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Perspective

Discriminative and Affective Touch: Sensing and Feeling

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The multimodal properties of the human somatosensory system continue to be unravelled. There is mounting evidence that one of these submodalities—touch—has another dimension, providing not only its well-recognized discriminative input to the brain, but also an affective input. It has long been recognized that touch plays an important role in many forms of social communication and a number of theories have been proposed to explain observations and beliefs about the "power of touch." Here, we propose that a class of low-threshold mechanosensitive C fibers that innervate the hairy skin represent the neurobiological substrate for the affective and rewarding properties of touch.

Introduction

Research into the sense of touch in humans has largely concentrated on describing the sensory and perceptual consequences of stimulation of low-threshold mechanoreceptors (LTMs) found in the skin and joints. In a broader description, the cutaneous senses are often described as encompassing the four submodalities of pressure/vibration, temperature, itch, and pain with LTMs sharing their anatomical locations in the skin with receptors that encode thermal and chemical stimuli. Each of these channels is capable of generating distinct sensory/perceptual qualities, processed by classes of stimulus-specific neurons that project in defined anatomical pathways to the cerebral cortex.

Historically, researchers have viewed the senses as generally subserving a primarily discriminative role (Mountcastle, 2005). Touch is inextricably linked to motor control. As a consequence, LTMs are innervated by myelinated Aβ afferent nerves enabling fast conduction velocities and supporting rapid central processing. The simple reflex arc allows a mechanical body sensation to rapidly trigger an action. However, hairy skin, the most abundant class of skin, contains proportionally fewer encapsulated LTMs and is also innervated by a class of unmyelinated low-threshold mechanosensory nerves, described as either C low-threshold mechanoreceptors (CLTMs) in animals or C-tactile afferents (CTs) in humans, with a conduction velocity about 50 times slower than myelinated afferents. Light-touch-sensitive C fibers mediate a wider bandwidth of mechanosensation than A fibers; only ~25% of somatosensory afferent nerves are in fact A fibers, with unmyelinated C fibers constituting the majority of afferents in all mammalian species (Willis and Coggeshall, 1978; Griffin et al., 2001). We therefore have a rapid "first" touch system, with obvious advantages for discriminative and sensorimotor functions and a slow "second" touch system, with less obvious advantages for survival. It is this second touch system that will be the focus of this Perspective, in which we will present a case for gentle touch-sensitive afferent C fibers providing the neurobiological substrate for the development and function of the social brain. The recognition that the afferent C fiber family includes pleasant touch, as well as pain, temperature, and itch, may open up opportunities to reinterpret our view of somatosensory processing in health and disease.

Discriminative Touch

For a sensory modality to perform a discriminative function, the speed with which an input signal is transduced, transmitted, and centrally processed is of paramount importance. The primary role of such systems is to detect, discriminate, and identify external stimuli with a view to ultimately making rapid decisions to guide subsequent behavior. Skin is classified as either glabrous, found only on the plantar and palmar surfaces, or hairy, which is found on the rest of the body. The sense of touch is classically described as being mediated solely by LTMs with rapidly conducting large myelinated (Aβ) afferents (Kandel et al., 2013; Mountcastle, 2005). Most primate research into skin sensory processing has focused on the glabrous surface of the hand, in particular the digits (for review see Mountcastle, 2005), where its high density of specialized mechanoreceptors underpins its remarkable capacity for encoding the spatial and temporal properties of surfaces and handled objects. Discriminative touch subserves the perception of pressure, vibration, slip, and texture, all critical in providing haptic information about handled objects and during exploratory procedures. Touch relies upon four different LTMs in the digit skin: slowly adapting type 1 (SA1), slowly adapting type 2 (SA2), rapidly adapting (RA), and Pacinian units. Each of these LTMs is specialized in transducing different aspects of mechanical stimuli into nerve impulses in Aβ large-diameter afferents. Although not the focus of this Perspective, there are also other classes of somatosensory afferents, besides LTMs, that innervate the human skin (Table 1).

Table 1. Main Properties of Primary Sensory Afferents Innervating Human Skin

Sensory Afferent Nerves			
Receptor Type	Modality	Axonal Diameter[a]	Conduction Velocity[a]
Aβ Fiber Group			
Low-threshold mechanoreceptors	Discriminative touch	10 μm	60 ms^{-1}
Aδ Fiber Group			
Nociceptors	Pain	2.5 μm	12 ms^{-1}
Cool receptors	Temperature	–	–
C Fiber Group			
Nociceptors	Pain	1 μm	<2 ms^{-1}
Warm and cool receptors	Temperature	1 μm	<2 ms^{-1}
Itch receptors	Itch	1 μm	<1 ms^{-1}
Low-threshold mechanoreceptors (CT)	Emotional Touch	1 μm	<2 ms^{-1}

[a]Approximate mean values.

Rapidly adapting receptors are associated with the anatomical end organs of Meissner and Pacinian corpuscles, responding to a temporally or spatially moving mechanical stimulus on the skin. SA1 receptors are associated with the Merkel and SA2 with the Ruffini end organs that continue to fire during a constant mechanical stimulus. A further classification relates to the LTMs' receptive field (RF), i.e., the surface area of skin to which they are sensitive. The RF is determined by the LTMs' anatomical location within the skin, with those near the surface at the dermal/epidermal boundary, Meissner's corpuscles and Merkel's disks, having small RFs, and those lying deeper within the dermis, Pacinian corpuscles and Ruffini endings, having large RFs. The four LTMs of the glabrous skin of the hand are thought to play different but complimentary roles in perception (Mountcastle, 2005). RA units are particularly significant for the sensation of localized flutter in response to low-frequency vibration (up to about 40 Hz), whereas Pacinian corpuscles are particularly significant for the sensation of poorly localized high-frequency vibration (above 40 Hz). However, there is no question that the two unit types account for other tactile percepts as well. SA1 units account for the sensation of sustained pressure.

Microneurography studies on single peripheral nerve fibers innervating the human hand have provided a generally accepted model of touch that relates the four anatomically defined types of cutaneous or subcutaneous sense organs to their neural response patterns (Hagbarth and Vallbo, 1967; Vallbo and Johansson, 1984; Johansson et al., 1982). A small pulsed current of a few microamperes may be delivered to selectively excite the nerve fiber, a procedure that demonstrates the perceptive qualities generated by electrical stimulation of an individual afferent (Ochoa and Torebjörk, 1983; Vallbo et al., 1984). These psychoneural relations are particularly pertinent in intraneural microstimulation (INMS) studies of single afferents, as they demonstrate that human subjects are able to report the sensations postulated by the Mountcastle (2005) model when an afferent is activated (Ochoa and Torebjörk, 1983; Trulsson et al., 2001; McGlone et al., 2002; Vallbo et al., 1984). The evoked sensations are perceived as emanating from within the receptive fields of the unit with sensory qualities characteristic of the respective afferent type. The exception is the SA2 system, which is likely to require spatial summation (i.e., a conscious sensation is not evoked until a number of SA2 units are activated in concert). This would be consistent with the interpretation that cutaneous SA2 units have a functional role in relation to kinaesthesia and motor control, their essential role being to provide information on body position and movements of joints (Backlund Wasling et al., 2005; Edin, 2001; Edin and Johansson, 1995).

Psychophysical studies have corroborated to some extent the neurophysiological findings, leading to a multichannel model of tactile sensitivity (Gescheider et al., 2010). This model had its genesis in seminal psychophysical studies by Verrillo (1963, 1968) with the discovery of two independent channels in glabrous skin that transduce low- and high-frequency vibrotactile stimuli—a P (Pacinian) channel responsible for high-frequency detection and a non-Pacinian (NP) channel for low-frequency detection. Further elegant psychophysical experiments led to a four-channel model of vibrotaction, proposing that the initial single NP channel comprised three separate NP channels (Gescheider et al., 1985). Each of the four channels has a specific type of Aβ nerve fiber and LTM (Bolanowski et al., 1988). The P system is purported to be served by the Pacinian afferents, the NP I system by the RA afferents, the NP II by the SA2 afferents, and NP III by the SA1 afferents. It is important to recognize in these psychophysical studies by Verrillo and colleagues that their four-channel model only pertains to vibtotactile detection threshold responses and that suprathreshold stimuli will activate all classes of LTMs.

These neurophysiological and psychophysical studies have provided some understanding of the operating characteristics of LTMs in the glabrous skin of the hand. However, there have been relatively few studies of tactile sensitivity on hairy skin. Five different types of mechanoreceptive afferents with fast-conducting Aβ fibers have been identified in the human forearm skin: SA1, SA2, and rapidly adapting field, hair, and Pacinian units (Edin, 1992; Vallbo et al., 1995). The relationship between these sensory fibers and tactile perception is still uncertain.

