C-tactile (CT) afferents: evidence of their function from microneurography studies in humans

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C-tactile (CT) afferents are low-threshold mechanoreceptors present in the skin of humans and are thought to convey positive and pleasant aspects of touch, due to their optimal firing during gentle, caress-like contact. This review explores their role and function through the evidence produced in microneurography studies, where it is possible to record from single CTs in awake, healthy humans. CTs send a relatively-delayed signal to the brain, due to their unmyelinated, slowly-conducting axon, and are highly sensitive to small displacements of the skin, especially from dynamic, moving touch. CTs are primarily mechanoreceptors, but show some thermal sensitivity, where neutral touch (at skin temperature ~32°C) is optimal, warm touch (~42°C) activates them less, and cool touch (~18°C) produces complex responses.

Highlights

- Unmyelinated C-tactile afferents can be recorded in humans via microneurography.
- They are highly sensitive mechanoreceptors, with low activation thresholds.
- They respond vigorously to dynamic, moving touch.
- They show characteristic responses to mechanical, thermal, and electrical stimuli.
- C-tactile afferents are believed to convey positive affective aspects of touch.

Key words: C-tactile, low threshold mechanoreceptor, microneurography, humans, affective touch, pleasant touch

C-tactile (CT) afferents (Box 1) are slowly-conducting, low-threshold mechanoreceptors that respond well to gentle touch. Microneurography studies in healthy humans (Box 2) have provided a wealth of information about the physiology of CT afferents, leading to theories about their function and role in touch. Primarily, they are believed to underpin the 'affective touch hypothesis', providing positive affective input about touch, such in gentle touch between family members and for social communication [1–3].

> **Box 1. C-tactile (CT) afferents**: A CT is defined as a mechanoreceptive afferent that is slowly-conducting, with a low mechanical threshold (<5 mN). C-tactile afferents are found in human nerves across the body, especially in hairy skin, and respond optimally to gentle, stroking touch. They have characteristic properties, such as being highly responsive to a slowly-moving stimulus and exhibiting after-discharges, and they show a specific response pattern to electrical stimulation.

History of CT afferents

C-low threshold mechanoreceptors (C-LTMs) have been documented in animals for many years [4,5], yet there was little evidence for the existence of their homolog in microneurography recordings in humans. This may have been due to the technical challenges of microneurography and that single C-fibers are generally more difficult to find and record from [6], thus meaning CTs were discovered later. This is also why only a handful of papers exist demonstrating CTs in humans, as there are many complex issues to consider in carrying out such investigations. In smaller nerves (e.g. the forearm, where CTs are numerous), single unit microneurography (Box 2) is more demanding, due to difficulties in accessing the nerve and stabilizing the electrode [6]. Additionally, recording from a CT is challenging, due to the small-diameter, unmyelinated C-fiber axon (~1 μm diameter, cf. ~10 m of Aβ myelinated mechanoreceptive afferents, [3]), and their delayed response to stimulation can resemble the activity of sympathetic C-fibers efferents (Figure 1) [7].

> **Box 2. Microneurography**: This technique of percutaneously inserting a needle electrode into a peripheral nerve in awake humans. In single unit microneurography, recordings are made from an individual axon and typically includes responses from myelinated Aβ afferents and unmyelinated C-fiber afferents. Stimuli can be applied to the receptive field and the subsequent activity is recorded to different interventions.

The first indication of C-LTMs in humans came in the late 1980s, where Johansson et al. (1988) found a potential C-fiber that was highly responsive to gentle touch during microneurography in the trigeminal infraorbital nerve of the face [8]. Not long after, Nordin (1990) showed unequivocal and thorough evidence for the existence of such touch afferents, in the trigeminal supraorbital nerve of the face, and compared their responses to C-nociceptors [9]. In the following years, the co-founder of the technique of microneurography, Åke Vallbo [6] and collaborators, published a series of papers using microneurography of the antebrachial nerve of the forearm, where they postulated a role for these low-threshold C-fibers in gentle touch perception [10], later naming them C-tactile (CT) afferents (Box 1) [11].

