text{difference}_{\text{test site}}} - \text{SD}_{\text{control site}} \]

**Somatosensory Changes after Incision in Humans**

**Area of Secondary Hyperalgesia**

The area of secondary hyperalgesia to pinprick was mapped by using a conventional 116-mN (4.93) von Frey filament along eight tracks at a 45° angle to each other just before the QST testing. The von Frey filament was applied along the tracks beginning outside the area of secondary hyperalgesia and moving centripetally toward the incision site until the sensation became painful or pricking. The eight points indicating the outer part of the secondary hyperalgesia zone were marked, connected, and traced on a transparent sheet of paper and scanned into the computer. The area between the connected points was calculated by using ImageJ National Institutes of Health, Bethesda, MD.

**Statistical Analysis**

All QST values with the exception of cold and heat pain threshold, vibration detection threshold, and paradoxic heat sensation were transformed into decadic logarithm to achieve a (secondary) normal distribution. To avoid a loss of zero values, a small constant (0.1) was added to all pain ratings (MPS, dynamic mechanical allodynia, and pain to incision) and the area of hyperalgesia before log transformation.22
Results

Pain Ratings Related to Incision (Nonevoked Pain)

Pain was maximal during incision (numeric rating scale 28.8, log: 1.459 ± 0.315 [SD]; fig. 2A) and decreased immediately until incisional pain was completely gone 9 h after incision in all subjects (ANOVA on time course: $F_{22,418} = 18.30, P < 0.001$). Within the first hour it appears that incisional pain was almost gone 8 min after incision (0.17 numeric rating scale; log $0.771 ± 0.609$ [SD]) but reincreased in more than half of the subjects with peak pain ratings at various time points between 10 and 60 min after incision (numeric rating scale 5.7, log: $0.753 ± 0.338$ [SD], range 2–20/100, n = 11; fig. 2B). However, this re-increase failed to be significant in post hoc Scheffé F tests.

Changes of the Perception to Natural Somatosensory Stimuli at and Adjacent to the Site of Incision

At baseline (QST preincision) there were no systematic differences between the test site (site of incision) and the contralateral control site. However, there were statistically significant lower cold pain thresholds at the test site (8.7 ± 5.6 [SD] °C) compared with the control site (13.5 ± 7.5 [SD] °C; $P < 0.01$; see table, Supplemental Digital Content 1, http://links.lww.com/ALN/A737, which listed all original QST values at baseline).

To allow comparison of the QST parameters independent of their physical dimension, somatosensory changes except for pain ratings to light tactile stimuli and numbers of paradoxical heat sensations were transformed into standard normal distribution (Z-score QST profile, fig. 3A and B). The QST profile, which was averaged over three measurements after incision at day 1 (1, 3, and 9 h after incision), revealed an increase in sensitivity to painful heat stimuli ($P < 0.01$) and to innocuous warm stimuli ($P < 0.05$) at the site of incision (primary zone). All other thermal submodalities did not change significantly.

The incision also induced an area of hyperalgesia assessed by enhanced pain to pinprick stimuli (mean radius averaged over 1, 3, and 9 h after incision: 1.1 cm; log: $0.024 ± 0.554$ [SD]; see next paragraph). The degree of secondary hyperalgesia to pinprick stimuli was quantified by a decrease of MPT and an increase of pain ratings to suprathreshold pinprick stimuli (MPS) when compared with the unconditioned control site (fig. 3A). The latter is displayed in detail in figure 4 and shows the upward shift of the stimulus-response function to pinpricks adjacent to the site of incision (fig. 4B), whereas pinprick-evoked pain at the uninjured control site remained unaltered (fig. 4D). Dynamic mechanical allodynia was neither reported at the test site nor at the control site (fig. 4A and C). Furthermore, windup ratio, mechanical detection threshold, and vibration detection threshold remained unaltered (fig. 3A). The effect sizes of QST measures that exhibited significant change ranged from 0.56 to 0.70, indicating that they are meaningful (table 1).

Time Course of Somatosensory Changes

Heat hyperalgesia at the site of incision was maximal at 1 h after incision and declined continuously thereafter. Significant heat hyperalgesia across all subjects was met 1 h after incision (fig. 3A). Heat hyperalgesia gradually resolved at days 2 and 3 (27 and 72 h). The decline of heat hyperalgesia over time, however, did not reach statistical significance across all subjects ($F_{4,76} = 1.69, P = 0.16$, fig. 5) because there was a marked variability of heat pain threshold across and within subjects. Moreover, only 7 of 20 subjects developed statistically significant heat hyperalgesia (two-tailed paired Student t test; $P < 0.05$). When analyzing only those...
subjects the decline over the 72-h observation period became statistically significant (n = 7; F,4.24 = 3.66; P < 0.05).