A recent view, mainly based on the anatomical organization of LTMs in mouse hairy skin and their central projections, suggests that integration of signals from the different LTMs takes place in the dorsal horn (Abraira and Ginty, 2013). This line of research puts the dorsal horn as the first important integration step rather than the somatosensory cortex as suggested by the "labelled line" multichannel view on tactile processing outlined above. However, regarding the molecular transduction properties and modality-specific functions of the different types of LTM outlined above, their patterns of spike trains—evoked or spontaneous—the central pathways and connections to the somatosensory cortex and beyond, the "logic" of the LTM circuit organization underlying the perception of touch remain unclear even after ~100 years of research into the *discriminative* properties of touch (Marshall and Lumpkin, 2012), and we are only now tackling those circuits and systems that underpin the *affective*

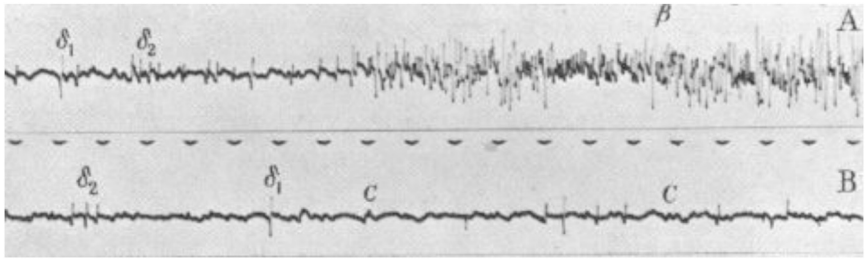

Figure 1. Axon Potentials Elicited by Stroking the Skin
To be read from right to left.
(A) The end of a firm stroke with a wooden pin.
(B) From the same record 3 s. later. Time is represented as 1/50 s.

properties of touch, which are mediated by a class of low-threshold mechanosensitive afferents—described in the next section—called C-tactile afferent (CTs). Fundamental questions remain concerning how LTMs, and now including CTs, with their individual encoding properties, operate together in the perception of tactile stimuli encountered during interactions with the natural environment (McGlone and Reilly, 2010).

Affective Touch

Touch's affective role has not been as well recognized. Unmyelinated or thinly myelinated afferents have long been associated with the processing of body signals, via *interoceptive* pathways that signal feeling rather than sensing states, as well as controlling organ functions that do not reach conscious perception. Their conduction velocities are typically in the range 0.5–2 m/s, as opposed to the more heavily myelinated Aβ fibers, discussed above, which conduct *exteroceptive* signals at speeds from 20–80 m/s. It is this interoceptive role for touch that is being introduced here, mediated by low mechanical threshold C fibers.

C fiber tactile afferents were first identified on basis of their low spike heights 75 years ago by Zotterman (1939) using a cat saphenous skin-nerve preparation (Figure 1). Subsequently, low-threshold mechanosensitive C fibers (CLTMs) have been identified in the hairy skin of various mammals (Bessou et al., 1971; Douglas and Ritchie, 1957; Iggo and Kornhuber, 1977; Kumazawa and Perl, 1977; Leem et al., 1993). Careful microneurography experiments demonstrated that human skin also is innervated by a population of unmyelinated CT afferents that respond optimally to gentle stroking touch. They were first reported in the infraorbital nerve (Johansson et al., 1988), and in the supraorbital nerve (Nordin, 1990). Subsequently evidence of a more general distribution of CT afferents has been found in the arm and the leg (Vallbo et al., 1993, 1999; Edin, 2001; Wessberg et al., 2003). Their terminal morphology is currently unknown, but electron microscopy data reveal a high degree of arborization of C fiber terminals at the dermal-epidermal boundary (Cauna, 1973). Although it is currently not possible to assess their density in human skin nerves, they are encountered as often as the Aβ afferents during microneurography sessions (Vallbo et al., 1999). Interestingly, CT afferents have never been recorded from nerves innervating the palmar skin of the hands (Figure 2).

CT Afferents: Neurophysiological Characteristics

CT afferents respond to very low indentation forces in the range 0.3–2.5 mM (Cole et al., 2006; Vallbo et al., 1999) and with high-frequency responses (50–100 impulses s^{-1}) to innocuous stimuli, such as gentle stroking with a soft brush. This impulse rate is close to the maximum reported for afferent C fibers (Kumazawa and Perl, 1977). Although C nociceptors have been shown to respond to light brush stroking, their responses never exceed more than a few impulses (Vallbo et al., 1999). The conduction velocity of CTs varies between 0.6 and 1.3 m s^{-1} and their adaptation characteristics are therefore intermediate between those of the slowly and rapidly adapting myelinated mechanoreceptors (Figure 3).

Low-velocity/force stroking movements provide a stimulus that is particularly effective in stimulating CT afferents (Nordin, 1990), and with repeated brushing it is often found that unit firing decreases, showing signs of fatigue. However, there is very large heterogeneity in CT responses, and units have also been found where there was *enhancement* compared to baseline with repeated stimuli. CTs may respond to innocuous cooling but not to warming or noxious heating (Nordin, 1990). The combination of mechanical stimulation and cooling gives a more vigorous response than either of the two alone (K. Wiklund Fernstrom and J. Wessberg, 2003, Soc. Neurosci., abstract). The consensus view emerging from studies of CTs is that they are a heterogeneous, but nonetheless electrophysiologically constrained, population of cutaneous afferents, the abiding properties of which are that their adequate stimulus is found at stroking velocities which correlate with subjective pleasantness ratings (Essick et al., 1999, 2010). The relationship between the electrophysiological properties of LTMs and CTs and the subjective responses evoked by stroking touch were reported in a paper by Löken et al. (2009). The relationship between brush-stroking velocity and firing rate was distinctly different between CT and myelinated afferents. CTs showed an inverted U-shaped relationship between brushing velocity and mean firing rate with highest responses between 1 and 10 cm/s^{-1} (Figure 4A). Subjects rating the positive hedonic quality of the brush stroking on a visual-analog scale showed a similar inverted U-shaped function with 1 to 10 cm^{-1} being rated as most pleasant (Essick et al., 1999, 2010). In contrast, mean firing increased monotonically with brushing velocity in all myelinated afferent type.

Not only are CTs velocity tuned, they are also temperature tuned (Ackerley et al., 2014). CTs are unique among mechanoreceptive afferents in that they discharged preferentially to slowly moving stimuli at a neutral (typical skin) temperature, rather than at the cooler or warmer stimulus temperatures. In contrast, myelinated hair mechanoreceptive afferents proportionally increased their firing frequency with stroking velocity, showing no temperature modulation. Their firing frequency also correlated with hedonic ratings to the same mechanothermal stimulus only at the neutral stimulus temperature, where the stimuli were felt as pleasant at higher CT firing rates.

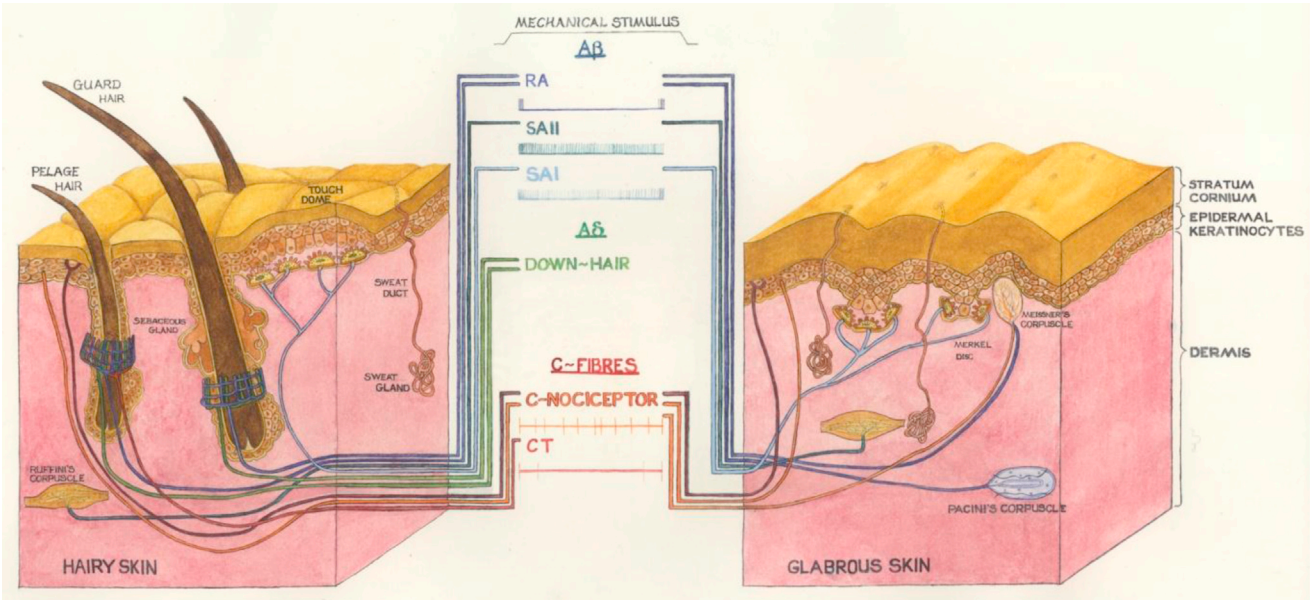

Figure 2. The Innervation of Hairy and Glabrous Skin Showing the Types of Nerve Fibers and Receptors
The discriminative aspects of touch are coded by LTMs present in both skin types, but the coding of affective touch (CT) is limited to hairy skin. Abbreviations: SA, slowly adapting; RA, rapidly adapting; LTMR, low-threshold mechanoreceptor; CT, C-tactile afferent.

Although microneurography has provided valuable insights into the electrophysiological properties of CTs, little is known about their molecular neurobiology or their cutaneous terminal anatomy. However, the recent discovery of a rare population of unmyelinated sensory neurons in mice expressing the Mas-related G-protein-coupled receptor MrgPRB4 that exclusively innervates hairy skin have been posited as the CLTM homolog of CTs (Dong et al., 2001; Zylka et al., 2003). MrgB4 is expressed in a subpopulation of unmyelinated, nonpeptidergic afferents innervating hairy skin of the mouse, with an increasing innervation density from distal to proximal body sites (Liu et al., 2007). Interestingly, MrgB4 does not appear to be expressed in glabrous plantar skin or the genitalia. The terminal structure of MrgPRB4 fibers consists of large arborizations sharing a similarity with the receptive fields found in a human microneurography study by Wessberg et al. (2003). MrgPRB4 fibers were found to encircle and penetrate the necks of hair follicles and were also found in the neighboring epidermis (Liu et al., 2007). A recent report used a genetic labeling method in a mouse model in order to identify the three subclasses of LTMs (Aβ, Aδ, and CLTM) and visualize their respective terminal endings in hairy skin and spinal cord (Li et al., 2011). Each of the three hair follicle types (guard, awl/auchene, and zigzag) was found to be innervated by a "unique and invariant combination of LTMRs." CLTMs, with longitudinal lanceolate endings, were most often associated with zigzag (80%) and awl/auchene (20%) hair follicles. According to Li et al. (2011), their location in fine hair follicles is not an indication that this end organ is the sole determinant of CLTM responses or of their adaptation properties.