To find CTs during a microneurography experiment, the skin is touched and stroked and CTs can be identified via their delayed responses to mechanical stimulation (i.e. due to their unmyelinated axon and thus slow conduction velocity of <2 cm/s). This delayed response separates them from all other faster-conducting myelinated types of mechanoreceptive fiber (Figure 1) and confirms it is a C-fiber. To distinguish the class of C-fiber, CTs are the only afferent C-fiber type that respond vigorously to gentle touch on its receptive field (i.e. it is a low-threshold mechanoreceptor). This includes tests like having a low force activation threshold, vigorous responses to moving touch (typically at <10 cm/s), or firing well to both innocuous and noxious indentation (Figure 1). This method of characterization was initially outlined in early work on CTs [9,10] and was followed up in a comprehensive paper by Vallbo et al. (1999) [11], where tactile tests were delivered to the receptive field as low-force monofilament indentation (<5 mN), slow stroking, and testing blunt (innocuous) and sharp (noxious) stimuli (where CTs do not discriminate between these, but C-mechanoreceptive nociceptors show stronger responses to sharp, noxious touch). Hence, using this approach, CTs can be rapidly and unequivocally classified during microneurography, setting CTs apart from all other peripheral nerve fibers (Figure 1). A further way of distinguishing CTs from other C-fibers is the use of repetitive 2 Hz electrical stimulation of the receptive field for more than 30 s, where CTs have a characteristic response profile, showing very little slowing in their response latency (<1%; Figure 1) [12,13].

Physiological properties and characteristics of CTs

CTs have an average conduction velocity of ~1 m/s (between 0.3-2 m/s; [7,8,17,9–16]), due to their small-diameter, unmyelinated axon. This relatively-delayed signal is clearly evident when the receptive field is touched and the response is recorded via microneurography. There is often a short barrage of responses from fast-conducting Aβ mechanoreceptors when the skin is stimulated, which is almost instantaneous with the touch, and a delayed response can be recorded originating from C-fibers (e.g. see figures in [18] and [12]). This delay can be measured by applying a mechanical tap or delivering electrical stimulation to the CT receptive field and measuring the distance between this and the microneurography recording site, to calculate the conduction velocity. Mechanical and electrical methods to establish the conduction velocity of CTs give similar values, although mechanical stimulation leads to a slightly longer delay, including time for mechanical transduction, which is by-passed by electrical stimulation [11,12]. Further, the unmyelinated nature of the axon is indicated by the shape of the recorded spike responses. Unmyelinated fibers typically produce a triphasic impulse, with a prominent negative deflection (Figure 1) [6,9,11,12], which is rare in Aβ mechanoreceptive afferents [6].

Like all low-threshold mechanoreceptors, CTs have low mechanical activation thresholds, as measured by the application of calibrated monofilaments to the receptive field. CTs will respond to monofilaments of less than 5 mN (~500 mg; Table 1) and may even have thresholds as low as 0.04 mN (~4 mg) [12]. Some C-nociceptors respond to monofilament mechanical stimulation as low as 2.5 mN and may show a weak response to a gentle brush stroke across the

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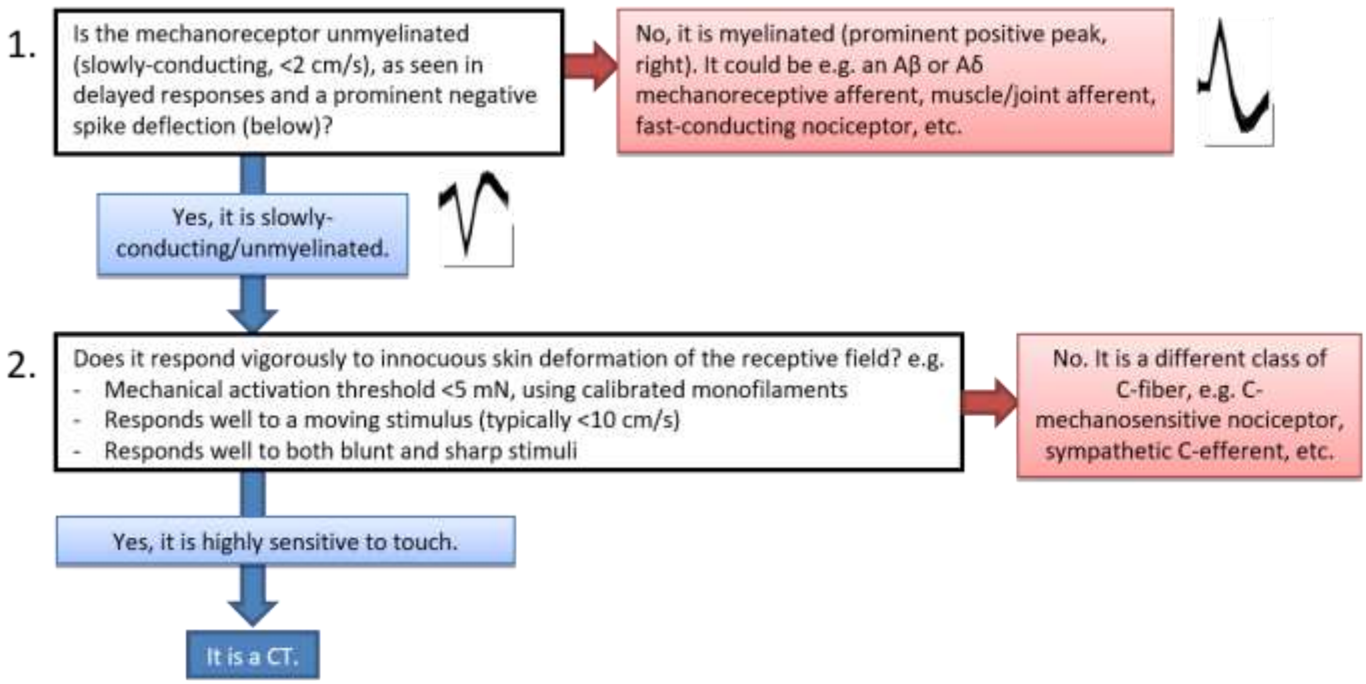

