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Review

The neurophysiology of unmyelinated tactile afferents

Håkan Olausson [a,*], Johan Wessberg [a], India Morrison [a], Francis McGlone [b], Åke Vallbo [a]

[a] Institute of Neuroscience and Physiology, University of Gothenburg, Gothenburg, Sweden
[b] Department of Neurological Science, University of Liverpool, Liverpool, UK

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ABSTRACT

CT (C tactile) afferents are a distinct type of unmyelinated, low-threshold mechanoreceptive units existing in the hairy but not glabrous skin of humans and other mammals. Evidence from patients lacking myelinated tactile afferents indicates that signaling in these fibers activate the insular cortex. Since this system is poor in encoding discriminative aspects of touch, but well-suited to encoding slow, gentle touch, CT fibers in hairy skin may be part of a system for processing pleasant and socially relevant aspects of touch. CT fiber activation may also have a role in pain inhibition. This review outlines the growing evidence for unique properties and pathways of CT afferents.

Contents

We rely on the haptic sense for the manipulation of objects and for the exploration of their shape, weight, surface structure, and other physical properties. But the sense of touch is also crucially important in the social realm, mediating the communication and interpretation of affective contact during our interactions with others (Gallace and Spence, this issue; Hertenstein et al., 2006). Our research on the electrophysiology of human skin receptors has led to the identification of a system of unmyelinated low-threshold mechanoreceptors (C tactile, CT afferents) that respond vigorously to tactile stimulus characteristics typically perceived as pleasant such as slow and light stroking with a soft object. Based on findings from distinctly different approaches including analyses of CT primary afferents, psychophysical studies in subjects lacking myelinated mechanoafferents, and brain imaging, we suggest that CT afferents contribute to pleasant touch and provide an important sensory underpinning of social behavior. Light touch that we experience as pleasant is an important part of social interactions and could play a vital role in forming and maintaining social bonds. Considering both these pleasant and social aspects of gentle skin-to-skin contact, we have put forward a framework within which to consider CT afferent coding properties and pathways: the "social touch" hypothesis. This hypothesis proposes that CT afferents have a particular potential to elicit pleasant subjective experience alongside behavioral, hormonal, and autonomic responses during gentle touch between individuals.

1. Tactile afferents in human skin

Human tactile sensibility is generally considered to be mediated solely by low-threshold mechanoreceptors with large

* Corresponding author at: Department of Clinical Neurophysiology, Blå stråket 7, Sahlgrenska University Hospital, S-413 45, Gothenburg, Sweden.
Tel.: +46 31 3422289; fax: +46 31 821268.
E-mail address: olausson@physiol.gu.se (H. Olausson).

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Table 1
Mechanoreceptive afferents in human nerves from glabrous and hairy skin.

Sensory endings and afferent unit acronyms		
Glabrous skin	Hairy skin	Adaptation
Merkel SAI	Merkel SAI	Slow
Ruffini SAII	Ruffini SA II	Slow
Pacini FA II (PC)	Pacini FA II (PC)	Fast
Meissner FAI (RA, QA)	Hair follicle unit	Fast
	Field	Fast
	C-tactile CT (CLTM)	Intermediate

The separate unit types were identified on the basis of microneurography recordings in man while types of end organ were inferred on the basis of physiological and morphological studies in various species. Slow and fast adaptation refers to the presence or lack of sustained response to stationary skin deformation. Most acronyms refer to adaptation properties (fast, rapid, quick or slow adaptation). Acronyms within parenthesis have mainly been used in studies of non-human species. All afferents listed are myelinated and fast conducting (Aβ fibers) except CT units which are unmyelinated (C fibers). The table includes highly sensitive afferents but not nociceptive afferents that may respond weakly to innocuous skin deformation. The table entries refer to glabrous skin of the hand and hairy skin of the forearm and are based on recent investigations. However, there are microneurography studies suggesting a somewhat different innervation pattern in particular skin regions, the existence of subgroups, and one or two additional mechanoreceptor types.