Unlike other molecularly defined mechanosensory C fiber subtypes, MrgPRB4$^+$ neurons do not respond to mechanical (brushing) stimulation of the skin in an ex vivo preparation (Vrontou et al., 2013). However, calcium imaging of the dorsal root ganglion (DRG) and dorsal horn spinal projections of these neurons in intact mice revealed that they are activated by gentle brushing of hairy skin but not by noxious mechanical stimulation. Evidence that CLTMs process the rewarding properties of gentle touch was shown using a conditioned place-preference test (Tzschentke, 2007), in which pharmacogenetic activation of MrgB4-expressing neurons in freely behaving mice led to a significant increase in the time spent in the test chamber where these neurones had been stimulated, indicating that this activation had a positive affective valence (Panksepp, 2011).

In mice, CLTMs in the DRG are marked by the expression of VGLUT3, a vesicular glutamate transporter (Seal et al., 2009), and also by the expression of tyrosine hydroxylase (TH) (Li et al., 2011). However, VGLUT3 is expressed widely in the nervous system, in addition to that found in CLTMs (El Mestikawy et al., 2011). VGLUT3 lineage sensory neurons can be divided into two groups based on *transient* or *persistent* VGLUT3 expression. The transient type are large-diameter myelinated mechanoreceptors associated with Merkel cell-neurite complex and the persistent type are small-diameter unmyelinated neurons containing two subtypes: tyrosine hydroxylase-positive (TH$^+$) CLTMs that form the longitudinal lanceolate endings, as previously described, and TH$^-$ neurons that form epidermal-free nerve endings. It was found that VGLUT3-persistent neurons express the runt domain transcription factor Runx1, critical in the development of VGLUT3-persistent neurons (Lou et al., 2013). Runx1 is required to establish mechanosensitivity in CLTMs by controlling the expression of the mechanically gated ion channel Piezo2 (Delmas et al., 2011). Lou et al. (2013) found that in Runx1 mutants' acute and chronic mechanical pain was unaffected, which, the authors state, argues

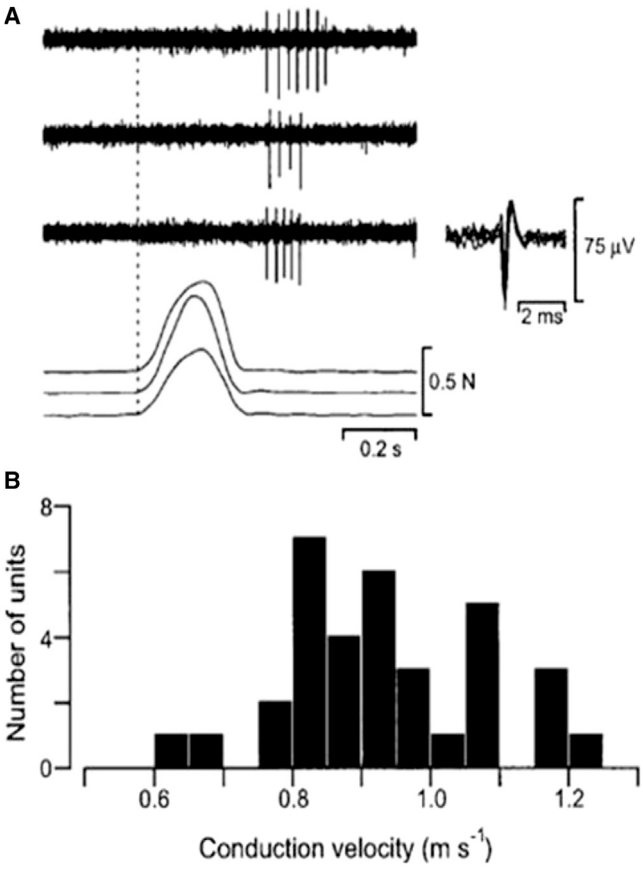

Figure 3. Conduction Velocity of Mechanoreceptive C Afferents
(A) Responses of CT afferent to three tap stimuli delivered to a highly sensitive spot within the receptive field, illustrating the method of conduction velocity assessment. Hatched line indicates 0 time for latency assessment corresponding to first increase in force record. Distance between receptive field and nerve recording site was, in this case, 274 mm, yielding a conduction velocity of 0.64 m/s. Unit's threshold to local indentation was 2.5 mN. Inset: on expanded timescale, the five action potentials of the bottom trace are superimposed.
(B) Distribution of conduction velocity of 34 C afferents, estimated on the basis of mechanical stimuli as in (A). Mean value was 0.9 m/s and the range 0.6–1.2 m/s.

against the recently proposed role of VGLUT3 in CLTMs mediating the allodynia often induced by nerve injury or inflammation.

Reilly et al. (1997), using the panneuronal marker protein gene-product 9.5 (PGP9.5) in a human volar forearm blister-base preparation (epidermis only), found an epidermal skin network of thin unmyelinated nerve fibers in all layers of the viable epidermis. Pretreatment of the skin in vivo with the neuropharmacological agent capsaicin resulted in a complete loss of epidermal fiber staining, indicating that these are sensory fibers of the primary C-afferent type. However, PGP9.5 staining of unmyelinated nerve endings in the epidermis cannot resolve subtypes of C fibers. It is unknown where CTs terminate in human skin, making it imperative that appropriate labeling techniques are developed.

Selective CT Stimulation

Determining a specific role for CT afferents in tactile sensation is confounded by the fact that it is not possible to stimulate them without also stimulating Aβ afferents in neurologically intact subjects. Working with two subjects who lack Aβ afferents but have intact C fibers as the result of sensory neuronopathy that destroyed all cell bodies in the DRG of the large primary sensory neurons (Sterman et al., 1980), we have been able to gain further insight into the contribution to tactile perception from CTs. As the neuronopathy selectively affects only myelinated fibers, sparing unmyelinated ones, these patients are assumed to possess CTs as their sole tactile afferents. Two subjects with such sensory neuronopathy 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 as they also lack muscle and joint mechanoafferents (Stenneken et al., 2006). Having established with microneurography studies that human skin is supplied with a system of unmyelinated mechanoafferents sensitive to light touch (Löken et al., 2009), it was decided to reexamine the tactile sensibility of neuronopathy subjects using more rigorous psychophysical procedures. It was found, in two-alternative-force-choice (2-AFC) tests, that subjects lacking Aβ afferents readily detected low-force/velocity brushing applied to the forearm skin, where CT afferents are abundant (Cole et al., 2006; Olausson et al., 2002, 2008), but failed altogether to detect the same kind of stimuli applied to the glabrous skin of the hand, where CT afferents are lacking. Additionally, neuronopathy subjects have difficulties detecting 50 Hz vibratory stimuli, which are known to give a poor excitation of CT afferents but a massive activation of Aβ afferents (Bessou et al., 1971; Iggo, 1960; Kumazawa and Perl, 1977; Olausson et al., 2002, 2008).

Although these observations agree that CT afferents may well account for detection of touch stimuli in subjects lacking Aβ afferents, it has been more difficult to obtain a clear and consistent understanding of the quality of the sensation perceived when CT afferents are selectively stimulated in these patients. It should be noted that stimulus detection in a psychophysical 2-AFC test does not demonstrate that the stimulus is very clearly perceived. However, 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 was very weak, vague, and inconsistent when slowly stroking a broad and soft artist paintbrush along the forearm of the neuronopathy subjects. In some trials, the subject reports no sensations at all. In others, he or she reports a sensation of light touch that is 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 varies from one occasion to the other and between the two subjects. Although the two neuronopathy subjects are not able to give a concise or detailed description of the sensation evoked by CT stimulation, some consistent features of the quality emerged. The sensation has no quality of pain, tickle, or itch. Further, they report that the sensation elicited by CT stimulation is slightly or moderately pleasant. The neuronopathy subjects' ability to spatially localize CT stimulation is very poor; in several trials they could not identify which body quadrant was stimulated. Nevertheless, CT stimulation evokes a sympathetic skin response in both subjects. The

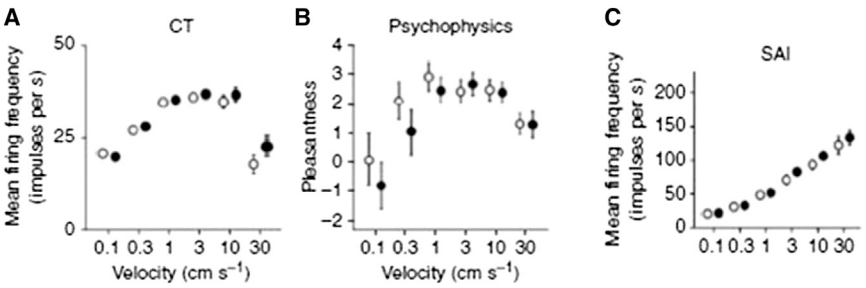

Figure 4. Brush Stimulation and Nerve Recordings

(A and C) Dots show average discharge rates during brush stroking for the two types of mechanoafferents depicted here that were explored with the full range of stimulus velocities (C-tactile, n = 16, A; SAI, n = 8, C). Note that scaling on the y axes is different for C-tactile and myelinated afferents.