Figure 1. How to classify a C-tactile afferent in microneurography.
Using two questions, it is possible to classify a C-tactile (CT) afferent, by excluding other fiber types via their specific responses. The spikes shown on the left are from a single CT, demonstrating the unmyelinated axon triphasic impulse response, with a prominent negative deflection (40 spikes overlaid, horizontal scale bar = 1 ms, vertical scale bar = 20 µV). Spikes shown on the right are from a single slowly-adapting type I (SA-I) mechanoreceptive afferent, demonstrating the difference in the myelinated axon spike shape, i.e. primarily positive-going (40 spikes overlaid, same scale bars).

receptive field [12]. Thus, care must be taken in classifying CTs, especially compared to such C-nociceptors with lower mechanical activation thresholds. The mechanical force activation threshold and response to moving touch over the receptive field generally provides a quick and simple test to confirm a CT afferent (Figure 1). CTs will respond well to such low intensity, mechanical stimulation with a burst of spikes, whereas C-nociceptors, at most, respond with only a couple of spikes [11,12].

Many microneurography studies have shown that CTs respond very well to slow, moving touch, showing strong responses to a hand, brush, cotton wool, needle, or smooth metal plate stroking over the receptive field (Table 1). Early reports found that CTs do not respond particularly differently to smooth or sharp stimuli (e.g. comparing a smooth probe with a sharp needle [9,11]). It is thought that response frequency is not strongly modulated by stimulus force in CTs [15], although mapping the receptive field with different indentation forces produces increases in firing frequency [18]. It is of interest to explore how CTs respond to a larger range of surfaces and forces, to give a better understanding of the role of CTs in typical every day touch interactions.

The evoked responses under controlled conditions (i.e. for force and speed) appear to be equivalent when using a soft brush [15], as compared to a smooth metal plate heated to around skin temperature [14], where CTs show optimal firing at velocities between 1-10 cm/s. When very slow moving touch is applied across the receptive field (<1 cm/s), CTs will fire a long barrage of spikes; however, the mean firing frequency is generally lower (~25 spikes/s) than at the optimal velocities (~40 spikes/s) [14–16]. Conversely, when a faster moving stimulus is applied (>10 cm/s), only a handful of spikes at most are generated and these are of lower mean frequency (~25 spikes/s) than at the optimal velocities [14,15]. These data have been analyzed using a log10 scale for stroking velocity, where the mean firing frequency of CTs over these velocities shows a negative quadratic (inverted U-shaped) relationship. A significant quadratic curve is found in around ~90% of CT afferents and correlates with the perception of pleasantness over the same velocities [14,15].