myelinated (Aβ) afferents conducting impulses at high speed (around 50 m/s). However, low-threshold mechanoreceptors with unmyelinated afferents were identified in the hairy skin of various mammals including cats and monkeys long ago (Bessou et al., 1971; Douglas and Ritchie, 1957; Iggo and Kornhuber, 1977; Kumazawa and Perl, 1977b; Zotterman, 1939). For a time, it was assumed that humans did not share this seemingly primitive tactile system with other mammals. Nevertheless, in recent years it has been demonstrated that human skin is also innervated by low-threshold mechanoreceptors with unmyelinated (CT) afferents conducting impulses with a speed of only about 1 ms^{-1}. In man, these nerve fibers were first found in microneurography recordings from the infra- and supraorbital nerves (Johansson et al., 1988; Nordin, 1990). Soon after, they were found in the arm and leg suggesting a more general distribution of CT afferents in man (Edin, 2001; Vallbo et al., 1993; Vallbo et al., 1999; Wessberg et al., 2003).

The different mechanoreceptors that innervate the human skin are summarized in Table 1. Although there is currently no accurate method to assess the innervation density of CT afferents it is a recurring experience in microneurography experiments that they are encountered as often as Aβ afferents. Interestingly CT afferents have never been found in the palm of the hand despite numerous microneurography recordings from this skin area. Hence, it seems reasonable to conclude that they are lacking in the glabrous skin.

2. CT afferents—receptor characteristics

CT afferents respond to indentation forces in the range 0.3–2.5 mN (Vallbo et al., 1999), as tested with von Frey monofilaments, and are thus as sensitive to skin deformation as many of the Aβ afferents. CT afferents respond with high frequency (50–100 impulses s^{-1}) to stimuli that are clearly innocuous, such as slow stroking with a soft brush. This impulse rate is close to maximal rates that have been reported for afferent C fibers (Kumazawa and Perl, 1977b). In contrast to C nociceptors, with mechanical thresholds of >2.5 mN, CT afferents do not distinguish between pin pricks and smooth probe indentations but respond equally well to both these types of stimuli (Vallbo et al., 1999). It is noteworthy that C nociceptors may also respond to light brush stroking but their responses never exceed a few impulses (Vallbo et al., 1999).

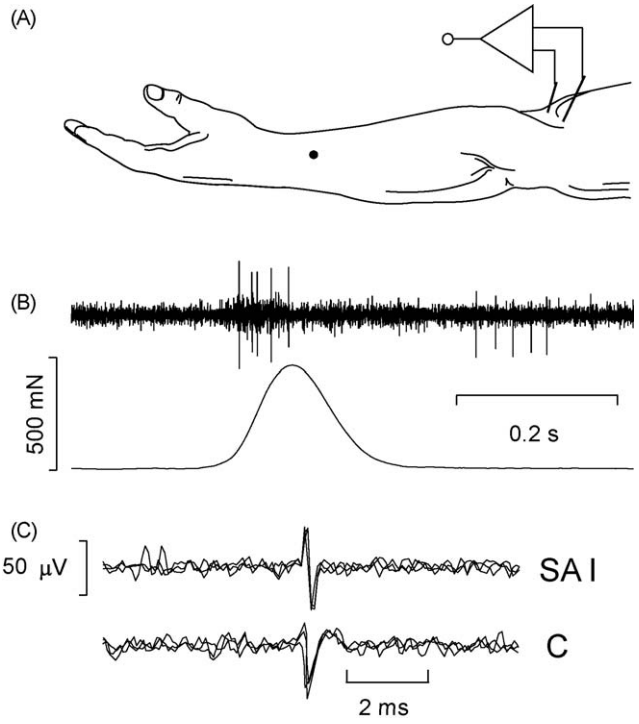

Fig. 1. Estimation of conduction velocity. A. Microneurography recording site in the upper arm and target point in the forearm for a mechanical tap stimulus illustrated in B. B. top: Responses of two separate afferents to an innocuous tap stimulus. The units had overlapping receptive fields at the target point. Bottom: Time course of skin indentation force. C. Nerve impulses from the record in B displayed on expanded time scale to highlight differences in shape. The fast afferent was a Merkel unit (SAI), whereas the slow afferent was an unmyelinated low-threshold mechanoreceptive unit (CT) with a monofilament threshold of 1.3 mN. Distance between stimulation point and nerve recording was 247 mm yielding conduction velocities of 30 ms^{-1} for the SAI unit and 0.8 ms^{-1} for the CT unit. From Wessberg et al. (2003).