(B) Average ratings of perceived pleasantness in response to soft brush stroking. Data are from ten subjects. Error bars indicate SEM.

CT system may thus have autonomic consequences despite the system's apparently weak perceptual impact (Olausson et al., 2008).

Spinal Processing of CTs

In mouse, the central terminals of low-threshold C fibers project to inner lamina II of the spinal dorsal horn (Sugiura, 1996), and there is a population of spinal neurons responding exclusively to slowly moving brushing stimuli with inputs solely from unmyelinated afferents and cell bodies in inner lamina II (Light and Perl, 1979). The morphological properties of these neurons identified include vertical neurons (Grudt and Perl, 2002) with axons arborizing in lamina I (Maxwell et al. 2007), where they would come into contact with the projection neurons (Lu and Perl, 2005). Andrew (2010), exploiting the preferential sensitivity to slowly moving versus rapidly moving stimuli of CLTMs, characterized the low-threshold response properties of lamina I projection neurons in the rat, showing that projection neurons in lamina I of the spinal cord transmit tactile information carried by C fiber mechanoreceptors to the brain. The authors further investigated the response properties of "wide dynamic range" neurons in lamina I that projected to the contralateral parabrachial nucleus using graded velocity brushing stimuli to identify whether low-threshold mechanoreceptor input to these neurons came from myelinated or unmyelinated nerve fibers. The most effective tactile stimuli for activation of "wide dynamic range" lamina I spinoparabrachial neurons are low-velocity brush strokes (mean velocity of 9.2 cm/s^{-1}) whose firing declined exponentially as brush velocity increases. These data indicate that C fibers, but not A fibers, convey low-threshold mechanoreceptor inputs to lamina I projection neurons. Two populations of mechanoreceptive WDR neurons have been identified in the dorsal horn—one in laminae I/II and one in lamina V (Sewards and Sewards, 2002). The authors suggest that nociceptive-specific neurons in laminae I/II relay what will be centrally processed as the "negative-affective" properties of somatosensation and that laminae I/II WDR neurons might also contribute to its "positive-affective" or hedonic aspects as they respond to mechanical stimuli in both the innocuous and noxious ranges. They concluded that lamina I WDR neurons represent hedonic components, with the lamina V WDR neurons representing the sensory/discriminative component.

The supraspinal circuits activated by CLTM activity in experimental animals are currently unknown, but a route via the parvicellular part of the ventral posterior and/or posterior triangular thalamic nuclei to insular cortex has been proposed on the basis of neuroanatomical tracing studies (Andrew, 2010). Evidence from human studies of the spinal projections of CTs has come from surgical sectioning of the anterolateral spinothalamic tract for treatment of chronic intractable pain. The earliest, wonderfully insightful, observation that cutting this tract impacts on aspects of affective touch (as well as pain and itch) was made by a remarkable German neurologist and neurosurgeon, Otfrid Foerster (Foerster et al., 1932):

> Except for the pain- and temperature sensations, also other sensory qualities were spoiled after the anterolateral transection. First of all, the feelings of tickle and itch were included, but so were all other feelings of pleasure and displeasure as well. (p. 43, translated from the original German)

This lack of "pleasure" after transection of the spinothalamic tract provides at least circumstantial evidence that CTs ascend in the same tract as C-nociceptors. Lahuerta et al. (1994) made similar observations in a cohort of anterolateral cordotomized patients, reporting that they do not experience cutaneous erotic sensation when receiving low-intensity tactile stimulation. These clinical observations support the existence of a spinothalamic pathway for signaling CT-mediated pleasant properties of touch and, by default, the existence of a C fiber-mediated affective touch system.

Cortical Processing of CTs

In control subjects, soft brush stroking on hairy skin activates the classical somatosensory areas S1 and S2 as well as the posterior contralateral insular cortex. Insular cortex is a region of great interest in relation to affective mechanisms and is considered as a gateway from sensory systems to the emotional systems of the frontal lobe (Augustine, 1996; Craig, 2008). When similar brushing stimuli are applied to the Aβ deafferented subject GL, no activation is found in the somatosensory areas, whereas the posterior insular region was activated (Olausson et al., 2002). In fact, CT stimulation evoked significant fMRI deactivation in somatosensory cortex with this inhibitory effect supporting the notion that CT is not a system for discriminative touch. Unmyelinated CT afferents, therefore, probably have excitatory projections mainly to emotion-related paralimbic cortical systems (insular cortex). Beyond the insular cortex, the posterior superior temporal sulcus and the medial prefrontal cortex (mPFC)/dorsoanterior cingulate cortex (dACC) are also implicated in processing CT-targeted touch (Gordon et al., 2013). The contribution of tactile Aβ afferents to emotional processing along with

the CT afferents has not been widely explored. It is obvious that Aβ afferents may well 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 (Francis et al., 1999; Rolls et al., 2003). However, when contrasting brain processing of CT-targeted touch on hairy skin and similar touch on glabrous skin, there are activations of the posterior insular cortex and midanterior orbitofrontal cortex for the CT-targeted touch and the somatosensory cortices for the glabrous touch (McGlone et al., 2012), consistent with the hypothesis that pleasant touch from hairy skin is processed in limbic-related cortex and represents an innate nonlearned process. That touch with glabrous skin is also perceived as pleasant is hypothesized to be due to a learned or secondary reinforcement mechanism underpinned by LTMs signaling in a pattern type of processing (McGlone et al., 2012). We have shown that pleasant touch from hairy skin is represented in the firing frequency of CT afferents (Löken et al., 2009) and processed in limbic-related cortex in a labeled-line type of fashion (Björnsdotter et al., 2009). There is no corresponding correlation between firing of myelinated mechanoreceptors and pleasant touch perception (Löken et al., 2009).

CTs and Pleasure

The consequences of afferent C fiber stimulation are more often associated with that of pain, temperature, or itch, and here we come to a pivotal point in this Perspective. It is now clear that human hairy skin is innervated by a fourth population of afferent C fibers, the adequate stimulus for which is a gentle, low-force stroking of the hairy skin—a stimulus that is not in the nociceptor range. What is the function of this population?

From a teleological perspective, any stimulus that is associated with a reward or punishment is linked to the simple purpose of survival. The functional significance for survival of a nociceptive system is unequivocal. It is generally accepted that cutaneous pain is signaled by two types of afferent nerves: a rapidly conducting system of myelinated Aδ fibers that signal the sensory properties of the stimulus and provide discriminative spatial information to identify, rapidly, where on the body the tissue-threatening stimulus is located and a slowly conducting system of unmyelinated C fibers responsible for the affective/motivational consequences of damage to the skin. Here we propose a similar duality for touch. First touch is mediated by myelinated fast-conducting Aβ nerves, signaling the presence of an object impinging the body surface and providing discriminative spatial information in order to identify, rapidly, where on the body the stimulus is located. The second touch system, mediated by CT afferents, is activated should the touching stimulus have the appropriate properties for CT's "adequate stimulus," i.e., is a low-force/velocity dynamic touch, the response to which would be an affective/motivational one. As CTs are additionally tuned to respond to tactile stimuli with the specific thermal characteristics of a gentle caress delivered at normal skin temperature (Ackerley et al., 2014), this reinforces their role as providing a peripheral mechanism for signaling pleasant skin-to-skin contact in humans, thereby promoting interpersonal touch and affiliative behavior.

It is clear from the preceding description of the peripheral-central pathways so far elucidated for CTs that there are labeled lines from the skin to regions such as insular and orbitofrontal cortex that transmit affective properties of social touch (Francis et al., 1999; Löken et al., 2009; McGlone et al., 2007; Morrison et al., 2010). What is pertinent here is that we posit that CT touch is rewarding and, as reward mechanisms are a central component for driving appropriate responses to stimuli and the development of goal-directed behaviors, that CTs provide an afferent cutaneous channel for processing "pleasant touch."

Further support for the CT-pleasant touch hypothesis comes from observations in patients with congenital loss of C fibers, most likely including CT fibers (Morrison et al., 2011a). The condition of the patients is classified as hereditary sensory and autonomic neuropathy type V and is associated with a mutation in the gene coding for nerve growth factor beta. The patients perceive CT-targeted touch as less pleasant than do matched controls and they also differ in their rating patterns across stimulation velocities. Further, patients' fMRI response in posterior insular cortex is not modulated by CT-targeted touch stimulation. Hence, perception of the hedonic aspect of dynamic touch likely depends on CT afferent density.

Nevertheless, contextual factors, i.e., top-down mechanisms, also influences the pleasantness of touch. A positive expectation to an inert nasal spray (placebo) enhances the pleasantness of CT-targeted touch (Ellingsen et al., 2014). This beneficial placebo effect is reflected in modulation of sensory processing. Specifically, placebo-induced improvement of pleasant experiences involves an *upregulation* of activity in the posterior insula, S1, and S2. In contrast, placebo-induced analgesia involved a *downregulation* of activity in these areas. These results indicate that increased early sensory processing of a stimulus of positive valence (e.g., pleasant touch) underpins hyperhedonia, in a similar manner as reduced processing of an aversive stimulus (e.g., painful touch) underpins analgesia. The placebo-induced improvement of positive and negative hedonic feelings are underpinned by recruitment of common circuitry associated with emotion appraisal; placebo-induced functional coupling between ventromedial prefrontal cortex and periaqueductal gray correlated with increased sensory responses to stroking touch but decreased responses to painful touch. Thus, similar modulatory circuits can up- and downregulate early sensory processing depending on whether the expectation is improvement of positive or negative hedonic feelings.