Although the threshold of warm sensation was significantly lowered (discussed previously), this effect remained constant throughout the entire observation period and did not decline over time (F,4.76 = 0.84; P = 0.51; data not shown).

Mechanical hyperalgesia to pinpricks in the secondary zone was also maximal at 1 h after incision and consistent between both intensity measures of pinprick hyperalgesia (MPT, MPS) with a drop of thresholds to 57% and an increase of pain rating to 149% of that of the control site. Mechanical hyperalgesia returned to control values at approximately 2 days after incision (fig. 5B and C). The decline over time of both measures (MPT, MPS) in the secondary zone was highly significant across all subjects (MPT: F,4.76 = 6.90; MPS: F,4.76 = 6.05; P < 0.001 each). The hyperalgesic area was already present 1 h after incision (mean radius 1.1 cm; log: 0.034 ± 0.708 [SD] fig. 5D), became maximal at 3 h (mean radius 1.6 cm; log: 0.191 ± 0.578, mean ± SD; fig. 5D) and gradually resolved more than 72 h after incision (ANOVA on time course: F,4.76 = 17.41, P < 0.001).

Correlations of QST Changes and of QST Changes to Incisional Pain

For correlation analyses only those QST parameters were analyzed that were significantly altered by experimental skin incision (table 1). Heat hyperalgesia and increased warm detection tended to correlate weakly (r = 0.41; P = 0.07), but neither was correlated to any measure of pinprick hyperalgesia (table 2) nor to pain related to the incision (averaged over 60 min).

MPT and MPS tended to correlate (MPT; r = 0.43, P = 0.06) or correlated (MPS; r = 0.47, P < 0.05) with the mean incision pain. The size of the hyperalgesic area, however, was not correlated with the mean incision pain (r = 0.28). In addition, MPT and enhanced MPS were highly correlated with each other (r = 0.66, P < 0.001), but not (MPT; r = 0.24) or only weakly (MPS; r = 0.51, P < 0.05) with the size of the hyperalgesic area.

However, this absent or weak correlation may partly be explained by the fact that the site of MPS and MPT determination lay outside the hyperalgesic skin in some subjects. In fact, subgroup analysis of only those subjects in whom MPS and MPT data have been obtained within the hyperalgesic skin (n = 14) confirmed a substantial correlation (MPT: r = 0.61; P < 0.05; MPS: r = 0.87, P < 0.001, n = 14).

Discussion

The current study adds major new findings to the pathophysiologic mechanisms of complex somatosensory changes after a surgical skin incision in humans. First, experimental skin incision was followed by biphasic ongoing pain. Second, pri-
mary heat hyperalgesia occurred but was brief and did not correlate with ongoing pain, suggesting that primary heat hyperalgesia and ongoing pain are mediated by different fiber types. Third, certain measures of secondary hyperalgesia correlated with ongoing pain, suggesting that the amount of the afferent input determines the level of central sensitization. Finally, primary cold hyperalgesia, dynamic mechanical allodynia, and an increase in windup to pinprick stimuli were not present after incision in humans. These findings have important implications for the underlying mechanisms of postoperative incisional pain, which will be discussed in the next paragraphs.

Mechanisms of Ongoing Pain after Incision
The duration of ongoing pain matched the temporal pattern of incisional-evoked pain in humans reported in previous studies. As shown recently, spontaneous activity in sensitized C- and Aδ-fiber nociceptive afferents induced by deep-tissue (muscle and/or fascia) injury has been suggested as a major contributor to nonevoked ongoing pain after incision in rats. However, the different role of cutaneous and muscle tissue injury to spontaneous pain after incision was not addressed here.

The apparent biphasicity within the first hour has not yet been described in models of incisional pain, maybe because ongoing pain has not yet been investigated in this temporal resolution. However, the reincrease did not reach statistical significance further studies with larger groups of subjects have to address this issue in future studies.