The conduction velocity of CT afferents, as assessed with mechanical or electrical stimulation, varies between 0.6 and 1.3 m s^{-1} (Fig. 1). With a sustained indentation they respond initially with a high frequency burst of impulses while the rate decreases to zero within 5 s. The adaptation characteristic of CT afferents is thus intermediate in comparison with the slowly and rapidly adapting myelinated mechanoreceptors (slowly adapting units continue to fire during a constant mechanical stimulus whereas rapidly adapting units fire only as long as the skin deformation is changing). In a subset of CT afferents the response may increase again after the initial period of adaptation with firing continuing for 1–2 min until it finally stops; a phenomenon we have described as delayed acceleration (Fig. 2). A related phenomenon has been described for rat nociceptors (Andrew and Greenspan, 1999).

A light touch slowly moving over the skin surface is a particularly effective stimulus for CT afferents (Nordin, 1990). The maximal unit response occurs for movement velocities around 3 cm s^{-1} whereas it is weaker for slower and faster movements. Another prominent feature of CT afferents is that they are highly fatigable. When several identical stimuli are given the response to the first one is usually much larger than the response to the following ones. When a skin deformation is released CT afferents may produce after-discharges that may last up to several seconds. CT units may respond weakly to innocuous cooling but they do not respond to warming or noxious heating (Nordin, 1990). The combination of mechanical stimulation and cooling gives a more vigorous response than mechanical stimulation alone (Wiklund Fernström and Wessberg, 2003). A mechanothermal interaction with enhanced response to mechanical stimulation when the skin

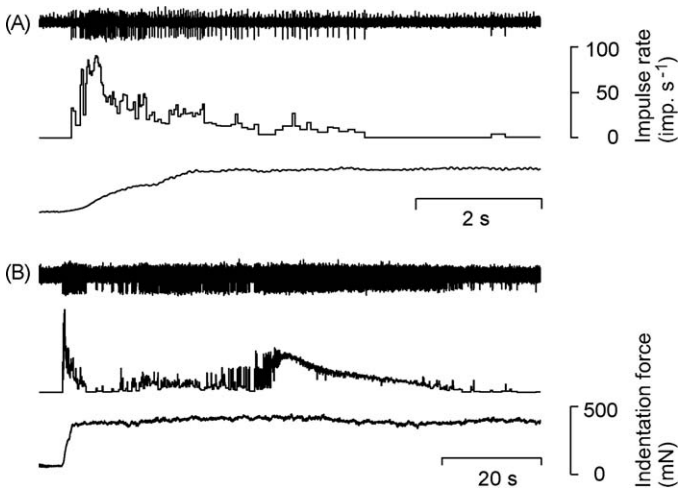

Fig. 2. Microneurography recording of adaptation and delayed acceleration of a single tactile C unit. Stimulus was a sustained indentation with a blunt probe. A. initial part of the test. B. Longer recording of the same test. The intermediate adaptation to sustained indentation is illustrated in A, where it may be seen that the impulse rate decreased to zero within 4 s. A delayed acceleration is illustrated in B, where the impulse rate started to increase again 12 s after the initial phase of adaptation. For a following period of 30 s firing was irregular with recurring short interspike intervals separated by much longer intervals. Then followed a period of more regular firing that climbed to a peak of 40 impulses s^{-1}, and then successively declined during a period of 40 s. The subject denied any unique or strange sensation from the skin during the delayed acceleration. From Vallbo et al. (1999).

temperature is decreased is not unique for CT afferents but has been observed for myelinated afferents as well (Iggo and Muir, 1969). The underlying sensory transduction mechanisms are unknown (Lumpkin and Caterina, 2007). CT afferents do not respond to capsaicin (Wessberg et al., unpublished observation), i.e. they do not express the TRPV1 (transient receptor potential vanilloid 1) transduction channel that seems to be involved in thermal nociception (Lumpkin and Caterina, 2007).