The interplay between the first and second touch systems is yet to be fully determined, and although the large-fiber deafferented patients we have tested report sensations of pleasant touch, these are at best minimal. Another contextual element depends on, in the case of interactive (other) touch, the relationship of the "touchee" with the "toucher" (Gazzola et al., 2012) and in intra-active (self) touch, the particular behavior being carried out, e.g., as in autogrooming. Interestingly, during self-touch, the body part responsible for delivering touch is the glabrous surface of the hand, which is not innervated by CTs. Does this provide a higher-order mechanism for the representation of self during self-touch? Of possible relevance here is a

finding from a recent study in which the authors asked whether the brain processing of pleasant touch differed between hairy and glabrous skin (McGlone et al., 2012). The forearm and glabrous skin were stroked with a soft brush, during positron emission tomography (PET), and the data showed that, when contrasting slow brush stroking on the forearm with slow brush stroking on the palm, there were significant activations of the posterior insular cortex and midanterior orbitofrontal cortex. The opposite contrast showed a significant activation of the somatosensory cortices.

However, there was a tendency toward activation in the angular gyrus when stroking hairy skin versus glabrous skin. The angular gyrus has been shown by Blanke et al. (2002) to trigger repeated out-of-body experiences when electrically stimulated in a study with an epilepsy patient. The activation in this area to CT-directed touch during the PET study poses an interesting question—do CTs play a role in coding for the sense a bodily self? Further support for this role for CTs comes from a recent paper study that found that slow-velocity gentle touch, delivered to CT-innervated skin, produced higher levels of subjective embodiment during the ubiquitous rubber hand illusion compared with fast touch (Crucianelli et al., 2013), providing support for the idea that affective touch, and more generally interoception, may have a unique contribution to the sense of body ownership, and by implication to our embodied psychological "self" (see also: van Stralen et al., 2014; Lloyd et al., 2013).

CTs and Pain

There is much to be learned from the dorsal horn/spinal cord anatomy of C-nociceptors that could be of value to that of CTs. They project to the same layers and the same spinal pathways and there is growing interest in the potential interactions between these two classes of C fibers. The superficial dorsal horn (laminae I/II) has been considered largely nociceptive in function (Todd, 2010). However, there is now evidence of neurons that also respond to inputs from CTs and, as with C-nociceptors, also have significance for emotional responses. CT afferents terminate mostly in inner lamina II, where all the neurons are local circuit interneurons, raising the possibility that injury-induced mechanical hypersensitivity may involve a change in the sensation conveyed by CTs, from pleasant touch to pain (Drew and MacDermott, 2009).

The first study to implicate CT afferents in allodynia used a VGLUT3 knockout mouse model specific for CLTMs (Seal et al., 2009). Mechanical hypersensitivity following inflammation, nerve injury, and trauma was reduced after the loss of VGLUT3 neurons and thus a critical role for CLTMs in the mechanical hypersensitivity was suggested. However, more recent evidence suggests that VGLUT3 lineage sensory neurons are divided into two groups depending on whether they exhibit a transient or a persistent VGLUT3 expression (see above). The VGLUT3-transient neurons are myelinated LTMs, whereas the VGLUT3-persistent neurons are CLTMs. Analysis of mice with a conditional knockout of VGLUT3-persistent (CLTM) neurons demonstrates that pain was largely unaffected. This suggests that VGLUT3-transient neurons, e.g., myelinated LTMs, may control mechanical hypersensitivity (Lou et al., 2013). This finding is more in line with a recent finding from our group where the contribution of CTs to the allodynic condition in humans was studied following the heat/capsaicin model of tactile allodynia (Liljencrantz et al., 2013). Healthy subjects reported tactile-evoked pain, whereas Aβ denervated patients did not. Instead, patients reported their C-touch percept (faint sensation of pleasant touch) to be significantly weaker in the allodynic zone compared to untreated skin. fMRI confirmed that stroking in the allodynic and control zones evoked different responses in the primary cortical receiving area for thin fiber signaling, the posterior insular cortex. These findings suggest that dynamic tactile allodynia is associated with a reduced CT hedonic touch processing; however, whether CT signaling contributes to the allodynic experience, or reduces the hyperalgesia, remains an open question (Delfini et al., 2013; see also Nagi et al., 2011).

The Skin as a Social Organ

Research in social neuroscience tends to focus on visual and auditory channels as routes for social information. However, because the skin is the site of events and processes crucial to the way we think about, feel about, and interact with one another, touch can mediate social perceptions in various ways (Morrison et al., 2010). Patients who are touched by a nurse the day before a surgical operation decrease their subjective and objective level of stress (Whitcher and Fisher, 1979). Gentle stroking touch has been shown by Knox and Uvnäs-Moberg (1998) and Uvnäs-Moberg (1997) to lower blood pressure, increase transient sympathetic reflexes (see Olausson et al., 2008), and increase pain thresholds. Many studies have demonstrated that interpersonal touch—specifically gentle touch—plays a crucial role in development (Field, 2001; Field et al., 1995), tipping in restaurants (Crusco and Wetzel, 1984), counselling sessions (Alagna et al., 1979), and even cognitive processes such as deferred-reward in preschool infants (Leonard et al., 2014).

What none of these studies provides, however, is evidence for, or recognition of, the neurobiological mechanism mediating these effects. This is no truer than when we look at the wealth of publications on Attachment Theory (Ainsworth, 1969; Bowlby, 1970, 1973; Bartholomew, 1993). According to Bowlby the "attachment-behavioral system" is engaged when an infant is distressed, such as after separation (the "strange situation"), leading the infant to seek proximity to the parent/caregiver in the form of physical contact, which Main and Hesse (1990) suggests is the primary signal to infants that they are then safe and secure (see also Ainsworth, 1979). There is growing circumstantial and now neurobiological evidence that touch is more than a sensory input for discrimination of what is on the skin, or control of movement, and that the rewarding value of physical contact in nurturing and social interactions reflects the presence of an evolutionary mechanism—mediated via CT/CLTMs—that promotes physical contact in specific contexts. Touch may be viewed as a biologically necessary form of stimulation, not just a sentimental and romantic human indulgence (Casler, 1961; Korner and Grobstein, 1966; Thayer, 1986). It could be argued that the need for touch does not diminish throughout life, that in order to flourish as an adult one needs physical contact with others and that this need actually increases in old age, when there are often much diminished opportunities for tactile social interactions.

The Neurochemistry of Social Touch

Studies into primate social systems have found that allogrooming provides a means for groups to form social bonds, especially with those in kinship (Silk, 2002). Monkeys spend much more time grooming than required for hygiene alone, suggesting that this behavior has an additional affective and social function (Dunbar, 1993, 1997). It has also been shown to stimulate the production of the body's natural opiates, the endorphins; in effect, being groomed produces mildly narcotic effects. Keverne et al. (1989), investigating the neurochemical basis of primate grooming, found that changes in the brain's opioid system were contingent on grooming duration in monkeys. Grooming frequency decreases under nonsedative doses of morphine and increased when the opiate antagonist naltrexone was administered, suggesting that endogenous brain opioids play a regulatory—reward—function in primate sociality. Furthermore, the amount of grooming given and received can be used to interpret an individual's social status (Henazi and Barrett, 1999), indicating that touch plays a more complex (beyond purely sensory) role in a social context. These studies only provide correlational data and a role for endorphins in regulating underlying psychological processes can only be hypothesized. Their role in pain control, however, and their release in response to low-level physical and psychological stress (Basbaum and Fields, 1984) strongly suggest that allogrooming is one source of social bonding, supporting the view that brain opioids are implicated in mediating social attachment. Their release via behaviors that preferentially activate CTs may provide the neural basis on which aspects of primate sociality has evolved. It is particularly interesting that the time spent on this behavior increases in larger social groups, suggesting that an essential role of grooming is to promote affectionate attachment between individuals and hence keep the group together (Dunbar, 2010). Further, ventral forebrain areas are important for opioid-mediated hedonic reward following sensory stimulation (Peciña et al., 2006), with a recent PET study using a μ-opioid receptor-specific ligand finding that social touch activates the brain's opioid system (L. Tuominen et al., 2013, Soc. Neurosci., abstract). This study used a social touch paradigm that involved participants being gently stroked on exposed skin sites by their partner, compared with a nontouch baseline, and revealed higher opiate receptor binding during the social-touch condition in ventral striatum and anterior cingulate cortex—key areas of the brain's reward circuit. This type of intimate social touch, specifically targeted to preferentially stimulate CTs, led the authors to conclude that the μ-opioid system provides the neurochemical mechanism underpinning the instigation, maintenance, and reinforcement of close social bonds between humans. Of possible relevance here is that endogenous opioid binding to μ-receptors is hypothesized to mediate natural reward and has been proposed to be the basis of infant attachment behavior. Moles et al. (2004) find that μ-opioid receptor knockout mouse pups do not show a preference toward their mothers' cues after brief maternal exposure, indicating a possible molecular mechanism for neurodevelopmental disorders that include in their spectra deficits in attachment behavior, such as autism (Naber et al., 2007) or reactive attachment disorder (Hanson and Spratt, 2000). This study showed that μ-receptors play a key role in attachment disorders adding support to Panksepp (1989)'s hypothesis that "a malfunctioning endogenous opioid system" may explain the social indifference typical of autistic infants. The present data also highlight mice lacking μ-opioid receptors as a useful animal model to evaluate the consequences of deficits in the affiliative system during development and adulthood (see also Walker and McGlone, 2013).

