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Discriminative and affective touch in human experimental tactile allodynia

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Abstract

Recently, several studies have suggested a role for unmyelinated (C-tactile, CT) low-threshold mechanoreceptive afferents in the allodynic condition. In this psychophysical study we explored the integrity of both A β and CT afferent processing following application of the heat capsaicin model of tactile allodynia on the left forearm in healthy subjects (n=40). We measured tactile direction discrimination (TDD) to target the integrity of A β processing (n=20). The TDD accuracy was significantly lower in the allodynic compared to a control zone. In addition, we measured the perceived pleasantness and pain of brush stroking at CT targeted (slow) and CT sub-optimal (fast) stroking velocities to investigate the integrity of CT processing (n=20). When comparing touch pleasantness in the allodynic and control zone, there was a significantly larger difference in ratings for CT targeted compared to CT suboptimal stimulation. The results suggest a disturbance in both A β -mediated discriminative and CT-mediated affective touch processing in human experimental tactile allodynia. Our findings support the canonical view that tactile allodynia is signaled by A β afferents but that CTs seem to contribute by the loss of a pain inhibiting role.

Keywords: C-tactile afferents; A β afferents; Heat/capsaicin; Psychophysics

Introduction

The canonical view is that tactile allodynia is signaled by fast-conducting, myelinated low-threshold mechanoreceptors ($A\beta$ -LTMRs) gaining access to pain signaling pathways following central sensitization [1]. The critical role of $A\beta$ -LTMRs in signaling tactile allodynia is based on numerous human selective nerve block studies indicating that tactile allodynia is abolished by compression or ischemic block of these afferents [1], but cf. [2].

However, recent studies show that slowly-conducting, unmyelinated, C-LTMRs may also have a role in the pathophysiology [2-5]. C-LTMRs are considered the animal homologue of human C-tactile (CT) afferents and, under normal conditions, CTs are thought to signal pleasant aspects of light, stroking touch [6-8]. However, in the heat capsaicin experimental model of tactile allodynia, the sensory input from CT afferents is altered [4]. This was demonstrated in two rare patients lacking $A\beta$ afferents who, following the application of the model, did not perceive allodynia but a reduced C-touch sensation [4, 9].

The heat capsaicin model of tactile allodynia induces a primary hyperalgesic area, surrounded by a secondary hyperalgesic area [10]. Generally, within the secondary hyperalgesic area a transient, smaller area of dynamic tactile allodynia develops. Sometimes this area is surrounded by, and incorporated within, a larger area of tactile hypoesthesia [11], which is considered to reflect altered central processing of $A\beta$ fiber input.

Tactile direction discrimination (TDD) is a psychophysical measure highly sensitive in detecting $A\beta$ deficits in the clinical setting [12, 13]. Here, we investigated TDD as an indicator of $A\beta$ processing in the secondary hyperalgesia and control zones.

CTs are highly sensitive mechanoreceptors and show fatigue (i.e. decreased responsiveness to repeated stimulation of the receptive field) [14]. CTs show strong responses to slow ($1-10\text{cm s}^{-1}$) stroking, but poor response to fast (30cm s^{-1}) stroking and CT firing correlates with ratings of pleasantness [6]. On the contrary, $A\beta$ afferents fire with a higher discharge rate to faster brush stroking [6]. This physiological difference provides a means for preferentially stimulating each afferent type [6, 15-17]. Here, our subjects rated touch pleasantness and pain for CT targeted and CT sub-optimal brush stroking as an indicator of CT processing in the secondary hyperalgesia and control zones.

We hypothesized decreased TDD accuracy, as well as reduced touch pleasantness, implying that both types of LTMR processing are affected in tactile allodynia.

Material and methods

Participants

The ethical review boards at the University of Gothenburg approved the procedures. The experiments were performed in accordance with the Declaration of Helsinki. Informed, written consent was obtained from 40 healthy subjects (median age 25 years, range 19-43 years, 20 men).

Heat/capsaicin sensitization

A Peltier thermode (3x3cm, Medoc, TSA 2001, Thermosensory Analyzer, Rimat Yishai, Israel) was used to deliver a 5min 45°C stimulus to the subject's left forearm dorsum. Then capsaicin cream (Capsina, 0.075%, Hants, UK) was applied to that same, preheated, skin area for 30min. The subjects reported ongoing pain from the treated skin as numeric ratings (No pain - Worst pain imaginable, 0-10). The median pain rating at the end of the heat stimulus was 1.1 (range 0-5.5) and after removal of the capsaicin 1.5 (range 0-5.1) (n = 40). All participants developed a flare.