In cats a subpopulation of CT afferents are very sensitive to hair movements (Iggo, 1960). This aspect has not been studied in detail in man, although qualitative observations indicate that most of the CT afferents are not specifically sensitive to hair movements. The receptive fields of human CT afferents are roughly round or oval in shape with no preferred orientation. Detailed analyses revealed that the field consists of one to nine small responsive spots distributed over an area up to 35 mm^2 as illustrated in Fig. 3 (Wessberg et al., 2003). The terminal arborization in the skin of the apparent mouse homolog of human CT afferents has recently been directly visualized using a genetically encoded tracer (Liu et al., 2007). The receptors are organized in a pattern of discontinuous patches covering about 50–60% of the area in the hairy skin, whereas they are lacking altogether in the pad skin (in analogy with the lack of CT afferents in human glabrous skin). The pattern of coverage seen in the mouse reflects a large degree of branching in terminal arbors, which is evident in humans as well (Fig. 3). The possibility of studying CT afferents using genetic tools opens avenues for further investigation of candidate receptor channels, for which no concrete evidence exists as yet.

3. Selective CT stimulation in subjects lacking Aβ afferents

Although CT afferents were identified in the cat almost 70 years ago, their functional role remained unclear, the prevailing hypothesis being that they underpin ticklish sensations (Zotterman, 1939). However, direct evidence for a specific role of CT afferents in tactile sensation has been difficult to achieve; a major reason being that it is not possible to stimulate CT afferents without also activating Aβ afferents.

Pertinent data can be collected from subjects who lack Aβ afferents but have intact C fibers as the result of sensory neuronopathy (a rare disorder of nerve cell bodies of the large primary sensory neurons) (Sterman et al., 1980). Two subjects with sensory neuronopathy and a complete lack of Aβ afferents in large skin areas are well described in the literature (Cole and Sedgwick, 1992; Forget and Lamarre, 1987). They have been studied extensively over the years particularly with regard to motor functions because of their proprioceptive deficit. It has also been reported, although merely in passing, that they lost all tactile sensations when they became ill. This observation was consistent with the view at that time that tactile sensation is altogether dependent on Aβ afferents. This view, in turn, was largely based on experiments in healthy subjects suggesting lack of tactile sensations when Aβ fibers are blocked by pressure onto the nerve (MacKenzie et al., 1975).

When it became evident that human skin is supplied with a system of unmyelinated afferents sensitive to light touch, it became necessary to re-examine the tactile sensibility of neuronopathy subjects using more refined approaches. Rigorous psychophysical tests were pursued to explore if the neuronopathy subjects were able to detect touch stimuli that activated CT afferents. It was found that subjects lacking Aβ afferents detected soft brush stroking and weak monofilament indentation on the forearm skin where CT afferents are abundant (Cole et al., 2006; Olausson et al., 2002; Olausson et al., 2008). Importantly, they failed altogether to detect the same kind of stimuli applied to the glabrous skin of the hand where CT afferents are lacking. An additional and highly relevant finding in accord with this idea is that the neuronopathy subjects were unable to detect vibratory stimuli which are known to a give a poor excitation of CT afferents but a massive activation of Aβ afferents (Bessou et al., 1971; Iggo, 1960; Kumazawa and Perl, 1977b; Olausson et al., 2002, 2008).