Further characteristics of CTs have been documented, yet often these have only been tested in a handful of CTs. These include intermediate adaptation to a statically-applied mechanical stimulus, showing the propensity for after-discharges, fatigue to repeated touch, and delayed acceleration of firing (after some adaptation to a static stimulus, a CT may show an increase in firing) (Table 1). It has been suggested that a potential sub-class of CT afferent may show burst firing [12], yet the function of this remains unknown. Very little is known about the responses of CTs to vibration, but preliminary work suggests that CTs show a comparatively poor following response to vibration, where they may follow up to 1 Hz and respond with a single phase-locked spike at vibration up to 50 Hz (Table 1). Finally, for mechanical response characteristics, CTs do respond somewhat to skin stretch, especially dynamic pulling of the skin (Table 1). Additionally, microneurographers report that CTs do not respond to gentle blowing on the skin and are not particularly sensitive to the movement of hairs [14], although a CT on the face located next to large scalp hairs was activated by moving the hairs [9]; however, the CT response may have been mainly due to skin displacement caused by moving such large terminal hairs.

CTs are not classed as thermoreceptors, but the temperature of mechano-thermal stimulation modulates their response, i.e. they are thermally-sensitive mechanoreceptors (Table 1). They show very weak, if any, responses to radiant thermal stimulation, usually only in response to cooling (~1 spike/s [16]). Higher rates have been observed during evaporative cooling of volatile liquids from the skin (~20 spikes/s [9]), which provides increased rates of skin cooling. When stationary touch is applied, a clear CT response is seen, which is lower for warmer (42°C) touch, as compared to neutral (32°C, skin temperature) or cool (15°C) stationary touch [16]. When touch is dynamic and moves across the receptive field, further differences are found. In general, neutral temperature touch (32°C) generates responses of higher mean frequency (~40 spikes/s) than cool (18°C) or warmer (42°C) moving touch (~30 spikes /s) [14,16]. However, at very fast velocities (30 cm/s), there is no significant difference between CT firing frequency for these three different temperatures [14]. This may be due to the generation of few spikes through stroking at 30 cm/s and that the thermal transfer for such a short duration of contact would be negligible.

The optimal responses of CTs to touch around skin temperature has further implicated their role in signaling affective touch between individuals, i.e. skin-to-skin gentle interactions [14]. However, there are many more aspects that need to be considered concerning how CTs encode touch. For example, at slow stroking velocities (e.g. 0.1 cm/s), a more complex pattern is seen for mechano-cool stimulation: the firing frequency is generally lower for cool touch than neutral temperature touch, yet the number of spikes generated is equivalent [16]. This effect is found due to afterdischarges, following mechanical stimulation of the receptive field, which are more pronounced after cooling. It has been postulated that small mechanical skin contractions induced during

Type of stimulus	Property	Characteristics	Papers
Mechan-ical	Low mechanical activation threshold	A CT will have a monofilament activation threshold of <5 mN. Observed in all CTs.	[7,8,18,9–16]
	Sensitive to moving touch across the receptive field	CTs will fire well to a touch stimulus moved across the receptive field. This may be a hand, brush, or any other surface. Observed in all CTs.	[7,8,17,9–16]
	Responds well to both a blunt and sharp probe	CTs will respond equally well to blunt or sharp indentation (compared to C-mechanosensitive nociceptors that respond well only to sharp indentation).	[9,11]
	Optimal firing for stroking velocities of 1-10 cm/s	CTs show the highest mean instantaneous firing frequency for 'intermediate velocities' (1-10 cm/s), where slower and faster stroking produces lower firing frequencies.	[14,15]
	Intermediate adaptation	When a mechanical stimulus is applied statically to a receptive field, the CT will fire initially with a burst of spikes, then will generally adapt to the stimulus within a few seconds (cease firing).	[8,11]
	After-discharge (firing after the removal of a stimulus)	When a mechanical stimulus is removed from the CT receptive field, there will often be a response of a few spikes just after removal.	[8,9,12,16]
	Fatigue to repeated stimulation	The propensity to fire (e.g. number of spikes generated, instantaneous firing frequency) will decrease somewhat when the receptive field is stimulated repetitively.	[9,11,17,19]
	Delayed acceleration (biphasic response to sustained contact)	When a mechanical stimulus is applied statically to a receptive field, after the initial spike burst and intermediate adaptation, the firing may resume and even build up to a considerable rate.	[11]
	Vibration	CTs show a comparatively poor response to vibration, where they may follow vibration to 1 Hz (few spikes) and may respond transiently with a single phase-locked spike at vibrations between 16-50 Hz.	[11,19,20]
	Skin stretch	Dynamic skin stretching can activate CTs and there may be continued weak discharge to sustained, static stretch.	[9,17]
Thermal	Radiant heating and cooling	Radiant thermal stimuli do not produce many spikes, although evaporative cooling may generate a low frequency response.	[9,11,16]
	Stationary mechano-thermal stimulation	Warm static touch generates less responses than cool or neutral (skin temperature) touch.	[16]
	Dynamic mechano-thermal stimulation	Generally, neutral temperature touch elicits higher mean firing frequencies than warmer or cooler temperatures, but this depends on the duration of stimulation.	[14,16]
Electrical	Marking technique (repetitive, low frequency electrical stimulation, with concurrent mechanical stimulation)	When a CT is activated by touch between electrical stimuli, electrically-elicited spike latencies are slightly slowed.	[9,12,13]
	Activity dependent slowing at 2 Hz stimulation	Repetitive electrical stimulation at 2 Hz produces a very small delay in the latency of the elicited spike.	[12,13,16]
	High-frequency electrical stimulation	CTs can follow short bursts of electrical stimulation up to rates of 100 Hz, with some increases in response latency over 50 Hz.	[12]