Somatosensory Changes at the Site of Incision (Primary Zone)
Somatosensory changes to thermal stimuli in humans at the site of an incision have not yet been studied. After experi-

![Fig. 4. Stimulus-response functions for pinpricks and tactile stimuli. (A and C) Dynamic mechanical allodynia did not develop after incision. Cotton wisp (cw) 3 mN, Q-tip (qt) 100 mN, brush (br) 400 mN. (B) In contrast, experimental skin incision resulted in mechanical pinprick hyperalgesia. The stimulus-response (S/R-) function for pinprick probes was approximately linear in log-log coordinates in normal skin (blue squares, blue regression lines). One hour after incision, there was a significant parallel upward shift by 91% of the S/R-function adjacent to the site of incision relative to the baseline (ANOVA (pre vs. post) F1,19 = 21.18, P < 0.001) (red squares). There was no change of the S/R-function at the uninjured control site (D). Mean ± SEM values across 20 subjects at baseline and 1 h after incision. Each data point represents average pain ratings on a 0–100 numeric ratings scale. A value of 0.1 corresponds to zero pain ratings because a small constant (0.1) had to be added before logarithmic transformation. Asterisk = P < 0.05, triple asterisk = P < 0.001 (post hoc Scheffé F test) before versus after incision.](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931110/ on 11/22/2018)
ment of skin incision human volunteers experienced primary heat hyperalgesia, which is similar to findings from other human pain models including topical capsaicin application, freeze lesion, and burn injury.\(^{16,28-32}\) Primary heat hyperalgesia is generally considered a perceptual correlate of sensitization of nociceptive afferents (peripheral sensitization).\(^{33}\) In agreement, sensitization of C-fiber nociceptors after incision has been demonstrated in rats\(^{18}\) and monkeys.\(^{8}\)

A drop in the threshold of heat-sensitive nociceptors below body temperature has been linked to spontaneous activity of C-fibers, which has been suggested to account for non-evoked resting pain under inflammatory conditions\(^{34}\) but may also underlie spontaneous pain after incision.\(^{18}\) However, the magnitude of primary heat hyperalgesia after incision in humans did not correlate with ongoing pain in the same volunteers. This finding is supported by findings in rodents\(^{26,27}\) and suggests that sensitization of different fiber types is involved in mediating ongoing pain and heat hyperalgesia after incision in humans. Whereas heat hyperalgesia may be mainly mediated by sensitized mechanooheat-sensitive C-fibers in hairy skin\(^{15}\) and glabrous skin,\(^{18}\) ongoing pain may be mediated both by a specific subset of cutaneous widely branched, peptidergic nociceptive C-fiber afferents, which are chemosensitive but insensitive to mechanical stimuli,\(^{36,37}\) and deep-tissue nociceptors (muscle and/or fascia).\(^{27}\) These fibers have been suggested to be involved in the induction of central sensitization.\(^{37,38}\) Ongoing pain after incision correlated with the occurrence and the degree of secondary hyperalgesia in humans (discussed later).

In contrast to animal studies, heat hyperalgesia after incision in humans was weak and lasted only briefly compared with that of rodents after incision.\(^{4}\) In addition to the differences between humans and animals, this finding may depend, first, on different mechanisms involved in the induction of heat hyperalgesia in glabrous and hairy skin.\(^{39}\) Second, heat hyperalgesia after incision in humans was probably underestimated because only those C-fibers are sensitized which are in close proximity to the incision\(^{8,38}\); therefore, the major part of the nerve endings in the receptive field covered by the thermode (16 × 16 mm\(^2\)) were probably not sensitized by the skin incision (4 mm). To investigate this finding in more detail we are currently determining the intensity and time course of hyperalgesia to heat by using a smaller thermode. Third, animal studies may also be confounded by learning processes, which may lead to an only ostensibly prolonged duration of heat hyperalgesia (reviewed by Le Bars et al.\(^{40}\)). Finally, mechanisms of heat hyperalgesia in rodents and humans might be mediated differently (or at least different in magnitude). For instance, TRPV1, a major molecule involved in heat hyperalgesia after incision in rodents,\(^{5}\) is more common in mice than in other species.\(^{41}\) This would explain the long-lasting and robust hyperalgesia to heat in rodents\(^{6,10}\) but not humans after incision (current study).

The enhanced warm detection (warm hyperesthesia) after skin incision remained stable over the entire observation period of 72 h. However, sensitization of warm fibers has not been reported so far\(^{30}\) and is thus unlikely to be the underlying mechanism. Alternatively, the warm hyperesthesia may be caused indirectly due to local warming by an increased blood flow;\(^{42}\) however, in rodents, local warming of the incision site is very discrete.\(^{43}\)

Cold hyperalgesia after incision in humans was not detected. Again, this might be because of the size of the thermode, which was probably too large. However, recent results from an animal experimental study support that hyperalgesia to cold does not occur after incision injury.\(^{43}\)