Following model application, half of the subjects participated in TDD and half in stroking pleasantness and pain testing. All testing was on the long axis of the forearm radial or ulnar to the primary hyperalgesia zone (depending on where the allodynic percept to light cotton swab stroking was most prominent). For comparison, the same stimuli were applied in a control zone, 12cm proximal or distal to the capsaicin zone. We used a pseudo-randomized block design; subjects were allocated in a balanced design for the site of model application (i.e. proximal or distal forearm), zone where testing commenced (i.e. allodynic or control zone), and all stimulus sequences (although limited to a maximum of 4 consecutive identical stimulations). The areas of punctate hyperalgesia, tactile hypoesthesia and tactile allodynia were quantified after the main test protocols. Subjects were prevented from seeing the tested extremity throughout the experiment. As all testing was completed within 30 minutes of the model application, rekindling was not required.

Questionnaire

After the testing all subjects completed the Short Form-McGill Pain Questionnaire (SF-MPQ) [18].

TDD

All stimuli were delivered by the same experimenter using a hand-held stimulator (half cylinder contact surface covered in fine woven fabric, diameter 4mm x length 15mm), vertical load 16g, stimulation velocity 1cm s⁻¹ [13]. Participants were instructed to verbally report the direction (distal or proximal) after each movement. The test started with motion over an 18mm distance: three

consecutive correct responses shortened the distance whereas one incorrect response increased it. The best (i.e. lowest) score obtainable was 18 points [12, 13] . The paradigm consisted of 32 trials in each zone.

Stroking pleasantness and touch evoked pain

Tactile stimuli were delivered manually (soft goat's hair brush: 0.5cm wide, 3cm long) to the allodynic and control zones, respectively (stroking distance 5cm, approximate application force 0.3N [4, 6]). Two different stimulation velocities were used for preferential activation; 3cm s⁻¹ for CT and 30cm s⁻¹ for A β afferents [6, 15-17]. To control for differences in stimulus duration 10 consecutive strokes were applied at 30cm s⁻¹ (10x30cm s⁻¹). A single stroke stimulus of 30cm s⁻¹ was also included. All stimuli were delivered manually by the same experimenter who was trained to apply the strokes with constant force and velocity. Ten stimuli of each type were delivered in each subject, pseudorandomized order. The participants were instructed to rate their subjective perception of each stroking on a computerized visual analogue scale (VAS) with the endpoints *Unpleasant* and *Pleasant* (0–10) [19]. Similarly a pain rating for each stroking stimulus was recorded using a VAS with the endpoints *No Pain* and *Worst Pain Imaginable* (0-10).

Mapping of the secondary zone

In all subjects, the areas of punctate hyperalgesia, hypoesthesia and tactile allodynia surrounding the primary zone were mapped. Skin stimulation was initiated outside the affected skin area and moved towards the primary zone along eight orientations (45°, 90° angles). Punctate hyperalgesia was mapped with a monofilament (calibrated indentation force 0.25N) and the area measured 1064mm²+/-118 (mean +/- SEM, n=40). Tactile hypoesthesia and allodynia were mapped by 0.5cm strokes with a cotton swab (approximate application force 0.3N) [4, 6]. Subjects were asked to report hypoesthesia i.e. sudden intensity drop or numbness of the tactile stimulus, area 652mm²+/-119 (mean +/- SEM, n=40) and tactile allodynia i.e. unpleasant or painful sensation to light touch, area 391mm²+/-72 (mean +/- SEM, n=40).

Statistics

Statistical comparisons were made using SPSS (PASW Statistics for Windows, Version 18.0. Chicago, IL). Significances were sought below $P<0.05$. Kolmogorov-Smirnov tests of normality were run for all data and parametric or non-parametric statistics were used accordingly.

Results

Questionnaire

The most common SF-MPQ descriptors selected for stroking in the allodynic zone were “hot-burning” (n=30), “tender” (n=22), and “stabbing” (n=10) (Fig.1). None of the descriptors were applicable in the control zone.