Although a number of observations lead to the conclusion that CT afferents may well account for detection of touch stimuli in subjects lacking Aβ afferents, a clear and consistent understanding of the quality of the perception when CT afferents are selectively stimulated has been difficult to obtain. Still, a number of interesting features emerged when the qualitative characteristics of the sensation were explored. First, it was obvious on the basis of subjective report that the sensation associated with a massive and selective CT input (soft brush stroking) was very weak, vague, and inconsistent. In some trials the subject reported no sensations at all. In others, he or she reported a sensation of light touch which was barely detectable and difficult to capture consciously and describe in detail. The weakness and vagueness of the sensation are further illustrated by the fact that conscious perception of CT stimulation varied from one occasion to the other and between the two subjects as well. One of the two subjects (GL) even reported that she began to feel more touch sensations in daily life, once she had had the experience of touch perception from the affected skin areas during the experiments and had become aware of the possibility. Although the two neuronopathy subjects were not able to give a concise or detailed description of the sensation elicited by CT stimulation, they reported that it was slightly or moderately pleasant with no hint of pain, tickle, or itch. Incidentally, it is noteworthy that neither of the two neuronopathy subjects feel tickle in affected skin areas which contradicts the old tickle hypothesis of CT function (Zotterman, 1939). The neuronopathy subjects' ability to spatially localize CT stimulation was very poor; they made mistakes when trying to identify which body quadrant that was stimulated, although they performed above chance level (Olausson et al., 2008). The weak perceptual impact of the CT

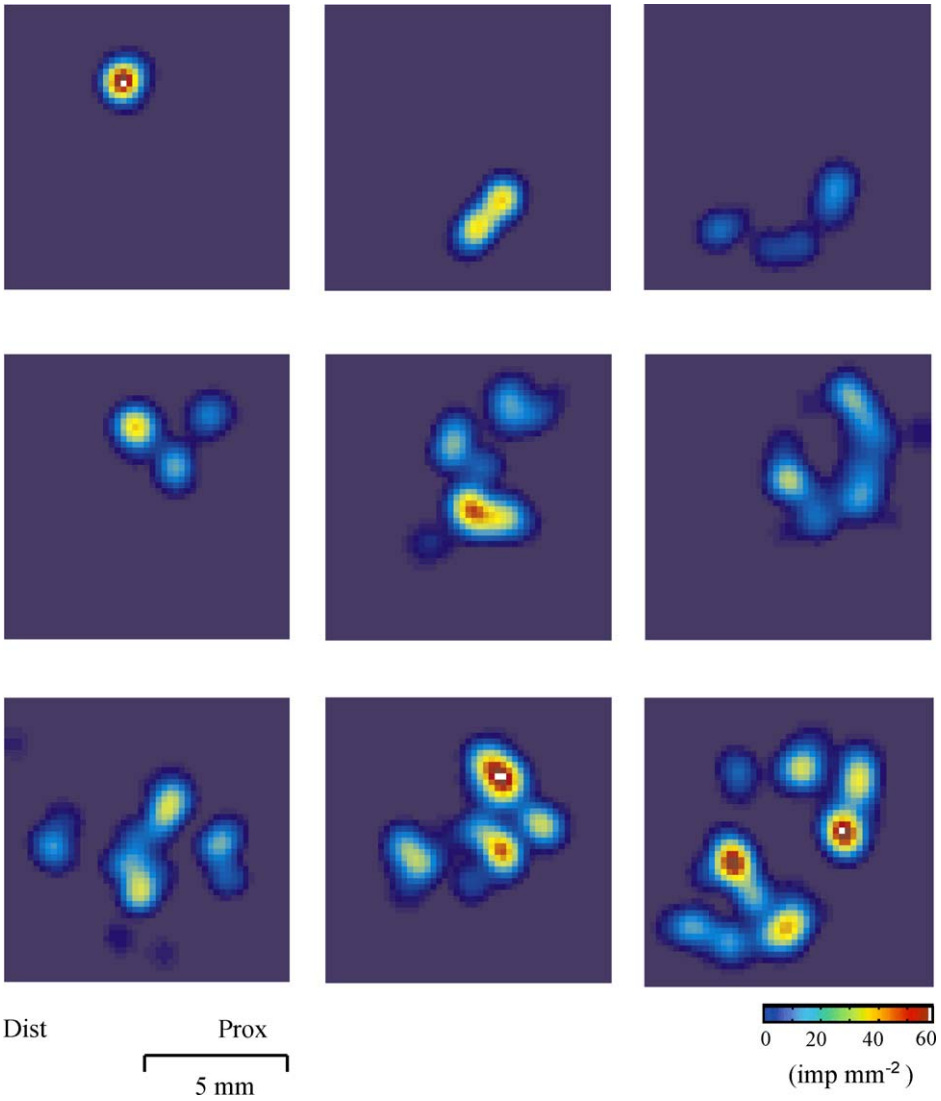

Fig. 3. Field topography of 9 tactile C afferents. The colors represent intensity of afferent firing. From Wessberg et al. (2003).

system suggests that much of the CT related processing takes place below a conscious level, at least in the artificial situation when Aβ afferents are not excited along with the CT afferents. Indeed CT stimulation evoked a sympathetic skin response in both Aβ denervated subjects demonstrating that CT activation may have autonomic consequences (Olausson et al., 2008).