Table 1: Properties and characteristics of C-tactile afferent responses to different stimuli.

cooling likely generate this additional CT activity, which can occur for up to 30s. Such afterdischarges are of low frequency and the participant does not overtly perceive any related sensation [16], yet they may still signal some part of the cold-touch stimulus. This may potentially be a negative affective component about skin discomfort, as seen in psychophysical ratings of cold touch [14].

CTs can also be activated electrically, by inserting electrodes into the receptive field and by-passing the mechanical encoding mechanism. Typically, other C-fibers show pronounced increases in response latency when electrical stimulation is delivered repetitively, but this effect is negligible in CTs (Table 1). For example, it is possible to 'mark' a C-fiber (slow down its electrical latency response) using concurrent mechanical stimulation between low frequency repetitive electrical stimulation. In CTs, a small increase in latency of only 0.05% per spike elicited via the mechanical stimulation is found, compared to a 0.5% shift for C-mechanosensitive nociceptors [12]. Additionally, for repetitive electrical stimulation of the receptive field at 2 Hz, CT response latencies show <1% increase, which is in stark contrast to much greater response latency increases in other C-fibers [12,13,21]. Finally, CTs are able to follow repeated short bursts of electrical stimulation up to 20 Hz, with no latency slowing. Further, CTs can follow electrical stimulation at rates of 100 Hz, but there is some slowing of their responses; however, they do not follow electrical stimulation at 200 Hz [12]. Electrical stimulation also sometimes elicits additional CT firing, akin to afterdischarges [12,16]. These can be modulated thermally and decrease during radiant skin warming, as compared to cooling or with no thermal stimulation [16].

Little research has been conducted on the activation of CTs by applying chemicals to their receptive fields. Preliminary evidence suggests that CTs show negligible or low sensitivity to topical application of capsaicin (2% solution) [20].

Anatomical properties and characteristics of CTs

CTs were first demonstrated on the face (infraorbital nerve [8] and supraorbital nerve [9]), then many proceeding studies have focused on the hairy skin of the arm, recording from the lateral and dorsal branches of the antebrachial nerve [7,10–12,14–16,18], where CTs are readily found (consisting ~40% of mechanoreceptive units sampled [10]). Studies have shown the presence of CTs in the leg, including in the lateral cutaneous femoral nerve of the thigh [17] and the peroneal nerve of the lower leg [13,22], yet it seems more difficult to record CTs during leg experiments (~10% incidence at the level of the thigh [17]); however, this could be somewhat biased or under-represented (e.g. by the search procedure to find afferents, by sympathetic activity masking the delayed responses).

There is evidence to suggest that CTs are readily found distally on the arm, as many are found near the hand in antebrachial experiments [12,14–16], and CTs have been demonstrated both in the superficial branch of the radial nerve [7,22] and the median nerve [7]. Concerning the finding of CTs in non-hairy, glabrous skin [7], the preliminary evidence shows the sparse existence of mechanoreceptors that are classified using the conventional criteria as CTs, although they are seldom encountered, which suggests a far lower density, even when overall nerve mechanoreceptor density is taken into account [7]. Thus, the implications of CT innervation of distal hairy and glabrous hand skin are yet to be elucidated in relation to the affective touch hypothesis and the putative glabrous skin CTs should be studied further to see whether they form a CT sub-group, although the animal literature on glabrous C-LTMs currently suggests no functional differences [23].