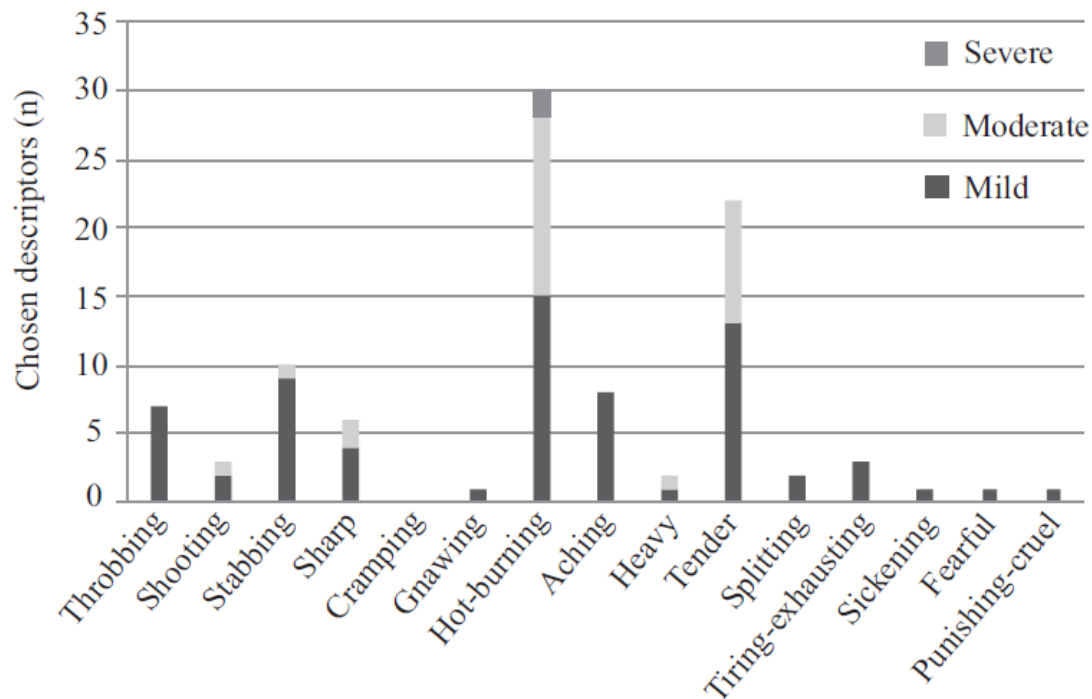


Figure 1. SF-MPQ of pain descriptors related to stroking stimuli in the allodynic zone, the most commonly chosen descriptors were “hot-burning”, “tender”, and “stabbing”.

TDD

Subjects were significantly less accurate in the allodynic compared to the control zone (Wilcoxon: $P=0.001$, allodynic median 21, control median 18, $n=20$; Fig. 2). There was no significant difference in ongoing pain ratings throughout the testing of the two zones (Wilcoxon: $P=1.000$). There was one extreme outlier (Fig. 2), but the difference remained significant after exclusion of this data point ($P=0.002$). There were no significant correlations between TDD scores and mapped areas of punctate hyperalgesia, hypoesthesia or tactile allodynia (Spearman’s rho).

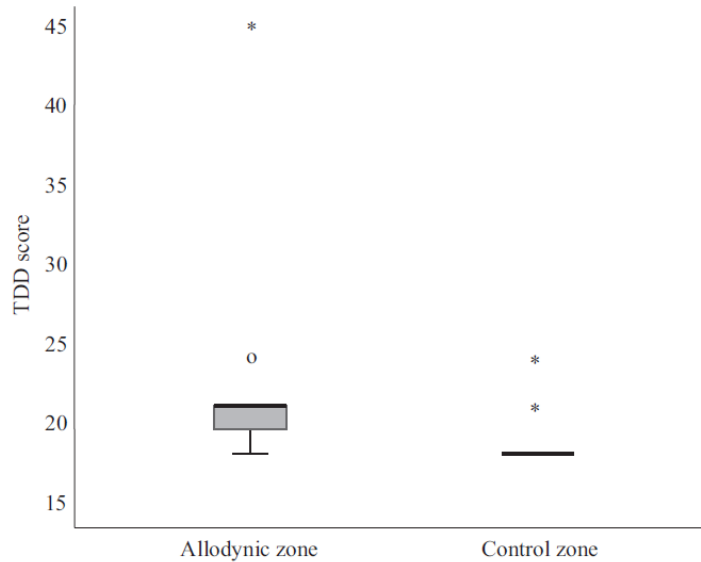


Figure 2. TDD accuracy was significantly less accurate in the allodynic compared to the control zone. The lowest TDD score obtainable is 18. T-bars extend to 1.5 times the inter-quartile range (IQR). Outliers are represented as circles and extreme outliers as asterisks (defined as values greater than 1.5 times and 3 times the IQR, respectively).