4. Cortical processing of CT stimulation

When functional magnetic resonance imaging (fMRI) was used to study brain responses to touch stimuli in healthy subjects and in neuronopathy subjects lacking Aβ afferents, different sensory areas were activated by the fast (Aβ) and the slow (CT) tactile afferents. In healthy subjects soft brush stroking activated the classical somatosensory areas S1 and S2 as well as insular cortex, notably the posterior part of the contralateral insular cortex (Olausson et al., 2002). Somatosensory areas S1 and S2 receive Aβ projections and are known to play crucial roles in discriminative touch. On the other hand, insular cortex is a region of great interest in relation to affective mechanisms, because it is considered as a gateway from sensory systems to the emotional systems of the frontal lobe (Augustine, 1996; Craig, 2008). When similar brushing stimuli were applied to a subject lacking Aβ afferents (GL), no activation was found in the somatosensory areas when the posterior insular region was activated (Fig. 4) (Olausson et al., 2002). The unmyelinated CT afferents, therefore, probably have excitatory projections mainly to emotion-related cortical systems (insular cortex).

The contribution of tactile Aβ afferents to emotional processing along with the CT afferents has not been widely explored. However, it is obvious that Aβ afferents may underpin pleasant sensations, because similar touch stimuli to the palm (where CT afferents are lacking) can be perceived as pleasant (Krämer et al., 2007), and give rise to fMRI responses in a target area for insular efferents in orbitofrontal cortex involved in complex emotional evaluations (Rolls et al., 2003). Since tactile stimulation is typically perceived as more pleasant on hairy than on glabrous skin (Essick et al., submitted for publication) it might be speculated that pleasant perception based on Aβ input (glabrous skin stimulation) is more dependent on contextual factors in a top–down manner than pleasant perception based on CT input.

5. CT system and homeostasis

Craig has suggested that the CT system may be regarded as a branch of a large afferent system which is concerned with monitoring the condition of tissues (in skin, muscle and viscera)

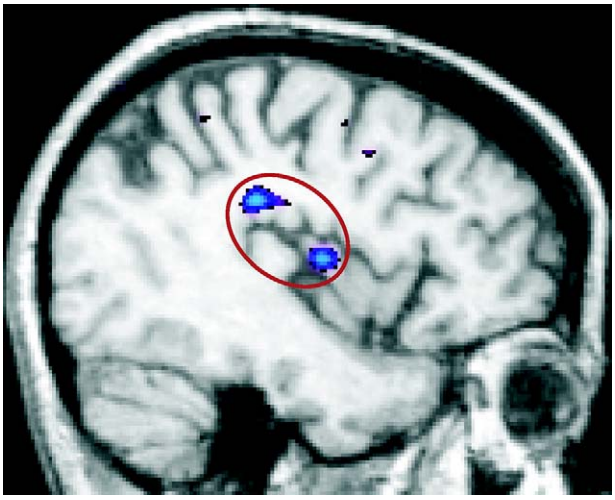

Fig. 4. fMRI activation in posterior and middle insular cortex evoked by selective stimulation of CT afferents in a neuronopathy subject lacking Aß afferents. The activation reflects differences in BOLD (blood oxygen level dependent) signal during soft brush stroking on the forearm and a baseline condition of rest. Adapted from Olausson et al. (2002).

alongside key physiological and chemical variables (Craig, 2002). This interoceptive system fulfils its basic role by integrating various signals from internal and cutaneous tissue, vital for maintaining a homeostatic equilibrium within the body. Interoceptive afferents have particular access to brain centers which control affective, hormonal, autonomic, and behavioral responses which operate to readjust the organism to adverse conditions and are therefore essential for survival. Included in the interoceptive system are afferents related to perception of pain, itch, temperature, air hunger, vasomotor flush, hunger, thirst, and a range of visceral sensations, as well as afferents which are essential for the subconscious control of physiological variables, such as blood pressure and concentration of blood gases.