Concerning CT receptive fields, studies have shown small, spot-like zones, with one or multiple small areas of sensitivity [9,18]. An in-depth study by Wessberg et al. (2003) provided detailed information about CT receptive fields structure, where CTs have 1-9 small spots of sensitivity (mean = 4), with a typical area of ~10 mm^2 [18]. During electrical stimulation experiments, the latency of CT responses sometimes jumps between discrete latencies, which may be attributed to the peripheral branching of a CT axon [12,13], thus reveals further information about the branching of the axon. It would be of interest to explore this branching further, especially if adaptation happens to certain branches and not others, and its impact on CT firing.

Conclusions

CTs are highly sensitive mechanoreceptors and it is evident that they play a clear role in encoding gentle, dynamic touch signals and conveying them to the brain. These signals are not believed to be useful for discriminative touch, due to their delayed nature of their input, but are implicated in the affective and emotional aspects of touch, such as in the reinforcement of gentle contact. There are few studies that have investigated the properties of human C-tactile afferents and further studies should be conducted into their functional characteristics (e.g. responses to different surfaces and forces, sensitivity to chemicals). Not all CTs display all the documented properties (e.g. delayed acceleration), therefore, it is of interest to explore potential anatomical and physiological sub-classes. As well as new investigations, the existing data from CTs could be analyzed further to explore how the exact firing patterns contribute to tactile perception, where other aspects (e.g. temporal components, bursting, duration of firing, differences in minimum/maximum firing rates) could reveal more about their role. This is especially complex when looking at very slow stroking touch that elicits plenty of CT activity, at highly variable rates, but where overall mean firing frequency and pleasantness is low.

Therefore, CTs are not necessarily tactile *pleasantness* receptors as such, but they play a clear modulatory and reinforcing role of gentle, comfortable touch interactions.

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Conflict of interest statement: None.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as: *of special interest **of outstanding interest

List of annotated references: papers of special interest (*) or outstanding interest (**):

**Vallbo Å, Olausson H, Wessberg J: Unmyelinated afferents constitute a second system coding tactile stimuli of the human hairy skin. J Neurophysiol 1999, 81:2753–2763.

This study explores and documents many different properties of C-tactile afferents, including many of their response characteristics to different mechanical stimulation.

**Löken LS, Wessberg J, Morrison I, McGlone F, Olausson H: Coding of pleasant touch by unmyelinated afferents in humans. Nat Neurosci 2009, 12:547–8.

This elegant study shows that C-tactile afferents show a tuning to the speed of touch to their receptive field. The mean instantaneous firing frequency was optimal at velocities of 1-10 cm/s and reduced for slower and faster velocities. This finding correlated with the perception of pleasantness of the same moving touch.

**Ackerley R, Backlund Wasling H, Liljencrantz J, Olausson H, Johnson RD, Wessberg J: Human C-tactile afferents are tuned to the temperature of a skin-stroking caress. J Neurosci 2014, 34:2879–83.

In a follow-up study to [15], this work showed that C-tactile afferents were tuned to both the velocity and temperature of a stroke across their receptive field. Neutral temperature moving touch (akin to skin temperature) produced higher mean instantaneous firing frequency than cooler or warmer touch.

*Ackerley R, Wiklund Fernström K, Backlund Wasling H, Watkins RH, Johnson RD, Vallbo Å, Wessberg J: Differential effects of radiant and mechanically applied thermal stimuli on human C-tactile afferent firing patterns. J Neurophysiol 2018, 120:1885–1892.

This study shows the complexity of CT afferent firing to different thermal and mechanical manipulations. It demonstrates that CTs respond to cooling, moreso than warming, yet the firing is typically of low frequency.

*Watkins RH, Wessberg J, Wasling HB, Dunham JP, Olausson H, Johnson RD, Ackerley R: Optimal delineation of single C-tactile and C-nociceptive afferents in humans using latency slowing. J Neurophysiol 2017, 117:1608–1614.

This work characterizes the response properties of CTs to electrical stimulation of their receptive field. It shows the unequivocal delineation between CT afferents and C-nociceptors, demonstrating that CTs form a distinct sub-population of C-fibers, with specific characteristics.

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