Stroking pleasantness and touch evoked pain

A significant decrease in pleasantness was found when comparing stroking in the allodynic compared to the control zone for 3 cm s^{-1} and for single 30 cm s^{-1} stroking but not for $10 \times 30\text{ cm s}^{-1}$ stroking (Fig. 3; Table 1). The decrease in pleasantness ratings between the allodynic and control zone for stroking at 3 cm s^{-1} was significantly larger than for $10 \times 30\text{ cm s}^{-1}$ but not for single 30 cm s^{-1} stroking (Repeated measures ANOVA: Wilks' Lambda = 0.6, $F(2,18) = 6.0$, $P=0.01$. Post-hoc Bonferroni corrected pairwise comparisons, $P=0.006$ and $P=0.18$ respectively; Fig. 3). There was no significant difference between the single 30 cm s^{-1} stroking and the $10 \times 30\text{ cm s}^{-1}$ condition ($P=0.22$; Fig. 3A).

Paradigm	VAS Pleasantness		Significances testing (Allodynic vs Control)	VAS Pain		Significance testing (Allodynic vs Control)
	Allodynic	Control		Allodynic	Control	
3 cm s^{-1}	6.1	7.4	$t=4.2$, $P=0.003$	0.09	0	$P=0.001$
$10 \times 30\text{ cm s}^{-1}$	5.6	5.9	$t=1.0$, $P=0.95$	0.06	0	$P=0.001$
30 cm s^{-1}	5.9	6.6	$t=2.8$, $P=0.03$	0.04	0	$P=0.003$

Table 1. Mean pleasantness values compared using Bonferroni corrected one sample t-tests against zero. Median pain values compared using one sample Wilcoxon signed rank test against zero.

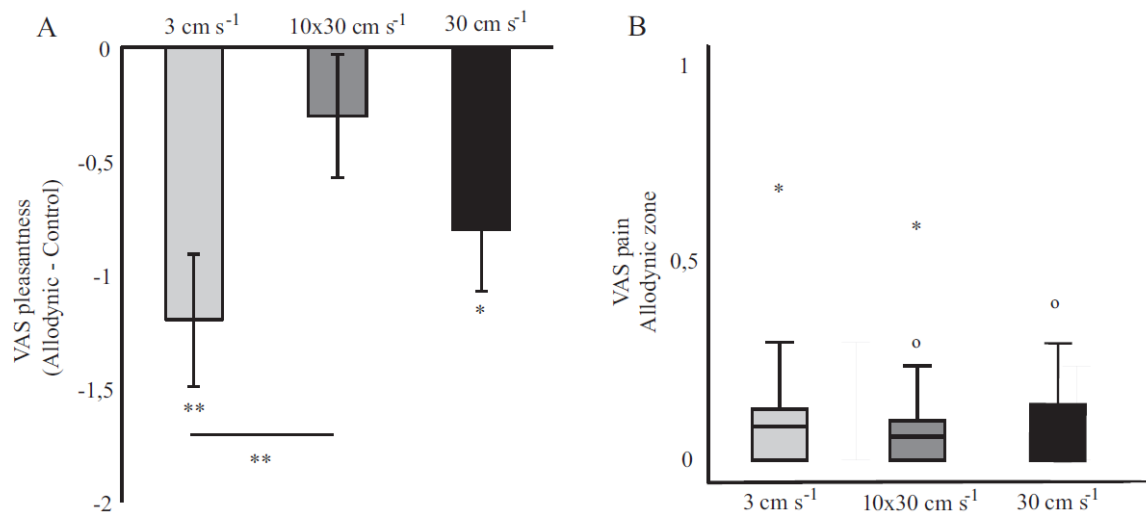


Figure 3. A) Psychophysical testing of perceived pleasantness. There was a significant decrease in pleasantness ratings, when comparing brush stroking in the allodynic and the control zone for stroking at 3 cm s^{-1} and single stroking at 30 cm s^{-1} but not for stroking at $10\times 30\text{ cm s}^{-1}$. The decrease in ratings were significantly greater for the CT targeted (3 cm s^{-1}) than the CT suboptimal ($10\times 30\text{ cm s}^{-1}$) brush stroking. Error bars indicate SEM. B) Pain ratings for touch in the allodynic zone. There were no significant differences in pain ratings across the three stimulus conditions. Conventions as in figure 2.