### Somatosensory Changes Remote from the Site of Incision (Secondary Zone)

In an area surrounding the site of incision we found increased pain to pinprick stimuli (secondary mechanical hyperalgesia), which confirms previous reports after incision in humans\(^{29,24}\) and after other types of actual or simulated tissue injuries in volunteers.\(^{16,28-32}\) Hyperalgesia secondary to mechanical stimuli is considered the perceptual correlate of central sensitization in humans.\(^{38}\) Increased pain to mechanical stimuli has been detected remote to a surgical incision in patients and correlated not with pain at rest but with movement-evoked pain and prolonged pain after surgery.\(^{44,45}\) It has been suggested that a persistent flow of nociceptive input from sensitized afferents may reinforce central neuronal plasticity leading to a maintained central sensitization, finally resulting in sustained and increased postoperative pain.\(^{46}\) Both the intensity of acute postoperative pain and sustained central sensitization have been implicated as potential risk factors for the development of chronic postoperative pain.\(^{47-50}\)

The significant correlation between certain measures of secondary hyperalgesia (MPS) and ongoing pain suggests

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**Table 1.** Quantitative Sensory Testing in Units of Standard Normal Distribution (Z-score)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Z-scores Mean (1, 3, 9 h)</th>
<th>Effect Size (Test vs. Control)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDT</td>
<td>-0.117 ± 0.970 0.12</td>
<td>0.597</td>
<td></td>
</tr>
<tr>
<td>WDT</td>
<td>0.453 ± 0.786 0.58</td>
<td>0.018</td>
<td></td>
</tr>
<tr>
<td>TSL</td>
<td>0.283 ± 1.844 0.15</td>
<td>0.501</td>
<td></td>
</tr>
<tr>
<td>CPT</td>
<td>0.003 ± 0.973 0.006</td>
<td>0.987</td>
<td></td>
</tr>
<tr>
<td>HPT</td>
<td>0.490 ± 0.725 0.68</td>
<td>0.007</td>
<td></td>
</tr>
<tr>
<td>MPT</td>
<td>0.483 ± 0.869 0.56</td>
<td>0.022</td>
<td></td>
</tr>
<tr>
<td>MPS</td>
<td>0.347 ± 0.498 0.70</td>
<td>0.006</td>
<td></td>
</tr>
<tr>
<td>WUR</td>
<td>0.009 ± 0.492 0.02</td>
<td>0.935</td>
<td></td>
</tr>
<tr>
<td>MDT</td>
<td>-0.035 ± 0.633 0.06</td>
<td>0.806</td>
<td></td>
</tr>
<tr>
<td>VDT</td>
<td>0.170 ± 0.656 0.26</td>
<td>0.261</td>
<td></td>
</tr>
</tbody>
</table>

Mean ± SD; two-tailed paired Student t test.

* DMA and PHS did not occur in normal skin and thus cannot be transformed into Z-scores.

CDT = cold detection threshold; CPT = cold pain threshold; DMA = dynamic mechanical allodynia; HPT = heat pain threshold; MDT = mechanical detection threshold; MPS = mechanical pain sensitivity; MPT = mechanical pain threshold; PHS = paradoxical heat sensation; QST = quantitative sensory testing; TSL = thermal sensory limen; VDT = vibration detection threshold; WDT = warm detection threshold; WUR = windup ratio.
that the degree of afferent input determines, at least in part, central sensitization. However, the correlation between other measures of secondary hyperalgesia and ongoing pain is low (MPT) or even absent (area of secondary hyperalgesia), suggesting that afferent input determining the degree of central sensitization may not be expressed dependably in the ongoing pain ratings. Similar weak or absent relationships between pain ratings and measures of central sensitization have been found earlier in humans.47–50 In addition, clinical studies indicate different drug effects on acute postoperative pain ratings and measures of sensitization, e.g., the area of hyperalgesia surrounding the incision after surgery.47–50 As sup-

![Figure 5](image)

**Fig. 5.** Time course of somatosensory changes after skin incision. (A) Heat hyperalgesia (HPT) was maximal 1 h after incision and declined continuously afterward. Mechanical hyperalgesia to pinpricks quantified by a reduction of mechanical pain threshold (MPT; B), an increase of pain ratings to suprathreshold stimuli (mechanical pain sensitivity, MPS; C) or the area of mechanical hyperalgesia (D) showed a time course similar to that of heat hyperalgesia but was highly significant across all subjects. Each dot represents either the ratio (B and C) or the difference between the injured and the uninjured contralateral site (C) or the mean radius of the hyperalgesic area (D). All values except in D were averaged over a 20-min time window. Mean ± SEM values across 20 subjects. Asterisk \( P < 0.05 \), double asterisk \( P < 0.01 \), triple asterisk \( P < 0.001 \) (post hoc Scheffé F test).