The peripheral afferents of the interoceptive system consist of small diameter nerve fibers (thin myelinated Aδ and C fibers) with projections to the superficial lamina of the dorsal horn in the spinal cord and nucleus of the solitary tract (Craig, 2002). CT afferents have been shown to project to lamina I and II in several mammalian species (Kumazawa and Perl, 1977a; Sugiura et al., 1986), consistent with the interpretation that they belong to the interoceptive system.

At higher levels the small fiber afferents project to a thalamocortical relay nucleus (VMpo) that in turn projects to the dorsal posterior insular cortex. This projection exists in primates, although the VMpo is greatly enlarged in humans relative to the macaque monkey (Blomqvist et al., 2000; Craig et al., 1994; Craig, 2008). Within the insula, an increasingly elaborated re-representation of the bodily state may progress anteriorly from this posterior region (Craig, 2008). According to this view, a progressively more complex re-representation from posterior to anterior insula comprises the integration of emotionally salient inputs from multiple sensory modalities in the middle insula and emotionally salient inputs from limbic cortical regions (anterior cingulate cortex, orbitofrontal cortex) in the anterior insula. This posterior-to-anterior progression of re-representation in the human insula may account for the integration of the homeostatic condition of the body with the sensory environment, motivational conditions, and finally with social conditions. Moreover, there are indications that the anterior insular cortex on the non-dominant side constitutes a still higher level representing the interoceptive image of the body's physiological condition. In man, this representation of the physical self is postulated to constitute a basic foundation of consciousness (Craig, 2008; Damasio, 1999).

6. CT system and social touch

In daily life, the tactile system continually captures details of temporally and spatially variant skin deformations, which is essential for discriminative touch. As a result we can readily perceive complex features, for instance, the direction of a stimulus moving along the skin. We can also discriminate the intensity of component indentations which are closely adjacent in time and space to assess shape and surface structure of objects. The high conduction velocity of the myelinated Aβ afferents is a critical feature for discriminative touch as well as for the guidance of motor activities.

The low conduction velocity of the CT afferents precludes these roles. First, the long delay (0.5–1.0 s) from stimulus to impulse arrival in the brain is hardly compatible with rapid integration with signals from fast Aβ afferents and other sensory systems, e.g. vision and hearing; integration that is indispensable for guidance of motor activities. Second, the documented inter-fiber variation in conduction velocity around 1 ms^{-1} implies that the volley of impulses in the sample of CT afferents excited by a local touch would arrive to the brain widely dispersed in time. As a result, the CT afferents produce a temporally blurred account of the peripheral event compared to that of the Aβ system. Altogether, it is evident that the CT afferents lack response properties required for serving discriminative touch.

The physiological evidence indicates that CT processing is tuned to slow, dynamic properties of light touch in hairy skin. Strikingly, it is just these aspects of touch that tend to be salient in affiliative tactile interactions between individuals (Gallace and Spence, this issue; Vallbo et al., 1999). Building on the intriguing similarity between socially relevant touch and the class of preferred stimuli for CT activation, we have thus proposed a "social touch" hypothesis that seeks to account for the known properties of CT afferents and their central projection.

Slow, gentle stimulation of hairy skin is likely to occur during close affiliative interactions with conspecifics, such as those between a parent and offspring, between siblings, between trusted associates, and not least between mates. Such affective touch may constitute a distinct domain of touch, characterized not by its sensory-discriminative functions, but by its social context and accompanying subjective component. As such, social touch may draw on a functionally and qualitatively different kind of information than that coded by Aβ afferents, requiring specialized functional organization in both the periphery and the central nervous system. CT afferents may thus constitute a privileged peripheral pathway for tactile stimulation that is likely to signal close, affiliative body contact with others: "earmarked" as distinct from other tactile sensation, and parceled for further affective valuation in the brain. The role of CT afferents in sexual functions has not been studied. Interestingly, studies on the distribution of the apparent mouse homolog of human CT afferents suggest they are lacking in the genital region (Liu et al., 2007).