Tactile stimulation with a soft brush stroke was rated as minimally painful for all touch conditions in the allodynic zone (Fig. 3B; Table 1). There was no significant difference in touch evoked pain between stimulus types ($P = 0.68$, related samples Friedman's two-way analysis of variance by ranks).

There was no significant difference in ongoing pain ratings throughout the testing of the two zones (Wilcoxon: $P=0.5$). There was a significant correlation between the differences in pleasantness ratings for the two zones and the area of punctate hyperalgesia for 3 cm s^{-1} (Pearson: $r=-0.63$, $P=0.003$) and for $10\times 30\text{ cm s}^{-1}$ (Pearson: $r=-0.58$, $P=0.007$). A correlation was also seen for the difference in pleasantness ratings at $10\times 30\text{ cm s}^{-1}$ and the mapped area of hypoesthesia (Pearson: $r=-0.53$, $P=0.02$). However, this significance was driven by one outlier ($>3\text{ SD}$); when this subject was removed the significance was lost. There were no significant correlations between the differences in pleasantness ratings for the two zones and the area of tactile allodynia (Pearson).

Discussion

Our findings suggest that there was a disturbance in both A β and CT afferent processing; the deficits were suggested from decreased TDD accuracy and reduced stroking pleasantness.

Decreased TDD accuracy in the allodynic zone

TDD testing evaluates A β function with high sensitivity and specificity [13]. Our findings show a consistent and significant decrease in TDD accuracy in the allodynic zone. It seems unlikely that distraction by the capsaicin induced pain could explain the difference in TDD scores since the ongoing pain from the treated skin area was the same after testing in the allodynic and the control zones.

It has previously been shown that following a capsaicin injection, there is numbness and reduced tactile detection in an area surrounding the allodynic zone [11]. This is explained in terms of pain-induced inhibition of non-nociceptive somatosensory input, i.e. tactile peripheral input is re-routed resulting in cross-talk into nociceptive pathways, leading to the loss of tactile sensitivity [11]. Physiological alteration of somatosensory processing supporting this inhibition has been demonstrated at the level of the spinal cord [20], the thalamus [21], and the contralateral primary somatosensory cortex [22]. We did not find a significant correlation between the degree of perceived hypoesthesia and TDD [11]. However, another method for quantifying the area of hypoesthesia (e.g. tactile detection thresholds using monofilaments) may have been more sensitive [23].

Two point discrimination (TPD) and other measures of tactile acuity are typically reduced in chronic pain conditions with (and without) allodynia [24-29]. Chronic pain patients may have a re-organization of somatosensory cortex and the extent of this re-organization seems related to their pain intensity as well as their reduced tactile acuity [30-33]. Further, as the pain diminishes the tactile acuity increases [32-34].

Pain and decreased touch pleasantness in the allodynic zone

Pleasant touch in humans is a construct of many factors; the input from CT afferents, A β afferents, homeostatic state as well as contextual factors [35]. Recent studies have implicated CTs in the pathophysiology of dynamic tactile allodynia [2-4]. In this study we present further evidence suggesting affected CT processing in experimental allodynia alongside with affected A β processing. In the current study, the greatest drop in pleasantness ratings in the area of experimental allodynia was seen for CT targeted brush stroking (3cm s⁻¹). This indicates an altered processing of CT

information [4], but does not indicate that CT afferents drive allodynia [2, 3]. In the allodynic zone, the pleasantness ratings for the CT targeted stroking dropped to that of the A β targeted stroking suggesting that the CT processing was suppressed [36]. A similar finding has been observed in CT-denervated patients [17]. The significant pleasantness drop seen for the single stroking at 30cm s⁻¹ may be explained by there being a slight, yet suboptimal, CT response in the control zone [6] that was suppressed in the allodynic zone. However, for the 10x30cm s⁻¹ intense stroking the CTs will fire even less due to the repeated stimulation which fatigues CTs, almost to the point of inexcitability [14]. For the decrease in touch pleasantness a significant correlation was found with the mapped area of punctate hyperalgesia; the area of hyperalgesia may be indicative of the extent of the development of the model.