**Table 2.** Correlation Matrix

<table>
<thead>
<tr>
<th>Scoring</th>
<th>Time</th>
<th>1 Inc. Pain</th>
<th>3 WDT</th>
<th>4 HPT</th>
<th>5 MPT</th>
<th>6 MPS</th>
<th>7 2°HA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incision pain (NRS)</td>
<td>Mean 60 min</td>
<td>1</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>WDT (Z-score)</td>
<td>(1 h)</td>
<td>3</td>
<td>0.18</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>HPT (Z-score)</td>
<td>(1 h)</td>
<td>4</td>
<td>0.12</td>
<td>0.41</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>MPT (Z-score)</td>
<td>(1 h)</td>
<td>5</td>
<td>0.43*</td>
<td>0.37</td>
<td>0.10</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>MPS (Z-score)</td>
<td>(1 h)</td>
<td>6</td>
<td>0.47†</td>
<td>0.36</td>
<td>0.04</td>
<td>0.66‡</td>
<td>—</td>
</tr>
<tr>
<td>2° Hyperalgesia (area)</td>
<td>(1 h)</td>
<td>7</td>
<td>0.28</td>
<td>0.44</td>
<td>0.07</td>
<td>0.24§</td>
<td>0.51†§</td>
</tr>
</tbody>
</table>

Bold type = significant correlations; * \( P < 0.1 \); † \( P < 0.05 \); ‡ \( P < 0.001 \); § = Correlation only if MPT and MPS lie inside the hyperalgesic skin: to MPT (\( r = 0.61, P < 0.03 \)); to MPS (\( r = 0.87, P < 0.001 \)).

HA = hyperalgesic area; HPT = heat pain threshold; Inc. Pain = incision pain; MPS = mechanical pain sensitivity; MPT = mechanical pain threshold; NRS = numeric rating scale; WDT = warm detection threshold.
ported by experiments in animals after incision, afferents involved in the experience of ongoing pain and the initiation and maintenance of central sensitization are, at least in part, different, and pain ratings to a given stimulus may exhibit only a loose correlation to nociceptive input.

Distinct to other types of tissue injuries and human surrogate models of chronic pain such as intradermal capsaicin, the heat-capsaicin model, or high-frequency electrical stimulation, we did not observe dynamic mechanical allodynia after incision. Compared with secondary mechanical hyperalgesia, the maintenance of allodynia is considered to depend on ongoing activity of nociceptive afferents. Thus, the type of sensitized nociceptors and/or the extent of nociceptor activation by the surgical incision do not induce central sensitization to tactile Aβ-fibers and therefore allodynia, emphasizing the need of specific surrogate models to study the neurobiology of pain caused by distinct types of tissue injuries.

Finally, we did not detect a change in the windup ratio after incision, indicating that a surgical incision induces central sensitization but not windup. This finding is consistent with the literature demonstrating that windup and central sensitization are distinct phenomena and windup is unchanged in secondary hyperalgesia.

Technical Considerations

Because of time limitations within the extensive study protocol, we were not able to examine somatosensory changes to thermal stimuli in the area remote from the incision (secondary zone of hyperalgesia). However, C-fibers remote to an incision in the rat were not sensitized to heat, and sensitization of nociceptors to heat in monkeys was absent after a cut injury outside their receptive field. Accordingly, secondary hyperalgesia to heat after incision did not occur in behavioral animal studies. This fits well with the general finding that hyperalgesia to heat is typically restricted to the site of the injury in humans. Moreover, we refrained from maintaining skin temperature because it is technically unfeasible to keep skin temperature constant at the incision site due to enhanced blood perfusion.

Conclusion

The presented data cast new light on the somatosensory profile of pain and hyperalgesia after incision injury in humans. The drop of heat pain threshold below body temperature cannot account for novenoked resting pain in postoperative patients as has been suggested for inflammatory pain. These findings point to principal mechanistic differences between incisional and inflammatory nociception. Moreover, the correlation between ongoing pain and the degree of some perceptual correlates of central sensitization in experimental skin incision provides a rationale for the preventive analgesia treatment strategy to avoid postoperative pain and hyperalgesia in patients. However, afferent fibers involved in the initiation and maintenance of the large area of hyperalgesia surround an incision, a surrogate marker for central sensitization that is assessed frequently in patients after surgery, need to be determined. Future studies using this human surrogate model for postoperative pain will be useful to help understanding the unique neurobiology of pain in humans after a surgical incision and translate these findings to postoperative patients.

References

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