There is also a wealth of research into the role of another neuropeptide, the posterior pituitary nonapeptide oxytocin, released during sexual as well as nonsexual social interactions (Carter, 1998; Panksepp, 2006). A human experimental study shows that the combination of oxytocin treatment and being touched by another human sharpens participants' social evaluation of others, such that faces with angry expressions are rated as less friendly and attractive, while faces with neutral or happy expressions are rated as more friendly and attractive (Ellingsen et al., 2014). The touch experience itself is rated as most pleasant when presented along with a happy face and least pleasant when presented with an angry face. However, there is no evidence that oxytocin treatment in healthy subjects by itself affects the touch experience.

The driving stimulus for oxytocin release during nurturing behavior is specifically the type of gentle stroking touch that is the preferred stimulus for CT stimulation (Uvänas-Moberg et al., 2005). The mechanisms by which oxytocin regulates social behavior has recently been elucidated in an elegant mouse knockin study by Yoshida et al. (2009) in which they generated an oxytocin receptor-reporter mouse, revealing that >50% of tryptophan hydroxylase-immunoreactive neurons in the median raphe colocalized oxytocin, suggesting a role for oxytocin in modulating serotonin release—another potential neurochemical protagonist in the upstream consequences of CT stimulation. Additionally, the colocalization was evident from embryonic day 17, suggesting that interactions between these two neurochemicals begin very early in brain development. The ascending serotonergic (5-HT) system modulates affective responses to environmental stimuli at the level of the prefrontal cortex (Cools et al., 2008)—further exploration of this interaction is crucial in fully understanding oxytocin's role in regulating social behavior (Heinrichs and Domes, 2008; Veenema and Neumann, 2008). Numerous studies demonstrate that 5-HT is a key modulator of social responses, with known effects on attachment formation, social bonding, and social perceptions (Raleigh et al., 1980, 1991; Bilderbeck et al., 2011, 2013; Kiser et al., 2012; Ellingsen et al., 2014). Disruption in the function of this system is linked to a number of affective disorders, with Deakin and Graeff (1991) hypothesizing that the interaction between social stimuli and 5-HT is important in the pathogenesis of depression and proposing that affiliative touch interactions may mediate the protective effects of close personal relationships.

As discussed above, offspring of mothers that show high levels of pup care, specifically that which involves licking and grooming behaviors and therefore of a type that would stimulate CLTMs, have reduced physiological responses to acute stress, implicating that an increased turnover in 5-HT linked to licking and grooming may underlie the protective effect on early affiliative interactions (Liu et al., 1997; Weaver et al., 2004; Meaney and Szyf, 2005). A reduction in brain 5-HT is one of the clearest

neurochemical effects of prolonged social isolation (Nelson and Panksepp, 1998) and long-term changes in 5-HT function are observed in monkeys raised in a poor environment (Clarke et al., 1999; Rosenblum et al., 1994). Evidence for a 5-HT link between deficient nurturing and antisocial behavior in humans comes from studies by Pine et al. (1997), who find that boys who grow up in families that provided deficient nurturing were not only more at risk of later delinquency than controls, but also showed abnormalities in 5-HT function (also see Nelson and Trainor, 2007 for a review). Taken together, these studies provide a potential link between deficiencies in an individual's early nurturing environment, 5-HT dysfunction, and later life defects in social behavior such as increased aggression and difficulty developing and maintaining social relationships.

Several studies show that 5-HT modulates sensory encoding of external stimuli during the early stages of perceptual processing (Hurley et al., 2004). A recent study demonstrated that an increase in 5-HT is necessary to precipitate the behavioral change from solitary to gregarious swarming phenotype in the desert locust (Anstey et al., 2009). The transformation depends upon two distinct sensory pathways: (1) the combined sight and smell of other locusts or (2) mechanosensory (moving tactile) stimulation of the hind legs of the locust, which typically occurs as a result of crowding, evidence that 5-HT is the mediator of behavior changes following close physical interactions. Of course complex affiliative behaviors are only observed in mammals (and some birds); however, 5-HT is a phylogenetically conserved neurotransmitter, distributed throughout the mammalian forebrain with receptors in neural networks modulating processes integral to complex social interaction and is a strong candidate for controlling responses to affiliative interactions (Insel and Winslow, 1998). Indeed a number of studies demonstrate that acute serotonergic interventions mediate responses to socially relevant stimuli in both humans and nonhuman primates. Raleigh et al. (1980) report that pharmacological interventions that enhance central 5-HT increased the incidence of affiliative behaviors including allogrooming in adult vervet monkeys, whereas decreasing 5-HT had the opposite effect. The recreational drug Ecstasy (MDMA)—interestingly first described as an *entactogen*—increases the desire to socially interact with others and heightens affective tactile experiences (Thompson et al., 2007; Nichols et al., 1993). It leads to increased 5-HT release in somatosensory thalamus (Starr et al., 2008), providing evidence that 5-HT-mediated distortion in somatosensory processing may play a causal role in enhanced prosocial behavior in ecstasy users.

Finally, an acute tryptophan depletion (ATD) study provides direct evidence for the role of 5-HT in modulating perception of affiliative social cues in healthy volunteers (Bilderbeck et al., 2011). Participants performed a novel task where they rated photographs of couples, standing either touching or apart, on various relationship metrics. The authors find that ATD significantly reduces appraisals of relationship intimacy and romance, as well enhancing participant's conflict resolution ratings for touching couples. In a follow-up study, this time increasing serotonin levels by administering the selective serotonin reuptake inhibitor citalopram, enhanced serotonergic activity was associated with judgments of closer reciprocity in emotional commitment, a state likely to be valued in intimate relationships (Bilderbeck et al., 2013). Thus, even passively observing others touching activates the observers' somatosensory and insular cortices, indicating that membership of a tactile group may well confer a vicarious benefit without participation in mutual or self-touch behaviors (Keysers et al., 2004; Blakemore et al., 2005; Ebisch et al., 2008; McCabe et al., 2008; Bastiaansen et al., 2009; Morrison et al., 2011b; Molenberghs et al., 2012).

The neurochemical systems responsible for the many types of positive and negative touch-dependent social bonding behaviors are undoubtedly based on interacting and interdependent neurobiological processes. As discussed here, there is evidence that oxytocin, opioids, and serotonin mediate and modulate the affective and behavioral responses to affiliative touch, as expressed via stimulation of CT afferents. However, other neurotransmitters, such as dopamine, have also been implicated in motivating such social interactions, and here we see how opioids would be associated with the experience of the affiliative pleasure generated by such motivated behaviors (Depue and Morrone-Strupinsky, 2005). For recent in-depth reviews of the growing body of evidence supporting the involvement of these neurotransmitters in affiliative and affective touch, see Dölen et al. (2013) and Walker and McGlone (2013).

Neurodevelopment

Hooker (1943, 1952) reported with in vitro studies that the human fetus responds to stroking with a fine hair around perioral regions from ~8.5 weeks, confirmed by Arabin et al. (1996) in in vivo embryos. These responses to gentle touch occur before specialized LTMs have developed, as cutaneous nerve endings are still below the surface of the epithelium (Humphrey, 1966). Research into the fetal development of cutaneous C fibers has focused solely on C-nociceptors, with a study by Bartocci et al. (2006), using near infrared spectroscopy (NIRS) in preterm neonates (28–36 weeks of gestation), finding that painful (and tactile) stimuli activated bilateral somatosensory cortex, implying conscious sensory perception in preterm neonates. As will be discussed in the section below—The Skin as an Antisocial Organ—the normal development of the infant's "sense-of-self," and therefore by default the "sense-of-other," may depend upon an optimally engaged and functional CT system.

We propose that one explanation for the early development of the sense of touch is that the affective architecture of the social brain is primed by activation of skin receptors (possibly CTs) via massaging by the amniotic fluid during the prenatal period. Bystrova (2009) has hypothesized a mechanism for human fetal growth regulation whereby the repeated oscillations of lanugo hairs during fetal movements in the amniotic fluid stimulate CT afferents, the function of which is to activate brain regions such as the hypothalamus and insular cortex. Indeed, it has been proposed that the developing social brain—and hence the sense of body self—is primed during gestation, and it has been suggested that this may have implications for the eating disorder anorexia nervosa (AN), in which these hairs often return in the same skin locations where they were present when that individual was in the womb (Strumia, 2005). Body image distortion is common in AN and it would be of interest to establish if such patients have normal responses to CT stimulation. There

is further support for a role of CTs in body image with recent rubber hand illusion RHI experiments (Crucianelli et al., 2013; van Stralen et al., 2014; Lloyd et al., 2013) and testing in amputees (Giummarra et al., 2010) that points to a role for the CT insula axis and could have implications for eating disorders.

Physical touch has been posited as expressing more emotion than that communicated via speech, and as conveying more genuine intention or meaning during social communication (Dunbar, 2004, 2010; Kaitz et al., 1992; Burgoon, 1991; Burgoon et al., 1992; Bottorff, 1993). This sensory modality is clearly a critical communication channel during nurturing behavior, a topic first addressed in the classical work of Harlow, who found that infant monkeys who had been removed from their mothers preferred a surrogate mother made of soft terrycloth to one made of wire that provided food (Harlow and Zimmermann, 1958; Harlow and Harlow, 1962). Harlow concluded from these findings that the absence of comforting touch led to psychological stress in the monkeys. Mother-infant social interactions can be seen as the prototypical affiliative bonding behavior, a prerequisite for which is that it is inherently rewarding for mother and infant in order to motivate such contact (Di Chiara and North, 1992). Tactile stimuli, mediated by CTs and potentially influencing Aβ-mediated touch, would be particularly effective in activating affiliative reward processes (Fleming et al., 1994). The neonatal period is a time of significant social interaction and neurodevelopment, and hence a period when the degree and type of social interaction is likely to have a disproportionate influence on the development and expression of social behavior. The stress-reducing effects of touch have been confirmed in rodent studies in which licking and grooming of rat pups by their mothers permanently change how the rat, as an adult, responds to stressful events (Champagne and Meaney, 2007). Menard et al. (2004) have also found that maternal licking-grooming in rats can affect the adult offspring's behavior and neuronal responses to a fearful stimulus, demonstrating that levels of affiliative and nurturing touch between the mother and offspring can affect a rat's behaviors and natural responses in its adult life. This is further supported by Hellstrom et al. (2012), who find that adult offspring with increased licking-grooming show lower responses to stress, stating that these effects are the result of epigenetic programming. This type of licking-grooming behavior targets specific body sites on the pup—dorsal back and head/ears—where it is known that CLTMs are most densely represented (Li et al., 2011; Liu et al., 2007; Vrontou et al., 2013).