One explanation for not finding any differences in pain ratings across the stimulus conditions could be that the rating scaled used was too crude in its endpoint Worst pain imaginable to detect the fine grain differences between the different stroking stimuli. This suggestion is supported by the fact that the pain ratings were indeed very low. Another explanation (in line with the canonical view), is that tactile evoked pain is solely mediated by A β afferents gaining access to pain signaling pathways. This theory is supported by two previous studies showing that A β denervated subjects do not develop experimental, tactile evoked pain [4, 9]. For CT afferents which are suggested to signal touch pleasantness through the spinothalamic tract under normal touch conditions there might be a gating resulting in a significant decrease in pleasantness perception [5, 35] to prioritize the nociceptive information from the periphery.

Previous work implicating CT afferents in experimental allodynia

Experimental evidence for a role for CTs in allodynia were suggested through a C-LTMR knock-out mouse model, targeted against the vesicular glutamate transporter type 3 (VGLUT3). The knock-out mice showed reduced mechanical hypersensitivity following inflammation and nerve injury [3]. However, more recent findings suggest that VGLUT3 lineage sensory neurons are divided into two groups depending on their VGLUT3 expression: transient expression neurons seem to be myelinated mechanoreceptors whereas persistent expressers are likely unmyelinated neurons [37]. Mice with a conditional knock-out of VGLUT3-persistent neurons have largely, but not completely, unaffected acute and chronic mechanical pain thus instead suggesting that VGLUT3-transient neurons may control the mechanical hypersensitivity [37].

This finding is more in line with a previous finding from our group. Following the heat/capsaicin model, two sensory neuronopathy patients lacking A β afferents did not report tactile allodynia (4) but instead reported their C-touch percept (faint sensation of pleasant touch) to be significantly

weaker in the allodynic zone compared to untreated skin. Accordingly, functional magnetic resonance imaging (fMRI) showed that stroking in the allodynic and control zones evoked different responses in the primary cortical receiving area for CTs: the posterior insular cortex. These findings suggest that dynamic tactile allodynia is associated with a reduced CT hedonic touch processing. A similar reduced hedonic touch processing was recently observed in patients with a congenital denervation of CT afferents [17]. Restoring normal CT processing may thus be a novel therapeutic strategy against neuropathic pain.

In a recent study this question was pursued using a novel specific marker of C-LTMRs: a chemokine-like secreted protein called TFAFA4 which is predominantly co-expressed with VGLUT3 [36]. The authors speculate that upon activation C-LTMRs might release TFAFA4, and that this protein then acts to prevent mechanical hypersensitivity. Following inflammation and nerve injury TFAFA4-null mice show enhanced mechanical and chemical hypersensitivity that was reversed by application of recombinant TFAFA4 protein [36] i.e. restoring normal C-LTMR functional signaling.

A previous electrophysiological study in rats suggested that C-LTMR targeted input may inhibit C-nociceptive messages in the dorsal horn [38]. A specific inhibitory pathway was identified between substantia gelatinosa neurons receiving direct peripheral C-LTMR afferent projections and other substantia gelatinosa cells receiving direct nociceptive input [38]. This unmyelinated circuit represents a potential pathway for innocuous C-LTMR impulses to suppress nociceptive impulses [38]. A disruption of this circuit due to central sensitization may cause a loss of the nociceptive balancing effect of C-LTMRs again supporting the notion that normalizing CT function may be a treatment strategy for tactile allodynia [3-5, 35, 37].

In summary, both A β and CT processing were affected in the allodynic zone of the heat capsaicin experimental model of human dynamic tactile allodynia. We found no differences in touch evoked pain between CT optimal and suboptimal stimuli suggesting that CTs do not have a critical role in mediating tactile allodynia [2, 3] supporting the view that A β afferents signal this sensation. Instead the contribution of CTs in allodynia seems to be the loss of a pain inhibiting role.

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