Touch in human social interactions (where CT afferents are likely to play an important role together with Aβ afferents) is ubiquitous despite cultural differences in its regulation. It can serve as an important conveyer of affective information, often qualifying or intensifying emotional information from other modalities (such as vision). Social touch has a characteristic subjective quality, such as the feeling of well-being from the touch of a loved one. However, light touch can also be distinctly unpleasant such as the disgust associated with an unwanted touch, illustrating the importance of higher level contextual processing.

Despite this, research on touch in humans has focused mostly on the sensory and multisensory aspects of discriminative touch, rather than on the, perhaps less tractable, social and emotional dimension.

This important socially specific and affective aspect of touch can contribute to communicative behavior as well. It has been demonstrated that individuals from two countries (the US and Spain) were able to discriminate different categories of emotion on the basis of how someone touched them (Hertenstein et al., 2006). People readily communicated three prosocial emotions using nonverbal behavior – love, gratitude and sympathy. Interestingly, the emotion of love was typically communicated as a slow and moderately intense stroking over the skin (Hertenstein et al., 2006). Further, research in rodents indicates that slow skin stroking promotes hormonal responses, i.e. endorphin and oxytocin (Uvanas-Moberg et al., 2005). It seems possible that the functional role of CT afferents has changed from being mainly related to nurturing in many subprimate species, to having an additional role of promoting inter-individual bonding in socially active species, particularly in primates. The social and interoceptive roles of the CT system are unified by the broader function of homeostasis. The continuous maintenance of the organism's physical and behavioral stability requires that multiple physiological, cognitive, and affective processes are integrated (Paulus, 2007). The CT system may contribute to such integration by representing socially relevant tactile information.

7. Future directions

The social touch hypothesis (which builds on the affective touch hypothesis) and the related interoceptive hypothesis provide tentative working frameworks for further investigation of CT fibers and related pathways and processes. Yet, there remain several outstanding questions which future research should pursue.

CT afferents have to be fully characterized functionally. Much work also remains to be done in charting their central pathways from the dorsal horn to the brain, in determining the relevant receptor channels of the sensory terminals in the skin, and performing phylogenetic comparisons among humans and other mammals. The increased responsiveness of CT afferent firing with respect to cool (compared to warm or neutral) mechanothermal stimulation warrants further investigation, not least because it seems one of the more difficult features to accommodate within the social touch framework. However, if the caressing hand is cooler than the other person's more proximal hairy skin surface, then the preferential CT responses to cool mechanothermal stimuli seems consistent with the social touch hypothesis. The sporadic after-discharge and delayed acceleration also need to be addressed in more detail.

Not only interactions with other afferent systems, but influences upon efferent systems, represent a potentially fruitful area of investigation. For instance, since CT stimulation can evoke a sympathetic skin response (Olausson et al., 2008), the effects of gentle touch on behavior may extend to autonomic efference. In addition, it is also possible that socially relevant tactile stimulation modulates corticospinal motor processing, whether directly or indirectly. This would be important if social touch accompanies contexts of safety in which the need for vigilance and rapid motor reactions is relaxed. Another issue is possible differences in perception and cortical processing of a CT input that is generated by an external stimulus (passive touch), or by the subject's own movements (active touch) (Bolanowski et al., 1999).

Properties of the CT system suggest a role related to pain perception. For example, CT afferents have partly similar projections as nociceptive afferents in the central nervous system, and CT afferents have been shown to reduce nociceptive signaling at the level of lamina II of the dorsal root in rats (Lu and Perl, 2003). Tactile allodynia may be a consequence of CT inhibition (Krämer et al., 2007; Linde et al., 2004), and CT stimulation is effective in reducing experimental pain (Krämer et al., 2006). These observations suggest that stimulating or preserving CT function may be an important future strategy in the treatment of chronic pain.

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