These studies, primarily in animals, indicate that social interactions during the neonatal period affect the subsequent expression of adult behavior by altering sensitivity to neuropeptides (e.g., oxytocin and arginine vasopressin), thereby influencing the expression of behaviors such as affiliation, aggression, sociosexual behavior, parental behavior, and responses to stress (Cushing and Kramer, 2005). Looking at human mother-infant behavior, Stack and Muir (1990) found that touch occurred ~65% of the time during face-to-face interactions, which, claim the authors, acts to reduce stress and increase positive affect (see also Hertenstein et al., 2006). Interestingly, it is not touch per se that affords these benefits to the infant, but the quality of the touch that mattered, demonstrating that it was stroking—CT adequate-stimulus touch—rather than passive touch that led to facial signs of reward, i.e., the infants smiling (Jean et al., 2009; Stack and Muir, 1990, 1992). In human infants, being touched decreased their stress-activated cortisol production with lower levels of cortisol correlating with increased cell development in the hippocampus, impacting on both short- and long-term memory function (Miles et al., 2006).

Animal studies have also found that prenatal stress can affect both physiological and emotional systems in adult life (Meaney et al., 2007) and that postnatal nurturing behaviors, i.e., licking and grooming, reduce fear responses and lower HPA reactivity. In fact, Soares et al. (2011) find similar stress-reducing effects of touch in the surgeonfish, which is groomed by cleaner wrasse that remove ectoparasites. Stroking surgeonfish with dummy cleanerfish models in the lab significantly lowers levels of cortisol compared with controls with access only to stationary models—possible evidence of an evolutionary mechanism.

To test whether postnatal maternal behaviors could modify the negative consequences of prenatal stress in human infants, Sharp et al. (2012) examined whether maternal stroking during the first weeks postpartum altered associations between prenatal depression and physiological and behavioral outcomes in infancy. The authors find a significant interaction between prenatal depression and maternal stroking where increasing maternal depression is associated with increasing negative emotionality only in the presence of low maternal stroking. Irrespective of the noise introduced by relying on self-report measures in this study, it nonetheless provides evidence that maternal stroking—CT touch—in infancy has similar effects to those reported in rodents, providing a modern epigenetic interpretation of the nurture/nature debate.

The earlier reports for the importance of nurturing touch in infancy came from Spitz (1945, 1946), who noted that foundling homes in Germany had high mortality rates in the first year of life even though the children had all their basic needs met—they were clean, well fed, and warm; what they lacked was physical touch. Suomi (2011), in a study with rhesus monkeys, separated the infant from the mother with a transparent screen—the infant could see, hear and smell their mother but was unable to touch her, resulting in a chronic activation of the HPA. Only through the introduction of peer touch relationships were they later to develop normally. Bystrova et al. (2009), noting that separation of mother and baby after birth still persists in many parts of the world, carried out a study with 176 mother-infant pairs who were randomized into four experimental groups: infants were placed skin-to-skin with their mothers after birth, infants were dressed and placed in their mothers' arms after birth, infants were kept in the nursery both after birth and while their mothers were in the maternity ward, and infants were kept in the nursery after birth. Only the group that experienced skin-to-skin contact for 25 to 120 min after birth showed a positive influence in mother-infant interaction 1 year later when compared with the groups where there was a separation of mother and infant. Further support for the role of affiliative touch in early life comes from research by Liedloff (1985), who carried out, over a 2.5-year period, a study of the indigenous Yequana people who inhabit rain forest in the upper Caura River basin of Venezuela. During this time, Liedloff reported that children were "uniformly well-behaved: never fought, were never punished and always obeyed

happily and instantly,'' concluding that such behavior was due to the constant baby carrying, breastfeeding on demand, and cosleeping. Although providing anecdotal evidence for the importance of caring touch in the early years of development, caution is required when translating such observations extracted from a hunter-gatherer society to a modern-day industrial society (Bobel, 2002).

The importance of touch in reducing aggression is reported in a multicultural study by Prescott (1979), who found a strong relationship between less physical affection toward children and later aggressive behaviors, compared with cultures in which affiliative nurturing behaviors were high, with a concomitant reduction in adult aggressive behaviors. Prescott (1979) suggests that adult aggressive behaviors may well have their origins in deprivation of nurturing/affiliative tactile reward in either infancy or in adolescence, arguing for a link between a lack of natural rewarding touch and subsequent self-gratification behaviors in adulthood. Francis et al. (1999) show that the orbitofrontal cortex (OFC), implicated in reward processing in human adults and nonhuman primates (Rolls, 2004) is activated by gentle stroking touch in an fMRI study, which led Kida and Shinohara (2013) to replicate this study in human infants at 2, 6, and 10 months of age, using functional near-infrared spectroscopy (fNIRS) to measure activity in the anterior prefrontal cortex (APFC). Only in the 10 month olds was there activation of the APFC in response to gentle stroking of the glabrous skin of the hand, indicating a developmental change occurring between 2 and 10 months in affective tactile processing. A similar study needs to be carried out delivering slow gentle touch to hairy (CT-innervated) skin sites, and although this finding alludes to a ''critical period'' between 2 and 10 months, this does not mean that this is the only touch-sensitive critical period during development. With the recognition that early touch deprivation can be linked to a ''fractured neurobiological/neuropsychological substrate'' and lead to dissociative behaviors such as depersonalization disorder and depression (Deakin et al., 1990; Prescott, 1979), we have a possible mechanistic explanation with the functional role of CTs.

A note of caution is however required when assigning such a critical role to a single class of afferent mechanosensory nerves because CTs are never stimulated in isolation from LTMs in neurologically intact individuals. Just how these slow (CT) and fast (LTM) mechanosensory systems interact centrally is currently unknown. Our studies with deafferented neuronopathy patients show that they sense C-nociceptor pain normally, but CT-targeted gentle touch does not evoke such a clear qualia. Of interest here is Bentley (1900)'s ''synthetic experiments'' on the perception of liquidity, as a demonstration of the integrative nature of perception. He showed that wetness perception depended upon the activation of sensory input from both pressure and temperature nerves and that the percept did not require the skin to be wet. Could similar a mechanism be operating with affective touch between CTs and LTMs?

The Skin as an Antisocial Organ

Could the ''socializing'' aspect of intra- and interactive touch play a potential role in autism spectrum disorders (ASDs)? Sensory-perceptual anomalies occur in approximately 70% of autism cases (DiCicco-Bloom et al., 2006) and are associated with difficulties in adaptive behavior (Rogers et al., 2003). Individual autobiographical accounts from verbal, high-functioning people with autism emphasize their unusual sensory experiences (Jones et al., 2003; Grandin, 1992), often describing overwhelming sensory input as an impetus for social withdrawal. Given the developmental nature of ASD, the fact that touch is the first sense to develop in utero, and the vital role touch plays in early social development, it is important to characterize the brain mechanisms for processing affective touch in children with ASD in order to better understand the neurobiological mechanisms underlying this neurodevelopmental disorder. In recent neuroimaging studies with neurotypical adult participants, Gordon et al. (2013) and Voos et al. (2013) have demonstrated the involvement of key nodes of the social brain network in processing CT-targeted touch. This network had previously been described by Kaiser et al. (2010) as being hypoactive during social perception tasks in individuals with ASD, raising the intriguing question of whether the autistic population exhibit abnormal brain mechanisms for processing CT-targeted affective touch. Unusually acute tactile sensitivity, or the inability to modulate tactile input, is hypothesized to impede social behavior that involves interpersonal touch (Grandin, 1992), and aversion to social touch is among several atypical behaviors seen in infants later diagnosed with autism (Baranek, 1999; Grandin and Scariano, 1986). Grandin, herself autistic, described her own experiences of wearing clothes with the light touch of fabrics causing extreme distress (mediated through CTs) but ''sheer joy'' was experienced by being held firmly or squeezed (a role of Aβ LTMs). The impact on her social development is captured in the following insightful statement, ''I feel that the lack of empathy may be partially due to a lack of comforting tactual input'' (*Temple Grandin: An Inside View of Autism*, http://www.autism.com/advocacy_grandin). In spite of these ecologically valid reports, and some clinical reports (Kern et al., 2007), recognition from experimental studies of tactile perception in autism is scarce. Among somatosensory submodalities that may contribute to tactile hypersensitivity in autism (Blakemore et al., 2005), the role of CT afferents presents an intriguing hypothesis, with a dysfunction of such a system being a prime candidate for the tactile hypersensitivity associated with this condition (Cascio et al., 2008). Finding affiliative (gentle) touch aversive could have as-yet-unknown consequences during a critical period and in the subsequent development of neural structures underpinning emotional, and thereby social, development. It is well known of course that sensory processing disturbance in autistic children typically include hypo-, hyper-, or normal responsivity to visual, auditory, olfactory, and gustatory stimuli, so it would need to be shown that disturbances in these modalities were as a consequence of an initial developmental failure in affective touch.

Although all of the discussion so far on the neurodevelopmental consequences of reduced nurturing touch has focused on the postnatal period, Bystrova (2009) has put forward a novel hypothesis of human fetal growth regulation that proposes a role for touch in utero. Touch is the first sense to develop ontogenetically (Montagu, 1978; Gallace and Spence, 2010) and, thus, may play a fundamental role in scaffolding the social brain as it is the

initial modality able to distinguish "self" from "other" in the developing brain. The fetus is covered in a fine downy hair—lanugo hairs—that are encased by vernix caseosa (a waxy substance found coating the skin of newborn human babies) and Bystrova suggests that fetal movement in the amniotic fluid stimulates (massages) CTs, which activate hypothalamus and insular cortex, thereby promoting an antistress effect through oxytocin release, as well as potentially providing the developing social brain with its primary template. A failure (genetic or otherwise) of the CT system to develop could significantly impact on the neurotypicality of the brain, and hence the expression of ASD. We would like to propose that a neurodevelopmental failure of the CT system and its central connections may contribute to the pathology in ASD. This is to some extent supported by an fNIRS study that finds activation of a cortical area implicated in social processing, the posterior superior temporal sulcus (PTS), for CT-targeted but not Aβ-targeted touch (Bennet et al., 2013). Additionally, individual differences in autistic traits were related to the magnitude of peak activation within PTS.

Although a neurobiological basis for responses to gentle touch being atypical in humans on the ASD spectrum are not understood, Cascio (2010) has suggested the possibility of a peripheral pathology of CT afferents. As outlined above, social isolation postpartum results in adult behavioral, emotional, and cognitive dysfunction, which Nagy et al. (2004) has shown correlates with white matter alterations in the frontal lobes. A recent study by Makinodan et al. (2012) finds that mice socially isolated for a 2-week period immediately after weaning showed functional deficits in prefrontal cortex (PFC) and its degree of myelination. After reintroduction into a normal social environment, it was found that these neural consequences of isolation were irrecoverable, indicating that early life social experiences are critical-period dependent in regulating PFC myelination and are vital for neurotypical development. However, a similarly based social isolation study, but this time with adult mice, also reported impaired reduced adult myelination in PFC but interestingly found that in adults social reintegration normalized levels of myelination (Liu et al., 2012)—reinforcing the previous finding that critical periods in the developing social brain are indeed irreversible. It is not possible to say whether this is solely, or at all, a CLTM effect, as social isolation during early development will impact multimodal sensory inputs and hence a number of critical periods.

Lyons et al. (2010), in a primate study, found that intermittent social isolation resulted in monkeys showing signs of enhanced negative feedback regulation of the HPA in response to stimulation by exogenous CRF, paralleling the rat studies by Meaney et al. (1996). It is only possible to conjecture at this stage that it is the lack of nurturing (CT?) touch that affects the monkeys' subsequent abnormal response to stress, but at least in the rat it is the lack of stroking touch that explains the stress experienced by the maternally deprived rat pups (Eghbal-Ahmadi et al., 1999). Nevertheless, patients with a congenital reduction in the density of C fibers, including CTs, do not show a high incidence of ASD (Morrison et al., 2011a), so clearly a variety of factors contribute. As Lovero et al. (2009) have pointed out, it is necessary to understand the neural architecture of human touch beyond the current focus on its purely sensory properties in order to expose how emotionally relevant touch may be implicated in individuals with mood, anxiety, or addiction disorders.

Conclusion

In somatosensory research, the canonical view is that touch is mediated by large-diameter, fast-conducting peripheral nerves and that the sensory acuity of touch across the body is highly heterogeneous with areas such as the digit tips and the lips being more densely innervated and more cortically represented than other body sites. With the dominance of the glabrous surface of the hand in all forms of exploratory and exteroceptive tactile behavior and object manipulation, it is not surprising that much is known about hand-brain neural systems. Here, in contrast, we have provided convergent evidence for another purpose to touch that is more interoceptive than exteroceptive and that is less accessible to conscious self-report, as evidenced by CT afferents projecting to emotional systems (insular cortex, orbitofrontal cortex) but less or not at all toward the discriminative-cognitive systems (classical somatosensory areas S1 and S2) (see Figure 5).

This observation seems to provide an essential support for the affective touch hypothesis. The physiological properties of the CT afferents, as well as the psychophysical and fMRI/PET responses to CT activation, converge toward an affective-emotional role. The "affective touch hypothesis" implies that the essential role of the CT system is to provide or support emotional, hormonal, and behavioral responses to skin-to-skin contact with conspecifics. On the other hand, it is also likely that a natural perceptive emotional response to pleasant touch is dependent on the combination of afferents from the two tactile systems, because selective CT stimulation fails to evoke anything like a full sensation of pleasant touch. The combination of CT and Aβ afferents is required for the complete feeling of pleasant touch in the hairy skin, and the intensity and even the quality of the emotional response evoked by a particular stimulus is highly dependent on contextual factors. It is pertinent here to cite another prescient insight from Foerster (1936) when describing the perceptual consequences, this time, of complete transection of the dorsal columns:

> This causes a very remarkable disturbance of the ability to discriminate between different sorts of pain. The patient has become unable to tell what caused the pain. They all feel the same, whether having been stuck by a needle, or if hairs are tugged, or if a muscle or bone is gripped tightly, or if a faradic current is applied to the skin … Hence, we come to believe that the dorsal column and the anterolateral pathway cooperate with regard to the tactile and pain sensibilities. It appears as if the anterolateral pathway can only transmit primitive, undifferentiated touch and pain sensations, and that the dorsal column delivers the accessory qualities … (p. 364, translated from the original German)

With the value of hindsight and an indication that CTs travel rostrally in the anterolateral tract, we can begin to see how interdependent the afferent cutaneous channels are in shaping somatosensory perception.

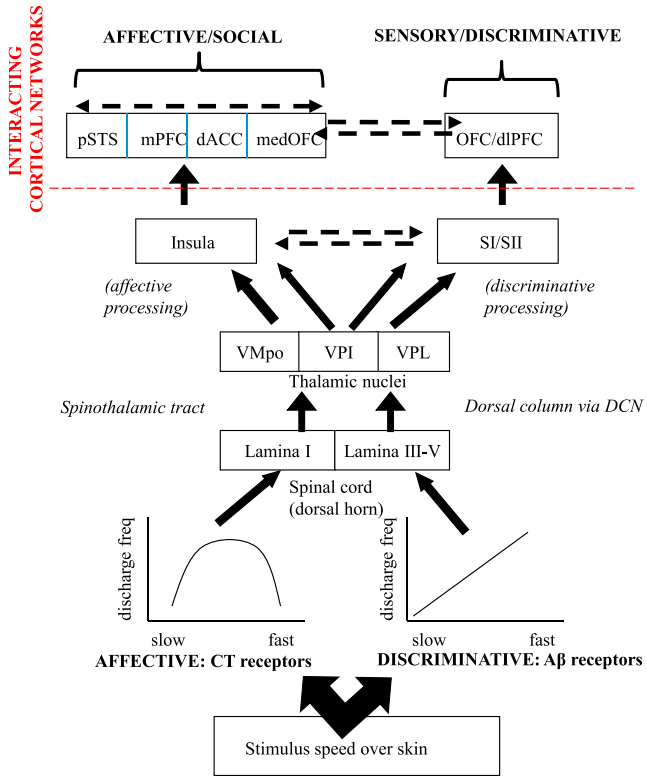

Figure 5. Schematic Diagram of Affective and Discriminative Pathways for Touch to Hairy Skin

CT afferents respond with an "inverted U"-shaped curve where the "adequate stimulus" is tuned to touch of affiliative or affective significance. Aβ afferent firing increases linearly with velocity, responding to the physical properties of the stimulus. Within cortex, reciprocal connections between posterior insula, mid insular, and secondary somatosensory cortex may allow mutual modulation of affective- and sensory-related processing. Forward projections from IC include social brain networks, with those from SI/SII only showing general OFC area. Dashed lines indicate putative pathways. Abbreviations: VMpo, ventromedial posterior nucleus; VPI, ventroposterior inferior nucleus; VPL, ventral postlateral nucleus; medOFC, medial orbitofrontal cortex; OFC, orbitofrontal cortex; dlPFC, dorsolateral prefrontal cortex; S1/S11, primary and secondary somatosensory cortex (Craig, 2002; Dum et al., 2009; McGlone et al., 2012; Francis et al., 1999; Petrides, 2005). Figure is adapted from Morrison et al. (2010).

In a wider perspective, the CTs may be regarded as an afferent system that is basically concerned with the representation of self, rather than external events, as conjectured by Craig (2002). The role of CTs as an afferent branch of a system guarding the well-being of the body would be to signal the reward and reassurance afforded by physical closeness of a caregiver, partner, etc. Many questions, however, still need to be addressed, and answered, with regard to the role of CTs, such as the absence of CT nerves in glabrous skin. Their precise anatomical location in human hairy skin is also unknown, and we do not know anything about their receptor neurobiology. Behavioral and neuroimaging studies (PET and fMRI) are addressing these issues, and there is increasing evidence for a different central neural representation to stroking hairy as opposed to glabrous skin in neurotypical and nonneurotypical populations in limbic brain structures rather than primary somatosensory structure areas (McGlone et al., 2012; Gordon et al., 2013; Voos et al., 2013). The significant advances made in understanding the C fiber "pain" system have been made possible because of the multidisciplinary efforts of scientists and clinicians from diverse backgrounds—the same will need to be the case for the C fiber "pleasure" system.

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